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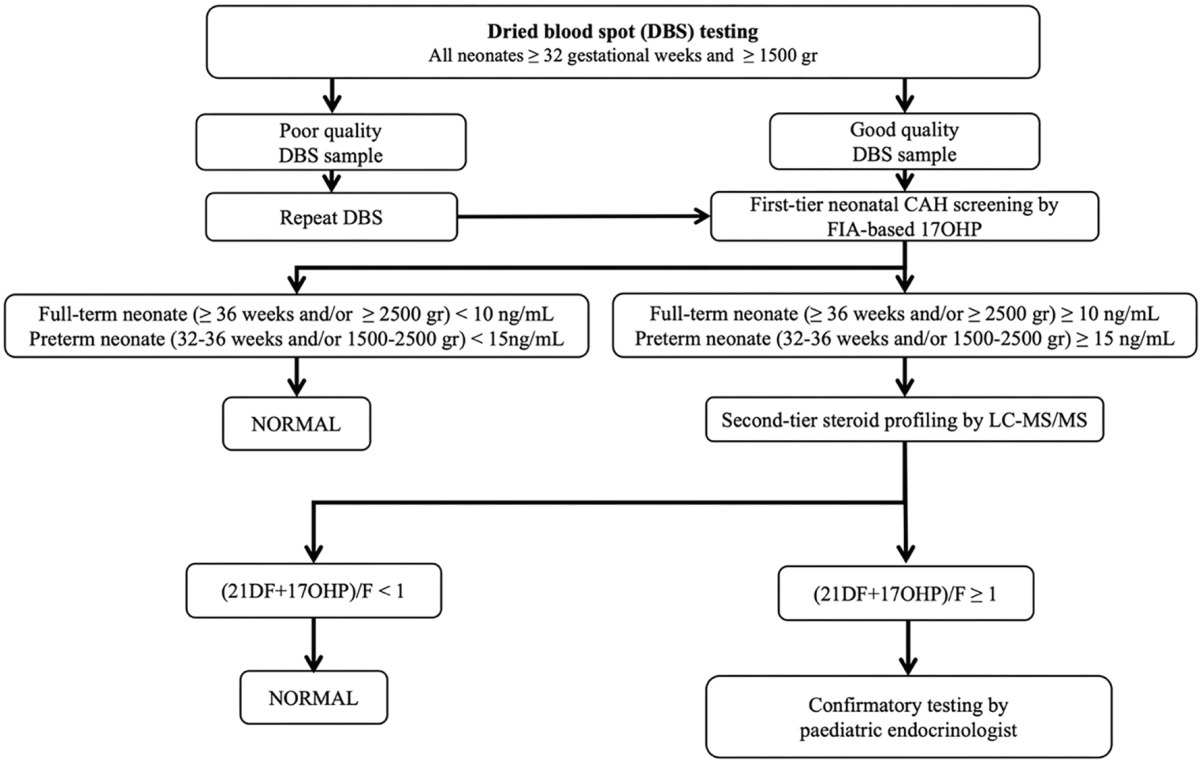

The First-Year Outcomes of the Nationwide Neonatal CAH Screening in Türkiye: High Rate of False Positives for 21-Hydroxylase Deficiency and a Higher Detection Rate of Non-Classical Cases

Güran T et al.

Page: 488-493

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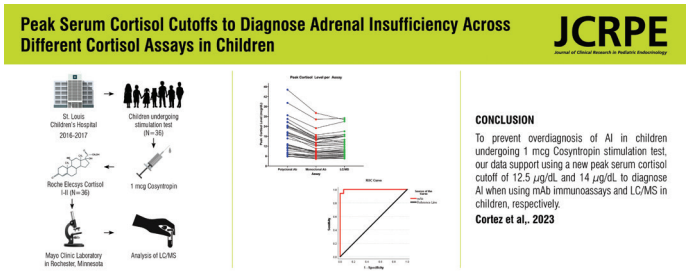

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REVIEW

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J Clin Res Pediatr Endocrinol 2025;17(4):370-378

Noonan Syndrome, Cancer Risk, and Growth Hormone Treatment

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Abstract

Cancer may occur in patients with Noonan syndrome (NS). Review of English literature revealed that myeloproliferative diseases are the most prevalent, followed by intracranial tumours. There is no genotype-phenotype relationship between germline pathogenic variants so it not possible to precisely predict cancer risk in NS, however some *PTPN11* variants are exclusively detected in juvenile myelomonocytic leukemia and are not observed in other types of cancer. Among patients on growth hormone, cancer development was reported in seven patients with genetically confirmed NS, and five patients with clinically diagnosed NS. However, information on growth hormone dose, timing, and follow-up characteristics in these cases is heterogeneous. In the light of current data, especially in cases for whom growth hormone therapy is considered, the diagnosis should be genetically confirmed, and the results of genetic analysis should be compared with the cases reported in the literature. Families should be informed about possible cancer risk and in cases predisposing to juvenile myelomonocytic leukemia, early initiation of growth hormone therapy should be avoided.

Keywords: Rasopathy, growth retardation, somatotropin, oncogenesis, malignancy

Introduction

Noonan syndrome (NS) is the most common type of RASopathy. Related main overlapping disorders are NS and multiple lentigines, cardiofaciocutaneous syndrome, Costello syndrome (CS), neurofibromatosis type 1 (NF1), Legius syndrome, and NS-like disorder with loose anagen hair (1,2,3). In this review, we focused on NS in order to ensure the accuracy of diagnosis and strengthen the reliability of the findings by minimizing potential misclassification of overlapping conditions.

Somatic mutations in the genes of the RAS/MAPK pathway, including *PTPN11*, *KRAS*, *HRAS*, *NRAS*, *NF1*, and *CBL*, which are involved in regulating cell growth, division, and differentiation in response to growth factors, have been shown to play an important role in the development of some cancers. For instance, *PTPN11* encodes SHP-2, a tyrosine phosphatase enzyme that modulates intracellular signaling. Some mutations in *PTPN11* lead to abnormal activity of this enzyme and disrupt normal signaling processes. Furthermore, somatic mutations in *PTPN11* enhancing phosphatase activity of mutant SHP-2 have been detected in childhood leukemia (4). Mutations in *KRAS* and *NRAS* may lead to hyperactive RAS/MAPK pathway due to defective intrinsic GTPase activity (5). Given this evidence, there have been concerns regarding the potential genetic predisposition to cancer in individuals with NS, which occurs with germline and mostly heterozygous changes of some genes in this pathway. The use of growth hormone (GH) therapy for short stature in NS further increases the concerns (6,7). However, GH therapy has been approved by the US Food and Drug Administration in 2007 for cases of NS with short stature, and there is still no global consensus on routine cancer screening in NS (8,9,10).

Considering that NS had an average prevalence of 1 in 2000 in the overall population, the number of reported cancer cases is relatively low. On one hand, this might be explained by the fact that certain cases of NS exhibit subtle symptoms,

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possibly resulting in underdiagnosis. On the other hand, NS-related variants might not be directly associated with cancer and various additional genetic changes may have indeed contributed to the development of oncogenic processes in cases of NS. Studies have recently shown the presence of hyperdiploid karyotype in the leukemic cells of a significant portion of acute lymphoblastic leukemia (ALL) cases (36-73%) carrying a germline *PTPN11* variant. It has been proposed that additional factors, such as chromosome breaks or certain epigenetic influences, may contribute to an increased susceptibility to cancer in patients with NS (11,12). Some studies observed a relationship between uniparental disomy in several genes and oncogenesis (13). Interestingly, in a NS patient with ALL, the germline *PTPN11* variant was not present in the leukemic cells, suggesting other mechanisms (14).

Methods

A literature review was conducted using web search tools including PubMed, OMIM, and Google Scholar (1987 to present; last access date September 23rd, 2024) using the search terms "Noonan" or "Noonan Syndrome" to identify all relevant case reports or cohorts. The reference list of all articles was also searched to identify further relevant publications. We included only patients clinically and genetically diagnosed with NS. All cases with NS-like syndromes, such as NF-1 with NS features, were excluded. We should point out that clinical and genetic data in the published reports were heterogenous; most articles presented insufficient clinical details about the cases, and there was a notable absence of comprehensive analyses of other conditions that might contribute to cancer predisposition. It was assumed that the cases did not receive GH treatment if it was not mentioned.

Cancer in Patients with NS Who did not Receive GH

There are various data regarding the general cancer frequency in NS. The first comprehensive report on this topic reviewing the literature from 1937 to 2010 found 46 cancer events in 45 cases (3.9%) among 1151 subjects with either a clinical or genetic diagnosis of NS (15). It was reported that the age at cancer diagnosis was similar to that seen in the general population. In this cohort, 73% of the cases were 20 years of age or younger, with the predominant cancers being neuroblastoma (n=8), ALL (n=8), glioma (n=6), and rhabdomyosarcoma (n=6). This article, which has frequently been cited in reviews, has important limitations, including a lack of genetic investigation in many cases and the exclusion of myeloproliferative disorders.

Table 1 presents the list of histopathologically confirmed malignant tumors reported in the literature among pediatric cases with NS, whose diagnoses were confirmed through genetic analysis. For the small number of cases with multiple cancers, we recorded the first one. Myeloproliferative diseases are the most common, followed by intracranial

Table 1. List of histologically confirmed malignant tumors reported in patients with a diagnosis of NS(the number is shown within parantheses when a mutation is reported in many patients)

Tumor	Gene	Germline variant at protein level	References
Juvenile myelomonocytic leukemia (n=40)	*PTPN11*	G60A D61G (2) D61H (2) D61N Y62D F71L A72G (3) T73I (11) E139D (3) F285L (2) N308D N308S G503A G503R (4) Q506P R65Q Y63C 179-181delGTG	(4,16,17,25,34,38,40,47,51,58)
	KRAS	T58I	(20)
	NRAS	G13D G12S	(28,43)
	RIT1	M90I	(56)
	RAF	S257L	(60)

Table 1. Continued

Tumor	Gene	Germline variant at protein level	References
Acute lymphoblastic leukemia (n = 19)	*PTPN11*	N58S G60A Q79R E139D (2) Y279C N308D (5) G503R M504V (3) R501K[a]	(11,14,21,35,40,54,58)
	SOS1	M269R M269T	(12)
	RIT1	D81G	(36)
	LZTR	R210*&c.2220-17C > A E563Q	(46)
Acute myeloid leukemia (n = 1)	*PTPN11*	G268S	(61)
Non-Hodgkin lymphoma (n = 1)	*PTPN11*	P491L	(18)
Dysembryoplastic neuroepithelial tumor (n = 6)	*PTPN11*	G60A D61G[a] E139D[a] N308D (2) N58K	(34,40,42,44,45)
Low-grade glial tumor (n = 1)	*RAF1*	G361A	(53)
High-grade glial tumor (n = 2)	*PTPN11*	T2I N308D	(48)
Glioneuronal tumor (n = 2)	*PTPN11*	N58D N308D	(29,49)
Pilocytic astrocytoma (n = 4)	*PTPN11*	G60A N308D[a] F491P	(30,40,45)
	KRAS	D153V	(40)
Pilomyxoid astrocytoma (n = 1)	*PTPN11*	E139D	(41)
Oligoastrocytoma (n = 1)	*LZTR1*	R284C[a,b]	(50)
Oligodendroglioma (n = 2)	*PTPN11*	E139N	(34)
		T22A	(22)
Hypothalamic glioma (n = 1)	*PTPN11*	E139D	(19)
Medulloblastoma (n = 1)	*PTPN11*	T468M	(37)
Neuroblastoma (n = 4)	*PTPN11*	G60A I282M I282V N308D(2) D61G	(11,23,26,34,58)
Rhabdomyosarcoma (n = 5)	*SOS1*	P102R[a] S548R L728I	(31,32,33)
	RRAS2	G23C	(52)
		G12R	(55)
Sertoli cell tumor (n = 1)	*SOS1*	M269T[a]	(33)
Hepatoblastoma (n = 1)	*PTPN11*	N308D	(27)
Giant cell tumour (n = 1)	*RIT*	A57G	(39)
Wilms tumor (n = 1)	*ERF*	I46N	(59)

[a]Treated with growth hormone, [b]Cancer was diagnosed at 22 years old

tumors among solid tumors. The cancers were generally linked to variants in *PTPN11*, a prevalent cause of NS. The T73I variant in *PTPN11* has only been found in cases with juvenile myelomonocytic leukemia (JMML), the other variants were present in various tumor types. Since many of the variants listed are also found in NS cases who did not develop cancer, no clear correlation can be established between the *PTPN11* variants and the occurrence of cancer (4,11,12,14,16-61).

Myeloproliferative diseases in NS may present in two different clinical situations. While most of the cases have a benign course, the remaining cases progress aggressively; this type is called JMML and it is rarely seen in children without NS. The association between this form of leukemia and NS was initially reported by Tartaglia et al. (16) in 2003. Nevertheless, comprehensive details regarding the clinical characteristics of the patients were not provided at that time. In a study covering a 10-year period from a reference hospital from France, JMML was present in 20 (3.12%) of 641 cases with NS with a *PTPN11* variant (Table 1). JMML-related findings had appeared in the first three months of life in all cases and, interestingly, a history of polyhydramnios may be a warning sign for development of JMML since its incidence was significantly higher in such cases (50%) compared to the NS cases who did not develop JMML (11.7%). In addition, the majority of the *PTPN11* variants detected in NS cases with JMML were also found in NS patients without myeloproliferative diseases (38). A study published later from the same center reported that ALL occurred in 4 out of 778 cases (0.5%) with a *PTPN11* variant and in 2 out of 94 cases (2.1%) with a variant in the *SOS1* gene (Table 1) (12).

In a study including data of NS patients collected from 25 molecular genetic laboratories in Germany, 8 out of 632 (1.27%) children had cancer. Importantly, all these cases had a *PTPN11* variant (Table 1) (40). Based on these findings, the risk of developing childhood cancer in NS was estimated to be 8.1-fold increased; however, the risk of developing ALL and neuroblastoma appeared to be similar with that of the general population. In the same study, the risk of developing cancer in those with CS and those with a *KRAS* variant was 42.4-fold and 75.8-fold increased, respectively.

In a study from the Netherlands, among 297 subjects with NS with a *PTPN11* variant, 12 (4.04%; 4 children, 8 adults) developed cancer during a median follow-up duration of 13 years. It was concluded that the risk of developing cancer until the age of 55 was 3.5 times higher compared to the general population (Table 1) (62).

In a study from Italy, among the 35 NS cases with a clinical and/or genetic diagnosis, 2 (5.7%) patients with a *PTPN11* variant had developed a cancer. Unfortunately, specific variants were not mentioned (63). A study from China reviewed 102 patients with NS, five of whom carried *PTPN11* variants and were found to have tumors. Among these, two were diagnosed with JMML, two with neuroblastoma, and one with ALL (58).

Among the 107 patients with NS and a *RAF* mutation reported in the Italian cohort, 20 were newly identified cases. Two cancer cases were noted, but the specific types of cancer were not provided (60). Genetic findings of subjects with NS and cancer reported as case reports have been given in Table 1, however, we could not include a 14-year-old boy with T-cell ALL and glioblastoma since the variant in *PTPN11* was not specified (64).

There are also a few case reports of rabdomyosarcoma in patients with a clinical diagnosis of NS (65,66). On the contrary, no cancer was reported among some studies from various countries which included over 1000 cases (67-78).

Cancer in Patients with NS Treated with GH

The relationship between GH therapy and cancer has been an ongoing debate for several years since elevated levels of insulin-like growth factor 1 (IGF1) have been identified as a potential risk factor for the development of certain tumors and congenital 1 deficiency appears to provide a protective effect against cancer (79). Based on data obtained from case series, the treatment of GH for idiopathic GH deficiency, idiopathic short stature, and short stature in infants born small for gestational age is generally not associated with an increased risk of cancer. Notably, cases with a history of cancer, those with predisposing conditions like neurofibromatosis, Down syndrome, chromosomal breakage, or DNA repair abnormalities have a natural vulnerability to developing cancer (80). In terms of NS, while various animal models with RASopathies exist, the effects of the relevant gene mutations in response to GH therapy have not been studied in these models (1). The outcomes of GH treatment in humans with NS have been reported in the medical literature since it was first used in 1987 (81). We categorized the reported cancer cases into two subheadings based on the type of diagnosis (clinical diagnosis only vs clinical and/or genetic diagnosis) given that NF 1, which is well known to have a predisposition to cancer, was reported to be the underlying condition in some patients with a clinical diagnosis of NS, even in the absence of café-au-lait spots (82). Furthermore, eight cases reported in congresses were not included (42). However,

the data exhibited heterogeneity in dose and timing of GH treatment, IGF1 levels, duration of follow-up, and genetic analysis information. We have summarized the relevant data as far as possible.

Cases with a Clinical Diagnosis of NS

In a single center study from Sweden, the outcomes of GH treatment in 25 children with NS were reported. Ten of the cases were initially treated with a dose of 0.23 mg/kg/week, while the remaining 15 were treated with a dose of 0.46 mg/kg/week. According to the study protocol, dose adjustments were made two years later, and after three years of GH treatment, one patient out of 25 (4%) developed lymphoma (83).

Data from the US registry of a GH manufacturing company revealed that a possible left parietal lobe tumor developed in one of 65 cases (1.5%). The reported average dose of the GH was 0.33 mg/kg/week, and the patient achieved adult height (84).

An atypical granular cell tumor, of which the histological features could not definitively distinguish between benign or malignant, was reported in a 10-year-old girl. The girl was treated with GH for three years; after surgical excision, no recurrence developed during three years of follow-up (85).

In a study performed on cases who received GH for a duration exceeding four years using an international registry of another GH manufacturing company, two cases, aged 9.5 and 10 years, developed glioneuronal tumor and a brain tumor (for which no clear information is available) after GH therapy for 1.2 and 2.5 years, respectively (7).

NS Cases with Genetic Data

In an international study published in 2010, *SOS1* analysis was performed in 102 cases without *PTPN11* or *KRAS* mutations. The study reported that a 4-year-old patient with the P102R variant in the *SOS1* gene developed rhabdomyosarcoma, while another 4-year-old patient with the M269T variant was diagnosed with a Sertoli cell tumor. Although GH therapy was noted in both cases, no further details regarding the timing, dosage, or follow-up of the treatment were provided (86).

In 2016, it was reported that an 8-year-old patient with NS who had been receiving GH therapy for the past 4 years and had an E139D variant in *PTPN11* was diagnosed with a dysembryoplastic neuroepithelial tumor. Upon reviewing the cranial magnetic resonance imaging (MRI) images taken for another reason when the patient was 1.5 years old, smaller lesions, previously described as "nonspecific", were identified in the same regions where the current lesions were found. However, no detailed information regarding endocrine follow-up was provided (42).

In 2017, an 8-year-old patient with a D61G variant in *PTPN11* was reported to have developed a low-grade dysembryoplastic neuroepithelial tumor in the 15th month of GH therapy. The dose was 0.3 mg/kg/week and an IGF-1 level 115 ng/mL during the first six months of treatment. A subtotal resection was performed, and the GH was stopped. At the end of the first year, due to a low growth rate, GH therapy was restarted without a stimulation test. The IGF-1 level was maintained between 1 and 2 SDS according to the patient's age and pubertal stage, and MRI follow-up showed no growth in the residual mass. In a second patient reported by the same center, with an N308D variant in *PTPN11*, no pathology was found in a cranial MRI taken for migraines at the age of 9.5 years. At 13.5 years of age, GH therapy was started without a stimulation test at a dose of 0.35 mg/kg/week. During follow-up, the maximum dose was 0.4 mg/kg/week and IGF-1 levels were in the normal range. In the 18th month of treatment, the patient presented to the emergency department with confusion and was diagnosed with pilocytic astrocytoma, leading to the discontinuation of GH therapy (45).

Recently, *LZTR1* mutations have been found to cause NS through either autosomal dominant or recessive inheritance. In 2020, it was reported that a patient with a heterozygous R284C variant in this gene, who had been using GH at a dose of 0.23-0.25 mg/kg/week between the ages of 15 and 17 years, developed an oligoastrocytoma at the age of 22 years (50).

In a study evaluating cases from an international database of a GH manufacturing company, including patients who had received treatment for more than four years, an adolescent with an unspecified *PTPN11* mutation was reported to have developed a pilocytic astrocytoma and spinal metastases after 2.5 years of GH treatment (79). A few years later, the same company reported another case, who was a 9-year-old male with an unspecified *PTPN11* variant and a brain neoplasm (dysembryoplastic neuroepithelial tumor) 14 months after initiation of GH treatment (82).

In another case report, the nine-year-old patient, who had been diagnosed with NS in infancy and carried a R501K variant in *PTPN11*, was diagnosed with medium-risk T-ALL after receiving GH treatment for a 3-year period. Unfortunately, no more information on GH treatment was given (54).

Conclusion

An article published by the Pediatric Endocrine Society (PES) in 2015 in the United States discussed the cancer risk in patients treated with GH, and NS was assessed as one of the conditions that predispose individuals to tumor development in these patients (80). Moreover, a report in 2017 published by a group primarily consisting of oncology specialists from the USA, Germany, Japan, and Canada stressed the importance of performing physical examinations, blood counts, and blood smear tests during the initial five years of life for cases with a genetic variant that may be associated with JMML. This report recommended using a blood smear as a screening method for this group. However, it was not recommended for cases with genetic variants that were not linked to developing JMML, as there was a minimal risk of developing cancer in this group. Therefore, routine screening was considered unnecessary, and it was suggested that cases should be warned to attend for further evaluation if they experienced any symptoms that may be a sign of a tumor (87).

As a general approach by the PES, if GH treatment is started in cases with a predisposition to cancer, such as a genetic disease, although there is no evidence to support or contradict it, the cautious approach is to keep blood IGF1 at age-appropriate levels and to perform routine cancer screening according to disease specific guidelines. However there are no generally accepted cancer screening guidelines for NS (84).

Based on the current literature and recommendations, particularly in cases of NS when GH treatment is being considered, it is advisable to: (i) confirm the diagnosis through genetic analysis; (ii) compare the identified genetic changes with cases documented in the literature; (iii) avoid early initiation of GH treatment in individuals who are at risk for JMML; and (iv) appropriately communicate potential risks with families and establish a comprehensive follow-up plan.

Footnotes

Authorship Contributions

Concept: Korcan Demir, Design: Korcan Demir, Data Collection or Processing: Korcan Demir, Kübra Yüksek Acınıklı, Literature Search: Korcan Demir, Kübra Yüksek Acınıklı, Writing: Korcan Demir, Kübra Yüksek Acınıklı.

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REVIEW

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Pediatric Type 1 Diabetes Care in Indonesia: A Review of Current Challenges and Practice

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Abstract

Type 1 diabetes mellitus (T1DM) is a chronic condition requiring lifelong management that affects a large number of children and adolescents globally. While diabetes care has improved over the years, low-middle income countries, such as Indonesia, still struggle to achieve optimal diabetes care due to limited access to healthcare professionals, insulin, diabetes technologies, and self-monitoring blood glucose (SMBG) devices. Data from the Indonesian Pediatric Society registry has reflected a stark increase in the number of children with T1DM, with the current prevalence significantly concentrated on Java island and a noticeable underreporting in rural regions. Another major challenge is the uneven distribution of pediatric endocrinologists, resulting in a low specialist-to-patient ratio. This imbalance, coupled with inadequate access to comprehensive diabetes care, complicates effective T1DM management. While the national insurance covers a portion of costs associated with T1DM care, vital aspects of T1DM management including SMBG devices are still not covered, resulting in significant financial burden to families. Access to diabetes technologies that improve glycemic control and quality of life of patients is also still largely limited. This paper evaluates the current state and future needs for insulin and SMBG in Indonesia, emphasizing the necessity of strategic interventions to improve access and quality of diabetes care.

Keywords: Pediatric, type 1 diabetes, challenges, practice

Introduction

Widely regarded as one of the most common non-communicable diseases (NCDs) in children, type 1 diabetes mellitus (T1DM) is a chronic condition that requires comprehensive and lifelong management. Insulin and self-monitoring of blood glucose are integral components of successful T1DM management. While access and availability of diabetes technologies, insulin, and self-monitoring blood glucose (SMBG) devices may be good in most high-income countries, low and middle-income countries, such as Indonesia, still struggle to provide attainable access to optimum diabetes care (1,2,3). As Indonesia works towards achieving Sustainable Development Goals target 3.4, which is to reduce premature mortality associated with NCDs, concerted efforts must be made to ensure the availability of insulin and other diabetes technologies. This paper evaluates the current situation and prospective needs for insulin and SMBG technology in Indonesia.

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Epidemiology of T1DM in Indonesia

According to Changing Diabetes in Children (CDiC) Indonesia database in January 2024, there were 1210 children and adolescents, aged 0-25 years, who have been diagnosed with T1DM (4). Based on the CDiC Indonesia registry, the highest population of T1DM in Indonesia is found on the island of Java, especially in Jakarta, and it is more prevalent in girls. However, this is probably attributable to low reporting and case finding in rural areas outside of Java Island. The population of T1DM in Indonesia up to January 2024 is shown in Figure 1. Based on the CDiC registry, the age-based population of T1DM is mainly between 11 and 15 years old (Figure 2). The data reported in this study is lower than that of most countries. This may be because the prevalence reported is hospital-based, whereby these are patients that are reported by each individual pediatric endocrinologist who manages them. Therefore, the number of children and adolescents living with T1DM is believed to be underreported.

Pediatric Endocrinologist in Indonesia

The Indonesian Pediatric Society (IPS) database shows that in 2024, there were 39 pediatric endocrinologists whose practices were located in 18 provinces (out of 38 provinces in Indonesia), reflecting the uneven distribution of pediatric endocrinologists in Indonesia (5). Figure 3 depicts the distribution of pediatric endocrinologists in Indonesia. Population data from 2023 shows that there are 84,198,626 children in Indonesia, while only 1,210 children and adolescents aged 0-25 years had been diagnosed with T1DM (6,7). This means that the ratio pediatric endocrinologists to children with T1DM is 1:134 and is 1:2,000,000 pediatric endocrinologists for the child population, indicating the low ratio of pediatric endocrinologists to the general Indonesian pediatric population. In Ethiopia, a low income country, the ratio is one pediatric endocrinologist for every 40,000,000 children (8). Along with the increase in the prevalence of children diagnosed with T1DM in Indonesia, this will increase demand for pediatric endocrine care and there is a clear need for more pediatric endocrinologists.

In Indonesia, T1DM patients are mainly under pediatric endocrinologist care. While in other countries, T1DM may be managed by a comprehensive team, including specialist diabetes nurses and dieticians. Low-middle income countries (LMICs) tend to approach T1DM care centered around pediatric endocrinologists, while high income countries (HICs) have dedicated interprofessional teams for T1DM care. In Pulungan et al. (1), data from 25 countries showed that only 24% of respondents reported that pediatricians were the chief healthcare professionals (HCPs) responsible for T1DM care. This study also described

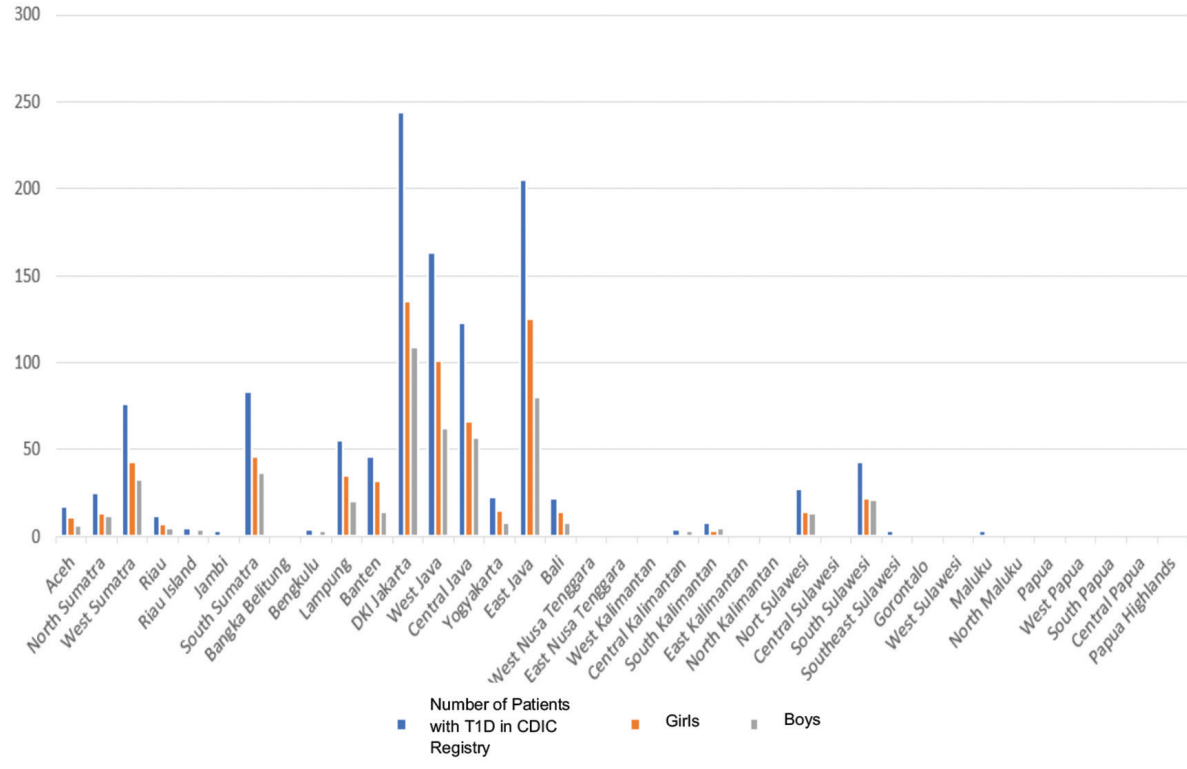

Figure 1. Distribution of type 1 diabetes mellitus in Indonesia up to January 2024

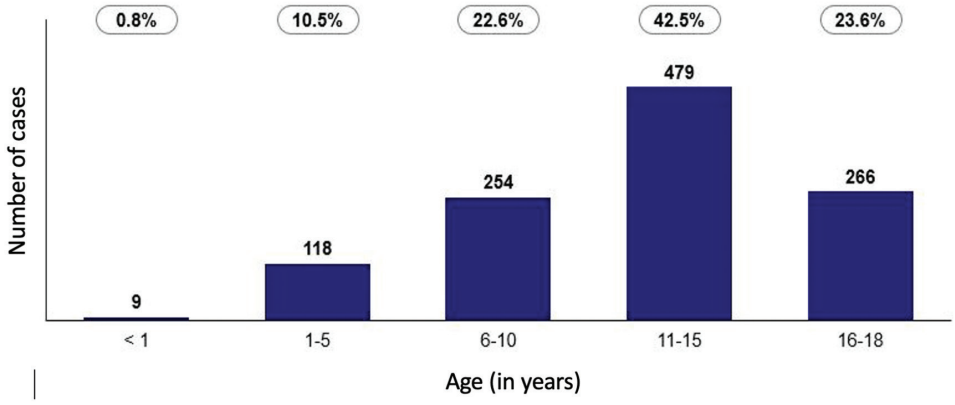

Figure 2. Distribution of type 1 diabetes mellitus in 1,126 young patients based on age as of January 2024

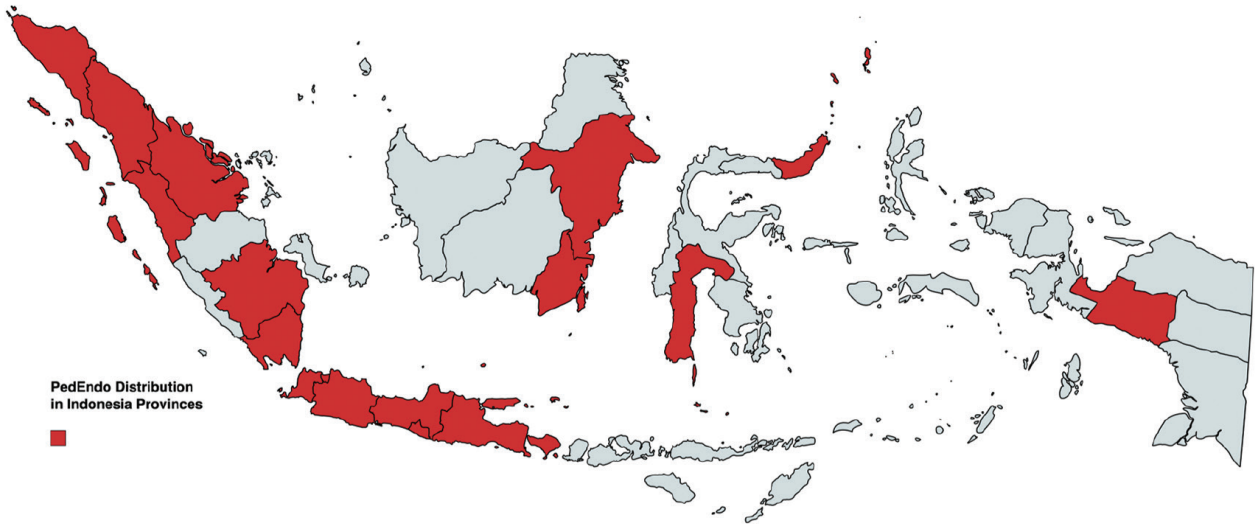

Figure 3. Distribution of pediatric endocrinologists in Indonesia

the need for a comprehensive team providing medical care for T1DM, which was mentioned by 36% of respondents (1). A persistent issue in LMIC is the insufficient number and uneven distribution of qualified HCPs. The absence of adequate technical guidance, training initiatives, and financial support for these programs exacerbates this challenge (9).

Pediatric endocrinologists often advocate for their patients, particularly in environments lacking universal healthcare coverage. The Think Tank Group outlined a 7-step cascade to assist these professionals in their advocacy role. The cascade begins with identifying the target population and progresses through ensuring service contact coverage, assessing input-adjusted coverage, intervention coverage, and quality-adjusted coverage. It further evaluates user adherence and outcome-adjusted coverage to ensure optimal care and desired health outcomes. This framework provides a structured approach for pediatric endocrinologists to optimize support for patients and families dealing with T1DM, and it can be adapted to various patient groups (10).

Insulin Supply in Indonesia and its Importance

Since its discovery in 1921, insulin has been the core life-saving treatment for T1DM. It is the cornerstone of optimal blood sugar control in countries with limited resources (11). Approaching normoglycemia is the goal of T1DM therapy, and this may only be achieved by using insulin in the majority of pediatric patients diagnosed with diabetes. Clinical use of insulin is remarkably complex, and optimal glycemic control can be challenging to achieve and maintain. There is rarely a treatment regimen that is applicable to all people because of the dynamic nature of growth, development, and hormonal changes during childhood and adolescence (12).

Insulin therapy plays a crucial role in the management of T1DM. A solid understanding of current insulin therapy methods is essential for effective management. Studies conducted by Sow et al. (11) have highlighted several shortcomings, including a low level of knowledge regarding insulin therapy. Sow et al. (11) recommended enhancing and monitoring T1DM management training for healthcare providers across various sectors.Children and adolescents with T1DM require multiple insulin injections every single day and often use a combination of fast-acting, short-acting, medium-acting, or long-acting insulin to achieve optimal blood sugar control. New insulin analogs and diabetes technology tools have transformed insulin treatment during the past few decades. Insulin pens have become a popular insulin delivery modality in young people with diabetes due to their ease of use and increased dosing accuracy compared to insulin delivery. In some countries, there are insulin pens connected with smart phone applications and continuous glucose monitoring (CGM) devices, allowing pen users access to benefits such as data collection, alerts and reminders, and dosing calculators that take insulin on board into account (13).According to the PrimaKu and CDiC database in January 2024, children and adolescents with T1DM use three groups of insulin: basal, bolus, and premix (14). The types of basal insulin used by patients are Levemir®, Lantus®, Ezelin®, and Sansulin®. The types of insulin bolus used in Indonesia are Apidra®, Novorapid®, Humalog®, and Lispro®. Premix insulin used in Indonesia is Humalog mix 25®, Humalog mix 50®, and Novomix®.

Based on the CDiC Indonesia registry, more than 50% of the 1,210 patients used Novorapid® in their daily blood sugar management (14). Novorapid® is commonly used in blood sugar management settings, often combined with basal and premix insulin therapies. The most frequently used insulin combination is the basal bolus combination.

The daily insulin dose for patients with T1DM is empirically recommended to be between 0.7 and 1.2 units per kilogram of body weight per day (12). The estimated national insulin requirement for children with T1DM is calculated based on the average daily dose and the average body weight of registered patients, who average 12.3 years old. Therefore, age limits of 12 and 13 years are utilized. The lower limit corresponds to the two-digit P50 rounding of the weight curve for 12-years-old boys, which is 35 kg (rounded up from 34.81 kg). The upper limit is based on the two-digit P50 rounding of the weight curve for 13-year-old girls, resulting in 40 kg (rounded up from 39.51 kg). The national growth curve used for this calculation is the Indonesian National Synthetic Growth Chart developed by Pulungan et al. (15) in 2018.

The calculation of the national insulin adequacy requirement involves estimating twice the number of patients currently registered in the IPS Endocrinology Working Group-CDiC Indonesia joint registry, which is almost 20% of the number reported by the International Diabetes Federation in 2022 (16). Calculation of the national insulin requirement can be seen in Table 1. Most patients use a basal bolus regimen with proportion 50:50. This proportion varies from what is generally used in other countries as children in Indonesia tend not to inject insulin whilst at school. Therefore, most pediatric endocrinologists opt to increase the basal insulin dose to compensate for not injecting during school hours. This highlights an existing need for greater support from schools as well. Insulin availability is generally in pen and cartridge form with a strength of 1 mL containing 100 insulin

Table 1. Calculation of national insulin needs

Body weight (kg)	Individual daily dose (unit/KgBW)		Number of patients	Monthly needs		Yearly needs	
	0.7	1.2		Minimal (unit)	Maximal (unit)	Minimal (unit)	Maximal (unit)
35	24.5	42	2204	1,766,940	3,029,040	21,203,280	36,348,480
40	28	48		2,019,360	3,461,760	24,232,320	41,541,120

Kg: kilograms, KgBW: kilogram body weight

Table 2. Forecast of national T1DM insulin cartridge requirement

Insulin	Monthly needs (cartridge)		Yearly needs (cartridge)	
	Minimal	Maximal	Minimal	Maximal
Basal	2,944.9	5,769.6	35,338.8	69,235.2
Bolus	2,944.9	5,769.6	35,338.8	69,235.2
Total	**5,889.8**	**11,539.2**	**70,677.6**	**138,470.4**

T1DM: type 1 diabetes mellitus

units, 300 units per-cartridge. Based on Table 1 with minimal and maximal insulin dose, calculation of the national insulin requirement for children and adolescents with T1DM in cartridges can be simplified, as shown in Table 2.

Insulin is a critical part of T1DM care. First introduced in 1962, insulin pumps have been largely instrumental in improving glycemic control in pediatric T1DM patients, with early studies demonstrating a clear benefit towards improving glycemic control with less fluctuations in glucose levels and lower incidence of hypoglycemia (17). As technology rapidly progresses, new hybrid closed loop system integrate CGM systems with an insulin pump and offer automated insulin delivery in response to blood glucose trends. Studies conducted in HICs have shown increased time-in-range, improved hemoglobin A1c (HbA1c) levels and a decrease in hypoglycemic events. Currently, insulin pumps are only available to a handful of those capable of paying personally or have access to private insurance that provides coverage. They are not provided by most insurance providers including the national health insurance. Our data estimates that insulin pumps are used by less than 2% of T1DM pediatric patients in Indonesia.

SMBG in Indonesia

Routine SMBG helps patients to adjust their insulin dose with food intake. Therefore, it also enables patients to correct their blood glucose when it is out of the target range when not associated with meals. Well-controlled SMBG further contributes to improved HbA1c levels. SMBG is also important for patients with T1DM when performing sports to adjust insulin dose before, during, and after physical activity to avoid the risk of hypoglycemia. Monitoring SMBG when patients are sick is also crucial (18).

The frequency of SMBG varies according to individuals and the availability of testing devices and strips. It also depends on patients' and caregivers' ability to recognize early signs of T1DM emergencies and conduct a blood glucose check. To optimize glycemic control, SMBG is recommended to be performed 6-10 times a day (19). There is no study from Indonesia that compiles the mean HbA1c levels for children nationally and data are limited to each center. As in Jakarta, the average HbA1c level is around 12.5%, whereas in Surabaya, the average HbA1c level is 10.7% (20).In Indonesia, finger stick blood glucose monitoring is the most widely used method to check patients' glucose levels periodically. Similar to the global data, this method is widely used in most countries, while CGM is only available in around a third of respondent countries (1). Data has shown that CGM is superior to the finger stick method for several reasons: 1) CGM is associated with lower HbA1c; and 2) the finger stick method requires patients' compliance and awareness (21,22). CDiC data indicated that 53% of registered patients regularly check their SMBG, with half of them infrequently checking their SMBG. Studies have shown that CGM is cost-effective in decreasing short-term and long-term complications and yields lower HbA1c levels compared to finger stick testing (21,22,23). Unfortunately, SMBG devices and glucometer strips are again not covered by the national health insurance, therefore making this a challenge for Indonesian children with T1DM.

CGM systems are more flexible than conventional finger-prick glucose tests and are especially beneficial for patients on intensive insulin therapy, reducing discomfort and allowing for easier glucose monitoring. Despite being registered in the Food and Drug Supervisory Agency, the use of CGM has not been widely established in Indonesia as payment has to be made personally, either by private insurance or out of pocket. It is not covered in the national insurance scheme, which the majority of T1DM patients in Indonesia rely on. While there are some private and company insurances that cover CGM, it is important to note that access to such insurance may be limited to those who can afford private insurance. Current efforts to improve diabetes care in Indonesia have yet to achieve an improvement in general access to diabetes technologies, as efforts are currently being directed towards the training of HCPs and expansion of access and availability to basic diabetes care, such as insulins and conventional SMBG technologies such as test strips and readers.

Current Situation and Challenges in Indonesia

"Children are not little adults" is a view stressed by the American Diabetes Association in their 2018 position statement on Type 1 Diabetes in Children and Adolescents (24). With its distinctive pathophysiology, epidemiology, psychosocial challenges, and developmental considerations, diabetes in children is very different from diabetes in adults (25). The pediatric and adolescent period comprise years of rapid growth and formative development. Coupled with the challenges that naturally occur during those years, children and adolescents living with T1DM have the added challenge of accommodating T1DM as part of their day-to-day lives (24). This includes regular insulin injections, blood glucose monitoring, nutritional planning, physical activity and concerns about high/low blood glucose (26). The importance of good T1DM management cannot be overstated, with its direct association with glycemic control, improvement in quality of life and protection from long-term diabetes-associated complications (27).To achieve optimal T1DM management, patients and families must be supported with

adequate means to attain access to treatment, including various forms of insulin, SMBG devices and monitoring examinations, comprehensive education and psychosocial support. Introduced in 2014, the main health insurance scheme available to Indonesian citizens is Jaminan Kesehatan Nasional (JKN) (28). Under this scheme, T1DM patients are able to access a monthly supply of basal and prandial insulin, based on the indicated doses, 90 pieces of needle and alcohol swab, as well as an HbA1c examination every three months. Insulin is available in all hospitals but not primary health centers. Therefore, most patients diagnosed with T1DM are able to access this basic care if they are enrolled in the national health insurance. However, SMBG devices, such as glucometers and glucose strips are not covered by the national insurance. Examination of diabetes-related autoantibodies are not routinely conducted in Indonesia, either in academic medical institutes or private practice. These tests are only available in a limited selection of centers. However, in 2024, pediatric endocrinologists were advocating for the examination of diabetes-related antibodies. These diagnostic tests for autoantibodies are equivalent with examinations, such as C-peptide. However, insulin autoantibodies are not routinely conducted but are available if paid out-of-pocket in several major health centers. Essential treatment in T1DM emergency, such as glucagon, is currently not under the coverage of JKN. Devices like insulin pumps and CGM are known to improve diabetes management. However, access and availability to such devices in Indonesia still needs to be improved, even in academic medical institutes, because even in these centers most patients rely on the national insurance.

The cost of SMBG devices in Indonesia range from Rp 300,000 to Rp 600,000 (19.21-38.40 USD), with a pack of 25 glucose strips ranging from Rp 60,000 to Rp 120,000 (3.84-7.68 USD). With a minimum requirement of four glucose tests a day and a recommended number of six tests per day, this totals up to Rp. 600,000 (38.40 USD) per month if families were forced to pay out of pocket. In a country where the monthly average household income is Rp. 3,178,227 (203.52 USD) in 2023, this places significant additional financial burden on patients and families (29). While insulin is generally covered by the national health insurance, there are still patients who have to pay out-of-pocket for insulin. It is not uncommon for patients to purchase insulin out-of-pocket as they found that the supply covered by the national health insurance is insufficient or with the intention of reducing the need for monthly visits, and thus the associated transportation costs and inconvenience associated with hospital visits, such as days off from work/school and having other children to take care of. When access to insulin and SMBG devices are threatened, so is overall management and glycemic control. Patients are also at higher risk of experiencing life-threatening complications (30,31).

One of the efforts to alleviate the challenges of equity of T1DM care is CDiC Indonesia. CDiC Indonesia is a public-private partnership focused on improving access to T1DM care (31). One of the programs includes providing blood glucose strips to patients registered in the program. T1DM patients between the age of 0 to 25 years old are eligible to receive four glucose strips a day and monthly supplies of glucose strips are delivered to patients' homes.

Another prominent multisectoral partnership is between the existing national health mobile application and information systems, namely PrimaKu and SatuSehat. PrimaKu is an application developed in collaboration with the Ministry of Health, the IPS, and the National Population and Family Planning Board. PrimaKu is a mobile application used by parents across Indonesia to monitor their children's growth and development (32). In 2023, PrimaKu was updated to include a Diabetes Diary feature, allowing T1DM patients to either connect their glucometers to PrimaKu for automatic syncing or manually input their SMBG results, which sync directly with a glucometer. The Diabetes Diary is not limited for use by only pediatric T1DM patients. As of November 2024, there are 1,408 people registered to use the diabetes diary.As part of an effort to integrate health information systems and to improve efficiency, PrimaKu has since launched a collaboration with SatuSehat. SatuSehat is a national initiative by the Ministry of Health that integrates patient medical record data at health facilities into one Indonesia Health Services (33). While Indonesia has seen substantial growth towards digitalization, not all patients are able to benefit from this, as there are still patients with limited access to mobile devices and the internet. For these patients, SMBG is recorded manually using pen and paper.

To reiterate, it is highly likely that the prevalence of T1DM reported in this study only reflects the tip of the iceberg. National databases are based on hospital-based data reported to CDiC or the Endocrinology Working Group of the IPS. With the false perception that the prevalence of T1DM in Indonesia is low, this contributes to the poor understanding and awareness of the general public, as well as health care professionals in Indonesia. In turn, the lack of awareness and knowledge of health care professionals also leads to cases being underdiagnosed and misdiagnosed. However, in recent years, through advocacy and public campaigns conducted by organizations like CDiC and the Endocrinology Working Group of the IPS, this has started to change. One campaign has been to initiate a national training programme in collaboration with the Ministry of

Health, to train HCPs on how to diagnose and manage diabetes in both children and adults.While several major government hospitals are working towards establishing diabetes clinics, these are still widely unavailable in Indonesia. International recommendations have highlighted the importance of a multidisciplinary diabetes team consisting of a pediatric endocrinologist, dietitian, a diabetes nurse educator and a mental health professional (34). Multidisciplinary care is hampered as Indonesia lacks the number and quality of training of HCPs (35,36). While several major hospitals may conduct in house training, training of HCPs in Indonesia is largely supported by organizations like CDiC Indonesia. CDiC Indonesia routinely conducts basic and advanced training regarding the diagnosis and management of T1DM in children and adolescents free-of-charge and open to HCPs nationally. As access to a multidisciplinary team in Indonesia is still limited, a lot of the burden of diabetes education is placed on pediatric endocrinologists, pediatricians or residents working in the endocrinology clinic of government teaching hospitals. The limited number of HCPs supporting the clinical management of children with T1DM will translate to less guidance provided to patients and their families, including support for insulin dose adjustments or management of acute conditions. This contrasts with the care available in the majority of HICs, such as the provision of 24-hour emergency call centers, a help center that answers queries and provides suggestions via email or telephone, as well as a diabetes clinic systems that link CGM data to diabetes clinics, enabling remote monitoring by the diabetes team (36).

Conclusion

The landscape of T1DM management in Indonesia reveals a multifaceted challenge requiring comprehensive strategies to address. Despite the concerted efforts of organizations like CDiC Indonesia and advances in insulin therapy and diabetes technology, significant gaps persist in access to care and resources. The epidemiological data underscores the growing burden of T1DM among children and adolescents, with many new cases probably being missed entirely, magnified by the uneven distribution of pediatric endocrinologists and limited access to insulin and SMBG devices. The current reliance on pediatric endocrinologists for T1DM care underscores the need for a more comprehensive, multidisciplinary approach to management, as seen in high-income countries. Furthermore, while the national health insurance provides some coverage for insulin, essential SMBG devices remain largely uncovered, posing major financial burdens on many families or threatening poorer overall glycemic control. Addressing these challenges necessitates not only improvements in healthcare infrastructure and access but also comprehensive education and support for patients and families. Collaboration between public and private sectors, along with expanded training programs for HCPs, will be pivotal in enhancing T1DM management and improving outcomes for affected individuals in Indonesia.

Ethics

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Footnotes

Authorship Contributions

Concept: Muhammad Faizi, Aman B. Pulungan, Design: Muhammad Faizi, Aman B. Pulungan, Data Collection or Processing: Muhammad Faizi, Ghaisani Fadiana, Dhiya Nadira, Angela Angela, Helena Arnetta Puteri, Aman B. Pulungan, Analysis or Interpretation: Muhammad Faizi, Ghaisani Fadiana, Dhiya Nadira, Angela Angela, Helena Arnetta Puteri, Aman B. Pulungan, Literature Search: Muhammad Faizi, Ghaisani Fadiana, Dhiya Nadira, Angela Angela, Helena Arnetta Puteri, Aman B. Pulungan, Writing: Muhammad Faizi, Ghaisani Fadiana, Dhiya Nadira, Angela Angela, Helena Arnetta Puteri, Aman B. Pulungan.

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ORIGINAL ARTICLE

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Attitudes Towards the Management of Congenital Hypothyroidism in Türkiye: National Survey Study

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What is already known on this topic?

In 2021, an international consensus guideline on congenital hypothyroidism was published by the European Society for Pediatric Endocrinology and the European Society for Endocrinology. The consensus guideline provides strong evidence-based recommendations for diagnosis and treatment. However, in cases with insufficient evidence, it asserts weak recommendations based on expert opinion. For this reason, there may be differences in attitude among physicians.

What this study adds?

Physicians working in Türkiye sometimes express attitudes toward the management of congenital hypothyroidism that differ from the European guidelines. Both working conditions and professional experience also affect these attitudes. Approaches may even vary between countries, depending on differences in local conditions. The data obtained from this survey may form the basis for a national consensus that could serve as a model for Türkiye and countries with similar socio-economic composition.

Abstract

Objective: This study was conducted to assess the perspectives of pediatric endocrinologists in Türkiye about the management of congenital hypothyroidism (CH) and to analyze the potential impact of work environment and professional experience on different attitudes.

Methods: The members of the Turkish Society for Pediatric Endocrinology and Diabetes were invited to participate in an online survey. An evaluation was made after obtaining survey responses from 95 (19%) of 502 members.

Results: Participants' mean age was 42.0 ± 9.6 years, 46.3% of them were working in a university hospital, and 48.6% had > 7 years of work experience. When the participants were asked about their approach to a 1-3-week-old neonate whose serum thyroid stimulating hormone (TSH) concentration was 6-20 mU/L with a serum-free thyroxine (FT4) concentration within the age-specific reference interval,

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97.7% of the participants preferred to monitor without medication. Only 24% of physicians consider starting treatment immediately if the serum TSH concentration is 20-40 mU/L with a normal FT4 level. While 5.3% of participants preferred dual imaging (ultrasound and scintigraphy), 90.5% requested only thyroid ultrasound for etiological investigation. When considering the discontinuation of levothyroxine (LT4) in patients with a normal thyroid gland and a low LT4 dose, 28.4% of the participants stated that treatment should be stopped at the earliest at the age of 3 years, 16.8% at 2 years, 5.3% at 1 year, 16.8% at 6 months, and 32.6% at any time if the TSH levels remain low despite the low dosage. Physicians with over 7 years of experience may discontinue medication if TSH is low, even with a lower dose, more frequently than those with less experience ($p = 0.011$). There were no significant differences in the approach of the physicians between employees at university hospitals and other health institutions.

Conclusion: Although the attitudes of pediatric endocrinologists working in Türkiye towards the management of CH are generally consistent with the recommendations of international guidelines, their approaches to the treatment for isolated neonatal TSH elevation, thyroid imaging preferences and time to discontinue treatment differ significantly. These different attitudes, which are similar between all subgroups by experience and work setting, reflect the differences in local conditions in Türkiye and underline the need for a national consensus on the management of CH.

Keywords: Congenital hypothyroidism, attitude in management, pediatric endocrinology, questionnaire, Turkish Society for Pediatric Endocrinology and Diabetes

Introduction

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth (1). Newborn screening programs (NSP) enabled early diagnosis before the onset of clinical symptoms, based on biochemical measurement of thyroid stimulating hormone (TSH) and thyroxine (T4). Since CH is one of the most common preventable causes of intellectual disability worldwide but treatment largely mitigates this, prompt diagnosis and treatment are vital to optimize long-term outcomes (2). In 2021, an international consensus guideline on CH was published by the European Society for Pediatric Endocrinology and the European Society for Endocrinology, to update the practice guidelines for the diagnosis and management of CH (3). The consensus guideline provided strong evidence-based recommendations for diagnosis and treatment. However, in situations with insufficient evidence, it makes weak recommendations based on expert opinion. For this reason, there may be differences in attitudes among physicians. In addition, alternative approaches may be needed in countries such as Türkiye, where transient neonatal hyperthyrotropinemia (NHT) and hypothyroidism are more common due to perinatal iodine deficiency or overload (4,5,6,7).

The aim of this national study was to determine the attitudes of pediatric endocrinologists in Türkiye regarding the management of CH and to examine the effects of work environment and professional experience on differences in attitudes. To the best of our knowledge, this is the first study to investigate Turkish physicians' attitudes toward CH management. We believe that the results obtained from this study may contribute to the development of a national consensus on the management of CH.

Methods

The survey was devised by six members of the Thyroid Working Group of the Turkish Society for Pediatric Endocrinology and Diabetes (TSPED). It was created in Google Forms based on the updated consensus guideline recommendations. The survey link, consisting of 24 questions, was sent to 502 members of TSPED via e-mail. While the initial four questions inquired about personal data, the subsequent questions assessed the practices of pediatric endocrinologists in diagnosing, treating, and monitoring CH. The entire survey is available as an online supplement (Supplementary File 1).

The study protocol was approved by the Local Ethics Committee of the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital, Health Application and Research Center (approval no: 4459, date: 09/07/2024).

Statistical Analysis

Descriptive statistics of the data included mean, standard deviation, median and range, frequency, and rate values. The chi-square test was used to compare qualitative independent data between subgroups based on professional experience (less than or more than 7 years of work experience) or place of work (university hospital or other). When test conditions were not met, the Fisher's exact test was used. Statistical analyses were performed using the SPSS, version 28.0 (IBM Inc., Armonk, NY, USA).

Results

Out of the 502 members questioned, 95 (19%) submitted valid surveys. Participants' characteristics are shown in Table 1.

Table 2 shows the responses regarding treatment approaches for newborns with elevated TSH and normal serum free T4 (FT4) levels. When the participants were asked about their approach to a 1-3 week-old neonate whose serum TSH concentration is 6-20 mU/L with FT4 concentration within the age-specific reference interval, most of the participants (94.7%) preferred monitoring without medication and retesting 1 to 2 weeks later to re-evaluate the need for treatment. When the serum TSH concentration is between 20-40 mU/L, only 24% of physicians consider starting treatment immediately. In addition, 42% reported that they decided on treatment according to the FT4 level, while the remaining 28% stated that they followed these babies without any intervention. In the survey, when asked about the approach to a baby with TSH between 6-20 mU/L for 3-4 weeks, the responses regarding treatment and monitoring were similar, but the frequency of decisions based on thyroid imaging increased significantly from around 2% to more than 20% (Table 2).

When asked about their approach to initiating levothyroxine (LT4) dose, 18% of physicians preferred to start treatment with 10-15 µg/kg per day for each case, while 25% favored starting treatment with 5-15 µg/kg per day based on FT4 level. In addition, 57% preferred starting treatment with 5-15 µg/kg based on FT4 level and etiology. While 52.6% of physicians always prefer branded LT4, 47.4% do not care whether it is brand or generic. When asked about the approach to LT4-liothyronine (LT3) combination therapy, 20% of the participants reported that they never used it; 80% reported that they could use it in cases with persistent TSH elevation. A 10% subgroup stated that LT4-LT3 treatment could also be used in cases of thyroid agenesis. When evaluating treatment response, 57% of the participants stated that the appropriate sample collection time for FT4 measurement was before taking LT4, while for 43% of the participants, at least 4 hours after taking LT4 was sufficient.

Attitudes towards determining the etiology of CH and possible associated problems are given in Table 3. In the etiological investigation of CH, 90.5% (n = 86) of the participants preferred thyroid ultrasound (US) alone, 5.3% (n = 5) preferred dual imaging (the combination of US and

Table 1. Characteristics of participants

Age and experience	Mean ± SD	Median (range)
Age (years)	42.0 ± 9.6	40 (30-74)
Experience in pediatric endocrinology (years)	8.7 ± 9.5	4.6 (0.2-40)
Place of work and title	n	%
University Hospital	44	46.3
Ministry of Health Training and Research Hospital	31	32.6
State Hospital	11	11.6
Private/Foundation University Hospital	5	5.3
Others	4	4.4
Fellow	27	28.4
Consultant	36	37.9
Assistant professor	6	6.3
Associated professor	7	7.4
Professor	19	20.0

SD: standard deviation

Table 2. Treatment approaches in newborns with elevated TSH and normal FT4 levels

Responses	TSH 6-20 mU/L		TSH 20-40 mU/L
	1-3 weeks old	3-4 weeks old	1-3 weeks old
Starting treatment immediately (%)	-	23.2	24.2
n		22	23
Monitoring without treatment (%)	94.7	24.2	28.4
n	90	23	27
Decision based on FT4 level (%)	3.2	26.3	42.1
n	3	25	39
Decision based on thyroid imaging (%)	2.1	22.1	1.1
n	2	21	1
Various individual approaches (%)*	-	4.2	4.2
n		4	4

*Other approaches include decisions based on TSH trend, a different TSH threshold or clinical findings.
TSH: thyroid stimulating hormone, FT4: free thyroxine

scintigraphy), while 4.2% (n = 4) stated that they did not want routine imaging. No one requested scintigraphy alone for thyroid imaging. When the radioactive element used in scintigraphy was investigated, technetium-99m and iodine-123 were reported as 45% and 18%, respectively. However, 37% of physicians were not aware of which isotope was used. Lack of knowledge about the substance used in scintigraphy was higher in those with less than 7 years of experience (51.7%) than in those with more experience (14.3%) ($p < 0.05$). This was one of the rare differences between the two subgroups (Figure 1). The most frequently requested tests (always/often) for the etiological evaluation of CH after thyroid US (96%) were thyroglobulin (71%), thyroid antibodies (42%), and urinary iodine levels (33%). In addition, 42% of physicians occasionally want to take knee X-rays to evaluate possible developmental effects of CH, while 58% never request it (Table 3). Only 4.2% of physicians request both echocardiography (ECHO) and abdominal US for all cases of CH, while 60-63% prefer these imaging studies only in the presence of dysmorphic findings on physical examination. Moreover, 22-29% of physicians state that abdominal US and ECHO are needed only in cases with thyroid dysgenesis (Table 3).

While 55% of the participants want genetic testing for patients with CH, 45% do not. Participants most commonly request genetic tests for patients with common accompanying anomalies or syndromic features (42%), those confirmed to have permanent CH (23.2%), and those found to have persistently high TSH (21%).

Fifty-three percent of physicians believe that the screening program should also cover central hypothyroidism cases, while 38% are undecided. The question "In which patient group would you consider a post-screening strategy?" was mostly answered as in premature babies (91%) by participants. Other respondents suggested, in order of frequency, sick babies (87.4%), infants with clinical suspicion of hypothyroidism (76.8%), low birthweight infants (72.6%), Down syndrome (48.4%), babies with congenital anomalies (40%) and twins (37.9%).

When asked about physicians' approach to the timing of trial off therapy in patients with a normal thyroid gland and a low LT4 dose (< 3 µg/kg/day), 28.4% of the participants stated that treatment should be stopped at the earliest at the age of 3 years, 16.8% at 2 years, 5.3% at 1 year, 16.8% at 6 months, and 32.6% at any time if the TSH levels remain low despite the low dosage. Physicians with over 7 years of

Table 3. Attitudes toward determining the etiology of CH and possible associated problems

Requested test	Responses (n = 95)			
	Never	Rarely	Often	Always
Thyroid ultrasound (n)	0	3	22	70
%		3.1	23.2	73.7
Thyroid scintigraphy (n)	24	62	6	3
%	25.2	65.3	6.3	3.2
Urinary iodine level (n)	28	36	19	12
%	29.4	37.9	20	12.7
Mother's urine iodine (n)	45	42	6	2
%	47.4	44.2	6.3	2.1
Breast milk iodine (n)	84	11	0	0
%	88.4	11.6		
Urinary iodine/creatinine (n)	58	28	6	3
%	61	29.5	6.3	3.2
Thyroglobulin (n)	1	27	36	31
%	1	28.4	37.9	32.6
Thyroid autoantibodies (n)	18	37	21	19
%	19	39	22	20
Genetic tests (n)	16	70	9	0
%	16.8	73.7	9.5	
Knee X-ray (n)	55	34	5	1
%	57.9	35.8	5.3	1
Echocardiography (n)	6	57*	28§	4
%	6.3	60	29.5	4.2
Abdominal ultrasound (n)	10	60*	21§	4
%	10.5	63.2	22.1	4.2

These imaging studies are only requested if there are dysmorphic findings on physical examination* or in cases of thyroid dysgenesis§.
CH: congenital hypothyroidism

experience were more likely to discontinue medication if the TSH was low, even with a lower LT4 dose, more frequently than those with less experience ($p < 0.05$) (Figure 2). No significant difference was found when comparing other survey responses between groups with experience of ≤7 years and > 7 years. Moreover, no significant difference was found between the survey responses of participants working in university hospitals and other healthcare institutions.

Discussion

The field of CH currently has a wealth of excellent guidelines and expert opinions. While these guidelines encompass various aspects of CH, clinicians may face challenges in evaluating the quality of evidence for specific situations related to CH (8). Thus, physicians may have different attitudes toward the management of CH. Working conditions and professional experience will affect these attitudes. Approaches may even vary between countries, depending on differences in local conditions. Therefore, there is a need to establish a national consensus for a common approach to CH in many countries, including Türkiye. The data obtained from this survey may stimulate the creation of such a consensus that could serve for Türkiye and as a model for similar countries.

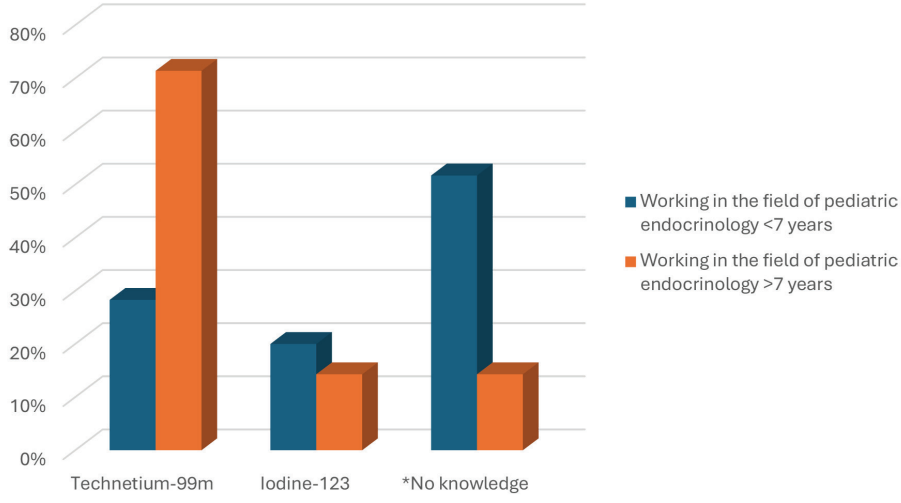

Figure 1. Knowledge of the substance used during thyroid scintigraphy at the institution

**Lack of knowledge about the substance used in scintigraphy was higher in those with less than 7 years of experience than in those with more experience ($p < 0.05$)*

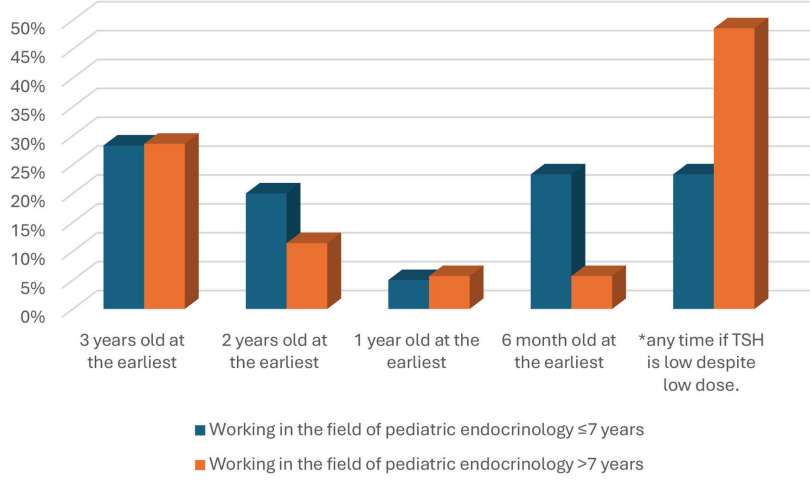

Figure 2. Approaches to the timing of drug withdrawal in patients with eutopic thyroid and receiving low-dose therapy

**Physicians with over 7 years of experience were more likely to discontinue medication if TSH was low, even with a lower LT4 dose, more frequently than those with less experience ($p < 0.05$)*

TSH: thyroid stimulating hormone, LT4: levothyroxine

Current consensus guidelines recommend starting treatment if venous TSH is above 20 mU/L even if the FT4 level is normal (3,9,10). This is an arbitrary threshold for treatment decisions and is based on expert opinion due to the lack of sufficient evidence. Despite the consensus recommendation, when the survey questions asked about TSH elevations of 20-40 mU/L in the first 3 weeks of life, only 24% of responding physicians stated that they would immediately start treatment in this case. In addition, 42% of the participants reported that they would take into account the FT4 level (in the lower or upper half of the reference range) for the treatment decision, and 28% would prefer follow-up without treatment. These responses indicate that most pediatric endocrinologists in Türkiye would not start treatment when serum TSH elevation is at a moderate level (20-40 mU/L). Likewise, if serum TSH is mildly elevated (6-20 mU/L), almost no one starts treatment.

The definition and management of NHT is unclear (11,12,13). NHT may be defined as an increase in serum TSH concentrations between 6 and 20 mU/L with normal FT4 concentrations in newborns (3,10,13). This description overlaps with the definition of subclinical (compensated) hypothyroidism (SCH) in childhood (14,15). The term SCH implies that elevated TSH secretion occurs to compensate for insufficient hormone production due to an impairment in the hypothalamic-pituitary-thyroid (HPT) axis and that this condition must be treated. However, TSH elevation can occur outside the HPT feedback loop, for example in response to stress, such as the neonatal TSH surge after birth. This increased TSH concentration at birth usually returns to normal within 24-48 hours. However, in some newborns, recovery from elevated TSH concentrations may take longer, possibly due to delayed HPT axis maturation (16). This transient NHT state, usually accompanied by high FT4 levels, does not require treatment. Indeed, transient NHT are most commonly caused by maternal iodine deficiency and/or perinatal iodine exposure (13). Of course, iodine deficiency or excess increases TSH secretion by impairing T4 production, but it is usually a temporary condition that resolves itself within a few days or weeks. LT4 treatment is not necessary unless the serum FT4 levels fall below normal limits, indicating true hypothyroidism. In Türkiye, mild iodine deficiency is still an ongoing problem in pregnant women and nursing mothers (4,5,17,18,19,20,21,22,23). Perinatal iodine exposure is also common due to the use of iodine-containing antiseptics during delivery (5). In addition, the use of a TSH cutoff as low as 5.5 mU/L whole blood in the national NSP has led to more frequent detection of false positives and transient NHT cases (7). Therefore, pediatric endocrinologists working in Türkiye are familiar with iodine problems in their environments and frequently encounter cases of iodine-related transient NHT. It seems that this experience of physicians is reflected in the high rate of "follow-up without treatment" responses in the survey. These responses also suggest that each country should determine its own TSH threshold values for treatment decisions in accordance with regional conditions. Otherwise, transferring guideline recommendations directly to daily practice may lead to unnecessary treatments, long-term follow-ups, and increased workload and costs.

Attitudes towards NHT lasting longer than 21 days varied among participants, with only 23% of participants reporting a preference for starting treatment immediately. As in the current consensus (3), physicians' treatment decisions are based on FT4 level, TSH trend, or further investigations, especially thyroid imaging.

Although scintigraphy is the most accurate diagnostic test for determining the etiology of CH, this study showed that pediatric endocrinologists in Türkiye did not prefer scintigraphy or dual imaging. The preference for less invasive and faster-yielding tests in the diagnosis of CH may lead doctors to prefer scintigraphy less frequently. However, there may be other explanations for the 90% preference for the US alone. In Türkiye, the incidence of CH at birth is as high as 1/650 (24), and more than half of the cases consist of transient hypothyroidism (6,7). On the other hand, in permanent CH, 40-80% of the patients have dyshormonogenesis, and this figure varies in direct proportion to the frequency of consanguineous marriage in the study area (6,7,25). In iodine-replete countries where the incidence of CH is relatively low and about 80% of cases are due to thyroid dysgenesis (1,2), scintigraphy may be the first-choice imaging modality, as recommended by guidelines. Considering the high number of cases of transient NHT and CH, and permanent CH with gland *in situ*, scintigraphy for treatment decisions or etiological investigation would not be the first choice for Türkiye (26). Furthermore, the lack of easy access to scintigraphy in most centers may have caused this option to be chosen less. Thus, this perspective is reflected in the responses that the majority of physicians prefer US as the first choice imaging method. Moreover point of care US performed by endocrinologists can be helpful in this situations (27).

After thyroid US, the most frequently requested tests were thyroglobulin, thyroid antibodies and urinary iodine concentrations, which is consistent with the high prevalence of transient hypothyroidism in Türkiye, and possible causes, such as iodine deficiency or overload and maternal blocking antibodies. On the other hand, knee X-rays are rarely requested, indicating that the physicians focus on the etiological investigation of CH rather than

its intrauterine effects. In addition, abdominal US and ECHO are occasionally requested in special cases such as dysmorphism or thyroid dysgenesis, which suggests that Turkish pediatric endocrinologists consider the cost-benefit ratio of expensive examinations.

The treatment goal is to quickly achieve euthyroidism and then maintain it consistently. Normalization of serum TSH and FT4 levels within 2 weeks after starting therapy appears to improve cognitive outcomes. Undertreatment in the first years of life is linked to adverse neurodevelopmental outcomes (28,29). However, it is also important to avoid overtreatment, which may also be harmful (30). In the survey, only one fifth of physicians chose directly a starting LT4 dose of 10-15 µg/kg/day, while the majority preferred doses ranging from 5-15 µg/kg/day, depending on FT4 levels (very low to normal) and/or etiology (athyreosis or not). This attitude is consistent with guideline recommendations and reflects sensitivity to overtreatment and its potential deleterious effects on brain development.

The data indicating the preference for brand-name LT4 over its generic counterpart is inconclusive. However, taking personal experiences and expert opinions into account, the general agreement leans towards recommending the brand-name medication over the generic version (3). According to survey results, half of the participants indicated that it does not matter whether the molecule is original or not.

A subgroup of infants with CH displays variable degrees of thyroid hormone resistance with persistently elevated TSH levels despite high-normal or frankly elevated free T4 concentrations (31,32). For these patients, adding LT3 to LT4 therapy can facilitate the normalization of TSH (33,34). Indeed, 80% of the survey participants reported that they were able to use the LT4-LT3 combination in CH cases with persistent TSH elevation despite high-normal FT4 levels. Although this response does not mean that 80% of physicians routinely use LT3 treatment in cases of persistent TSH elevation, it does show that they are aware of this treatment option and may prefer it in some cases. Interestingly, 10% of physicians stated that they could also use LT3 in patients with thyroid agenesis. This response was attributed to the knowledge that central T4 resistance is more common in patients with thyroid dysgenesis (33).

Recent studies have shown that transient CH is very common among CH patients with gland *in situ* (7,35). The consensus suggested that early treatment withdrawal to assess the necessity of further treatment may be considered and done from the age of 6 months onward, particularly in patients with a gland *in situ*, a negative first-degree family history of CH, or in those requiring a low LT4 dose (< 3 µg/kg per day) (3). While 17% of physicians follow this recommendation, a larger group prefer to re-evaluate at any time if TSH is low regardless of LT4 doses. The preference for early cessation of treatment is probably based on the physicians' observations that thyroid dysfunction due to iodine deficiency or excess resolves in a relatively short time. At this point, the difference in experience is striking, as more senior physicians are more likely to discontinue LT4 therapy whenever the possibility of overtreatment appears, regardless of guideline recommendations and therefore a time limit. In the entire survey, it was observed that professional experience did not cause any difference in attitudes towards CH management, except for the time of drug withdrawal. Similarly, work dynamics (employed in university hospitals and others) did not seem to affect the participants' responses.

In TSH-based neonatal screening programs, some groups of children, such as preterm or low birthweight and sick babies may not be able to generate an adequate TSH response in the first weeks of life. They pass their initial screening test but are at high risk for later development of mild CH (36,37). Therefore, consensus strongly recommends re-screening for these groups. Moreover, in patients with Down's syndrome, measuring TSH at the end of the neonatal period is a strong recommendation (3,10). While almost all of the survey participants stated that they re-screened preterm and sick babies, only less than half re-screened for Down's syndrome. The reason for this might be that since individuals with Down syndrome have frequent doctor visits, there is a higher likelihood of detecting high TSH levels during routine appointments. In contrast, approximately half of the participants reported re-screening babies with congenital anomalies, even though there is no recommendation in the consensus. CH appears to be associated with an increased risk of congenital malformations. In one study of 1420 infants with CH, extrathyroidal congenital malformations had a prevalence of 8.4% (38). Thus, babies with congenital malformations can also be re-screened.

Although there are not many studies in the literature reporting physicians' attitudes toward CH, a survey study was published in the United Kingdom in 2009. A questionnaire survey of the British Society for Pediatric Endocrinology and Diabetes membership was undertaken to examine clinical practice in CH. Results were compared with published management guidelines from Europe and the United Kingdom. There were differences in preference for tablet or liquid preparation, method of tablet administration, time of seeing infant after notification, the interval between the initial-first follow-up visit, and initial LT4 dose (39). In a survey study conducted by Cielonko et al. (40) in 2017 with 44 respondents, differences were found regarding imaging methods and the dose of LT4.

Study Limitations

This study has some limitations. The main limitation is the low response rate for the survey, which may limit the generalizability of the findings to the broader population of pediatric endocrinologists in Türkiye. Those who choose not to respond may differ significantly in the results. Another limitation is that, like all other survey studies, respondents may not accurately reflect actual behaviors, attitudes, or experiences.

Conclusion

Although the attitudes of pediatric endocrinologists working in Türkiye towards the management of CH are generally consistent with the recommendations of international guidelines, their approaches to the treatment for isolated neonatal TSH elevation, thyroid imaging preferences and time to discontinue treatment differ significantly. These different attitudes, which were similar between subgroups defined by experience or work setting, reflect the differences in local conditions in Türkiye and underline the need for a national consensus on the management of CH.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee of the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital, Health Application and Research Center (approval no: 4459, date: 09/07/2024).

Informed Consent: Survey study.

Presented in: The study was presented as an oral presentation at the National Pediatric Endocrinology and Diabetes Congress on 03.04.2024.

Footnotes

Authorship Contributions

Concept: Elif Sağsak, Aydilek Dağdeviren Çakır, Yavuz Özer, Gül Yeşiltepe Mutlu, Bahar Özcabı, Cengiz Kara, Design: Aydilek Dağdeviren Çakır, Cengiz Kara, Data Collection or Processing: Elif Sağsak, Aydilek Dağdeviren Çakır, Yavuz Özer, Gül Yeşiltepe Mutlu, Bahar Özcabı, Cengiz Kara, Analysis or Interpretation: Elif Sağsak, Aydilek Dağdeviren Çakır, Yavuz Özer, Cengiz Kara, Literature Search: Elif Sağsak, Yavuz Özer, Cengiz Kara, Writing: Elif Sağsak, Cengiz Kara.

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ORIGINAL ARTICLE

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Automatic Bone Age Determination in Adult Height Prediction for Girls with Early Variants Puberty and Precocious Puberty

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What is already known on this topic?

Predicted adult height (PAH), which is traditionally measured by the clinician using Bayley-Pinneau (BP) or Roche-Wainer-Thissen methods on the basis of bone age, is one of the parameters used in treatment decision-making in girls presenting with signs of precocious puberty.

What this study adds?

PAH-standard deviation score (SDS) calculations made with the BP method based on the Greulich-Pyle measurement of the BoneXpert program estimates the near-final height-SDS with the closest accuracy.

Abstract

Objective: In cases of precocious puberty, the determination of bone age (BA) is usually performed by clinicians using the Greulich-Pyle (GP) atlas, and there can be significant variation between assessors. The aim of this study was to compare predicted adult height (PAH) calculations based on BA read by the automated BA method "BoneXpert" (BX) with clinician-determined BA-based PAH calculations.

Methods: Girls who presented with suspicion of precocious puberty and normal pubertal variants, such as premature thelarche and premature adrenarche, and whose BA determined by both BX and two different clinicians were followed up until reaching near-final height (NFH). Those whose breast development started before the age of 8 years were considered as precocious puberty. Four PAH calculations were performed with two different estimated height calculation methods, the Bayley-Pinneau (BP) and Roche-Wainer-Thissen based on two different BA predictions (Clinician-GP and BX-GP). PAH-standard deviation score (PAH-SDS) and NFH-SDS values of the patients were compared.

Results: The median chronological age of the 44 girls included at presentation was 9.3 years, while the median BA was 10.4 years and 10.6 years according to clinician-GP and BX-GP, respectively; mean height-SDS was 0.75 and target height-SDS was -0.28. When they reached NFH, the height-SDS was -0.02. Final analyzes were performed in 26 cases who did not have low birth weight and did not receive puberty-arresting treatment. Delta PAH-SDS-NFH-SDS (Δ-SDS) was compared according to the four different PAH calculations. The closest PAH-SDS value measurement to NFH-SDS was calculated by BP based on BA determined by the BX-GP method (-0.09).

Conclusion: PAH calculations using the BP method based on BX-derived GP readings most accurately predict NFH in girls with precocious puberty, and normal pubertal variants.

Keywords: Bone age, BoneXpert, early puberty, normal puberty variants, predicted adult height

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Introduction

Early variant puberty is a source of concern for families and often leads to pediatric outpatient clinic visits. This concern primarily arises from the potential psychosocial challenges and fears that the child may have a shorter adult height (1,2). However, only 10% of children presenting with complaints of early variant puberty fulfills the criteria for precocious puberty (3). Some of the visits are due to premature thelarche and premature adrenarche, which are considered as normal variants of puberty. Premature thelarche is the onset of isolated breast development before the age of 8 years and is benign and self-limiting (4). Premature adrenarche is the onset of pubic or axillary hair growth in girls before the age of 8 years and there are no other accompanying pubertal findings. However, both situations may progress to precocious puberty and require follow-up (5).

Especially in the last 20 years, there has been an increase in cases of so-called "precocious puberty" in girls aged 7-9 years (1). Although the reason for this increase is not known, it is thought that various environmental, genetic, and hormonal factors may play a role in the etiology (6,7). One of the parameters that determine treatment and follow-up decisions in the management of these cases are evaluation of bone age (BA). Comparison of predicted adult height (PAH) based on BA with target height (TH) is one of the important criteria in deciding whether to start treatment or not (8,9).

BA determination can be performed by pediatric endocrinologists and radiologists using conventional BA atlases or by automated BA determination methods. Traditional methods are often used in Türkiye, but they have various limitations. The most important of these are that they are time-consuming, have high intra-rater and inter-rater variability, and make chronological comparison difficult (10).

Automated BA determination methods, on the other hand, provide instant results, eliminate assessor variability, and require only access to software. There are a number of ongoing studies in this field and the results are promising. The reliability of these programs has been verified by comparison with traditional methods (7).

The aim of this study was to compare the BAs measured by the BoneXpert (BX) method, one of the available automatic BA determination methods, with BA values traditionally determined by the clinician according to BA atlases. To evaluate which measurement method is the most successful in predicting near-final height (NFH) by comparing the PAH and PAH-standard deviation scores (SDSs) calculated based on these measured BAs with NFH and NFH-SDS in order to determine which method would be most appropriate to use when making treatment decisions in clinical practice.

Methods

Between June 2016 and November 2018, girls between the ages of 6 and 10 years who were admitted to the Pediatric Endocrinology Outpatient Clinic of Koç University Hospital with suspicion of precocious puberty were evaluated. Girls who were evaluated for BA by both the clinicians and the BX program during the first visit and continued to be followed up were included in the study. Those with chronic diseases, drug use that may affect weight gain or growth rate (such as steroids, psychostimulants, antiepileptics, thyroid hormone and growth hormone replacement therapy) were excluded from the study.

The ages, height, height-SDS, body mass index (BMI), BMI-SDS and pubertal stages of these cases were recorded at the time of first visit. Cases with breast development between stages 2 and 5 or pubic hair development between stages 2 and 5 with puberty onset after the age of 9 years were considered to have normal pubertal development. Those with puberty onset before the age of 8 years or between the ages of 8 and 9, breast development in stages 2-5 or pubic hair growth in stages 2-5 and luteinizing hormone (LH) level <5 IU/L were considered as early variant puberty. Cases with breast development between stages 2-5, no pubic hair and peak LH level <5 IU/L were considered as premature thelarche. Cases with pubic hair in the range of stage 2-5, no breast development and peak LH level <5 IU/L were considered as premature adrenarche. Cases with a peak LH level ≥5 IU/L or LH/follicle stimulating hormone ratio >0.66 or LH ≥0.3 IU/L with onset of breast development before the age of 8 years were considered as true central precocious puberty (CPP) (11).

At the time of initial presentation, BA determination was performed by two pediatric endocrinologists using the Greulich-Pyle (GP) atlas (clinician-GP), and by the BX method according to the GP (BX-GP) in two different ways. In the evaluations performed by clinicians, the BA value was decided by taking the arithmetic mean of the BA value determined by two different clinicians (12). The BA calculation with BX takes place in three different stages. In the first stage, it reconstructs and validates 15 bones, including the radius, ulna, all metacarpals, and all phalanges of fingers 1, 3 and 5. It rejects bones that are not correctly positioned or are severely dysmorphic. In the second stage, the BA value is determined for each bone separately. If a BA value deviates from the mean of all bones by more than 2.4

years, it is not evaluated. If less than 8 bones are valued, an average BA value is not reported. In the third stage, it converts the average of these values according to the GP and Tanner-Whitehouse (TW) scale (13).

Then, four different PAHs were calculated using two different estimated height calculation methods; Bayley-Pinneau (BP) and Roche-Wainer-Thissen (RWT). These different PAH values were: PAH_1 - the PAH calculated by BP based on the BA determined by the clinician using the GP method; PAH_2 - the PAH calculated by RWT based on BA determined by clinician using GP method; PAH_3 - the PAH calculated by BP based on BA determined by BX-GP method; and PAH_4 - the PAH calculated by RWT based on BA determined by BX-GP method. The BP method calculates PAH using tables based on the principle that each BA represents a percentage of the child's adult height. The RWT method uses sex- and age-specific coefficients to calculate the PAH based on the child's recumbent length, weight, BA and the mid-parental height (MPH) (12).

The attainment of final height (FH) or NFH of these cases were assessed by looking at the annual growth rate and BA. An annual growth rate of less than 1cm or a BA of 14 or more was considered as NFH (14). To determine BA, left hand-wrist radiography was taken and evaluated with the BX program. To ensure a more uniform study group, participants with a history of low birth weight and those who received puberty-arresting treatment at the baseline or during follow-up were excluded from the final analysis. The final evaluation was conducted with 26 cases (Figure 1). Four different PAH and PAH-SDS values, NFH and NFH-SDS, TH and TH-SDS, and PAH-SDS - NFH-SDS difference (Δ-SDS) of these cases were compared. In addition, correlations between the calculated PAHs, as well as their relationships with MPH were analyzed.

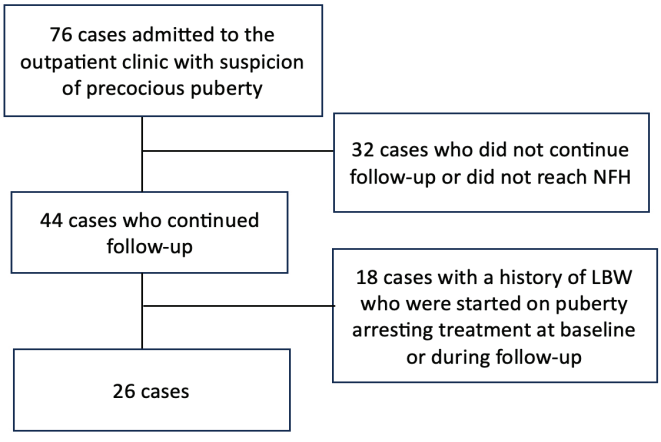

Figure 1. Consort diagram

LBW: low birth weight, NFH: near final height

The Olcay Neyzi growth charts were used to calculate the auxological data through www.ceddcozum.com (15). PAH_{1-4} calculations were also made on the same website by using PAH calculator (15). The approval of the Koç University Faculty of Medicine Ethics Committee dated 19.01.2022 and protocol number 2022.006.IRB1.006 was obtained for this study, which was designed as a single-center, retrospective cohort study. Written informed consent was obtained from the parent/legal guardian of participants prior to the study.

Statistical Analysis

Data were analyzed in the Statistical Package for the Social Sciences, version 26 program (IBM Corp, Armonk, NY, USA). The median and interquartile range values were used to describe continuously distributed variables; frequency and percentage terms were used to describe categorical variables. Mann-Whitney U test in independent groups, Wilcoxon test in dependent groups and Friedman test in more than two dependent groups were used to determine statistically significant differences in pairwise group comparisons for continuous variables that were not normally distributed. Paired group comparisons were made with the Wilcoxon test to determine which of the groups the difference was between. Chi-square test was used to determine the statistical difference between categorical variables and Fisher's exact test was used if the expected value was below 5. Spearman's correlation analysis was used to evaluate the correlations of variables with each other. A value of $p < 0.05$ was considered statistically significant.

Results

Of the 44 cases who were followed up until reaching NFH, 25 (56.8%) were diagnosed as early variant puberty, 6 (13.6%) as CPP, 5 (11.4%) as premature thelarche, and 8 (18.2%) as premature adrenarche at presentation. The median chronological age (CA) and BA at presentation of these cases were 9.29 years and 9.97 years, respectively. Median height and height-SDS at the first visit were 137.8 cm and 0.71. Median BA was 11 years according to clinician-GP and 10.7 years according to BX-GP. At the last visit, the median NFH and NFH-SDS were 158.4 cm and -0.76, and the median TH and TH-SDS were 161.2 cm and -0.32.

The demographic characteristics of the study group (n = 26) in which the final analyzes were conducted are given in Table 1. Of these cases 11 (42.3%) were diagnosed as early variant puberty, 6 (23.1%) as CPP, 4 (15.4%) as premature thelarche and 5 (19.2%) as premature adrenarche. The median BA estimates of these cases were 10.4 years according to clinician-GP and 10.6 years according to BX-GP ($p = 0.620$). The interobserver coefficient of variation for the

BA value was 0.966 (95% confidence interval 0.952-0.975). The median value of NFH and NFH-SDS were 158.4 cm and 0.02, respectively.

The PAH-SDSs of the cases according to their BAs calculated by clinician-GP and BX-GP and the comparisons of them with TH-SDS and NFH-SDS are shown in Table 2. There was a significant difference between PAH_1-SDS calculated with BP based on clinician-BA measurement and PAH_2-SDS calculated with RWT ($p = 0.011$), whereas there was no significant difference between PAH_3-SDS calculated by BP based on BX-GP measurement and PAH_4-SDS calculated by RWT ($p = 0.137$). When PAH-SDSs, NFH-SDS and TH-SDS were compared statistically, there was no significant differences between them ($p = 0.080$). In the correlation analysis between PAH-SDSs, the closest correlation was found between PAH_1-SDS and PAH_3-SDS ($r = 0.758$, $p \leq 0.001$). PAH_1-SDS was significantly lower than PAH_2-SDS ($p = 0.011$) and PAH_4-SDS ($p = 0.019$). PAH_1-SDS, PAH_2-SDS, PAH_3-SDS and PAH_4-SDS were statistically similar to NFH-SDS ($p_1 = 0.298$, $p_2 = 0.611$, $p_3 = 0.409$, $p_4 = 0.696$). PAH_1-SDS and PAH_3-SDS were statistically similar to TH-SDS ($p_1 = 0.684$, $p_2 = 0.849$) while PAH_2-SDS and PAH_4-SDS were significantly greater than TH-SDS ($p_3 = 0.021$, $p_4 = 0.037$).

Table 1. At initial presentation, anthropometric datas, puberty stages, target heights, BA values according to clinician and BX program, and PAHs (n = 26)

	Median (IQR)
Age, years	9.3 (8.7-9.5)
Height, cm	136.4 (132-142.7)
Height-SDS	0.75 (0.2-1.5)
Height age	9.7 (8.9-10.6)
BMI, kg/m^2	18 (15.9-19.2)
BMI-SDS	0.7 (-0.2-1.1)
Thelarche, %	
1	8
2	38
3	31
4	23
5	-
Pubarche, %	
1	34
2	27
3	31
4	4
5	4
BA by clinician-GP, years	10.4 (8.9-11)
BA by BX-GP, years	10.6 (9.1-11.1)
PAH_1 (cm)	160.8 (155.6-164.4)
PAH_1-SDS	-0.4 (-1.2-0.23)
PAH_2 (cm)	161.8 (160-164.5)
PAH_2-SDS	-0.2 (-0.53-0.25)
PAH_3 (cm)	161.6 (157.7-164.8)
PAH_3-SDS	-0.25 (-0.93-0.29)
PAH_4 (cm)	161.6 (160.3-164.5)
PAH_4-SDS	-0.25 (-0.47-0.24)
TH, cm	161.3 (157.3-163)
TH-SDS	-0.28 [-0.98-(-0.01)]
NFH, cm	158.4 (154.8-161.7)
NFH-SDS	0.02 (-0.7-0.3)

BA: bone age, BMI: body mass index, BX: BoneXpert, GP: Greulich-Pyle, PAH: predicted adult height, IQR: interquartile range (25^{th}-75^{th} percentile), SDS: standard deviation score, TH: target height, NFH: near final height

Table 2. Comparisons of the PAH-SDSs to TH-SDS and NFH-SDS

Median	Median	p
PAH_1-SDS (-0.4)	TH-SDS (-0.28)	0.684
PAH_1-SDS (-0.4)	NFH-SDS (0.02)	0.298
PAH_2-SDS (-0.2)	TH-SDS (-0.28)	0.021
PAH_2-SDS (-0.2)	NFH-SDS (0.02)	0.611
PAH_3-SDS (-0.25)	TH-SDS (-0.28)	0.849
PAH_3-SDS (-0.25)	NFH-SDS (0.02)	0.409
PAH_4-SDS (-0.25)	TH-SDS (-0.28)	0.037
PAH_4-SDS (-0.25)	NFH-SDS (0.02)	0.696

PAH: predicted adult height, SDS: standard deviation score, TH: target height, NFH: near final height

The differences (Δ-SDS) between PAH-SDS and NFH-SDS were analyzed. Specifically:

- The difference between PAH_1-SDS and NFH-SDS (Δ1-SDS) was -0.20.

- The difference between PAH_2-SDS and NFH-SDS (Δ2-SDS) was 0.18.

- The difference between PAH_3-SDS and NFH-SDS (Δ3-SDS) was -0.09.

- The difference between PAH_4-SDS and NFH-SDS (Δ4-SDS) was 0.18.

There was a significant difference between the Δ-SDS values. In pairwise comparisons, Δ1-SDS was significantly higher than Δ2-SDS ($p = 0.011$). However, the following pairs were statistically similar:

- Δ1-SDS and Δ3-SDS ($p = 0.414$)

- Δ1-SDS and Δ4-SDS ($p = 0.190$)

- Δ2-SDS and Δ3-SDS ($p = 0.101$)

- Δ2-SDS and Δ4-SDS ($p = 0.750$)

- Δ3-SDS and Δ4-SDS ($p = 0.137$)

Among the PAH-SDS calculations, PAH3-SDS (Δ3-SDS: -0.09) was the closest to NFH-SDS.

In the study group, age at presentation, height, height-SDS, BMI, BMI-SDS, HA, thelarche stage, pubarche stage, TH and menarche age were statistically similar when the cases who reached TH (n = 20) and those who did not reach TH (n = 6) were compared with each other. The median value of NFH was 159.8 cm and the median value of NFH-SDS -0.54 in those who achieved TH, while the median values of NFH was 152.4 cm and the median value of NFH-SDS was -1.68 in those who did not achieve TH and there was a significant difference between them ($p_1 = 0.045$, $p_2 = 0.015$).

Discussion

The results of this study showed that the BA-based PAH-SDS calculation determined by the BX-GP in girls with precocious puberty and normal pubertal variants was found to be closest to the NFH-SDS. In a study by van Rijn et al. (16) in which the BX program was used as an automatic BA determination method, it was observed that BA was measured 0.28 years behind in boys and 0.2 years behind in girls compared to CA in 226 healthy male and 179 female cases and it was concluded that the BX program was a reliable BA prediction tool. In a study in which 13 male and 103 female patients with a diagnosis of precocious puberty were evaluated, automatic BA measurements made by the clinician and BX were compared and it was found that the mean difference between BX-GP BA and clinician-GP-BA was -0.19 (17). In another study in which 392 patients were evaluated, it was found that BX-GP BA was not significantly different from clinician-GP BA, but BX-TW BA was significantly lower than clinician-BA (18). As in previous studies, the present study found the difference between BX-GP BA and Clinician-GP BA to be similar (median 0.005 years, p = 0.620)

BA assessment can be performed using different methods and based on these, PAH calculations can be made with different methods. In a study conducted by Jeong et al. (19) three different BA assessment methods used by pediatric endocrinologists were compared and it was shown that PAHs calculated by BP, TW2 mark, and RWT showed a good correlation with NFH and when the PAH-NFH difference was considered, PAH calculation by BP method was found to have a closer estimation compared to TW2 mark and RWT methods. In another study conducted by Akın Kağızmanlı et al. (12) the BAs of 48 girls who were treated for puberty precocity were evaluated to compare PAH estimations according to BP, RWT and TW2 methods. These authors reported that the closest estimate to NFH was that made using the BP method. Roemmich et al. (20) reported that the method with the closest PAH estimation was TW2, followed by RWT and BP, respectively. In the study by Brämswig et al. (21) it was reported that the best prediction method for male cases was RWT, whereas the three methods were not different from each other for female cases. Some studies have shown that the RWT method, which also takes TH into account, leads to an overestimation of PAH (2). In the present study and similar to the studies by Jeong et al. (19) and Akın Kağızmanlı et al. (12), the closest PAH measurements to NFH were those based on BP method.

There are very few published studies evaluating FH/NFH based on BA and PAH calculations using the BX method. In a study of 82 patients, 48 of whom were female, with chronic endocrinopathy (congenital adrenal hyperplasia, growth hormone deficiency), BA determination was analyzed both conventionally (by clinician) and using the GP method with BX and PAH was calculated. The mean PAH calculated by the BX method was 156.2 cm and 153.9 cm by the conventional method and the mean NFH evaluated during the transition of these patients to the adult endocrinology outpatient clinic was 156.3 cm (13). In two different studies by Thodberg et al. (23), 231 healthy children in the first and 108 healthy children in the second were followed until they reached FH/NFH (22). In both studies, the mean squared error was used to evaluate the model performance and it was concluded that the BX method provides an objective PAH calculation. In the present study, the median NFH of the cases in the group in which the final analyses were performed was 158.4 cm and NFH-SDS was 0.02. In this group, TH was 161.4 cm and TH-SDS was -0.28 SDS. In the evaluation of PAH by four different methods in these cases, PAH-SDS calculations by Clinician-GP-BP method and PAH-SDS calculations by BX-GP-BP method were similar to each other, but the closest measurement to NFH-SDS was the measurement made by the BX-GP-BP method.

Study Limitations

This study is not without its limitations. It has a small sample size, as not all invited cases could participate in the study. The low participation rate may be related to the Coronavirus disease-2019 pandemic during the follow-up period of our research. Some of the subjects presented to the study with a single parent; therefore, height measurements of both parents could not be performed and therefore, the calculation of TH had to be based on verbal information obtained from the family. Another limitation of this study is that PAH calculations based on RWT were performed based on height measured while standing.

Conclusion

The BX automated BA determination method seems to have the closest estimation for NFH-SDS in cases of precoccious puberty and early pubertal variants. It may be preferable

in terms of being a more objective option, ease of use and time-saving. The BA estimates obtained with this method, and the adult height estimates based on this, may make it possible to give parents who are already worried during outpatient visits a range rather than a single adult height estimate. However, further research on larger groups is needed before the widespread use of automated BA determination systems is common.

Ethics

Ethics Committee Approval: The approval of the Koç University Faculty of Medicine Ethics Committee dated 19.01.2022 and protocol number 2022.006.IRB1.006 was obtained for this study, which was designed as a single-center, retrospective cohort study.

Informed Consent: Written informed consent was obtained from the parent/legal guardian of participants prior to the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: All authors contributed equally to all contribution sections.

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Evaluation of Heavy Menstrual Bleeding in Adolescents

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What is already known on this topic?

Heavy menstrual bleeding (HMB) is a common issue among adolescents, with differential diagnoses ranging from anovulation to coagulopathy. Excessive menstrual blood loss can severely impact both emotional and physical quality of life. Currently, there are no specific guidelines for managing adolescent HMB, though cases involving heavy bleeding require immediate intervention.

What this study adds?

Anovulatory cycles are the primary cause of HMB in adolescents; however, other potential causes must also be considered. The initial treatment for adolescent HMB typically involves hormonal or hemostatic therapies. In addition, this study demonstrated that adolescents with severe uterine bleeding but no anemia were successfully treated with tranexamic acid monotherapy.

Abstract

Objective: Heavy menstrual bleeding (HMB) in adolescents often manifests as "excessive bleeding" and may result in acute anemia requiring emergency treatment. The aim of this study was to evaluate the diagnostic and management options for adolescents with HMB.

Methods: Retrospective data were collected from patients' medical records. Adolescents were classified based on the degree of anemia: Group 1 included patients with hemoglobin (Hb) levels of < 8 g/dL; Group 2, Hb levels of 8-10 g/dL; Group 3, Hb levels of 10-12 g/dL; and Group 4, Hb levels of ≥12 g/dL. Admission and follow-up characteristics were compared across groups.

Results: The cohort consisted of 122 adolescents with a mean age of 13.7 ± 1.9 years, 42.7% of whom experienced menstrual irregularity within two years of menarche. The median duration of bleeding was 16 (10-30) days. Anovulation was identified in 57.8% of patients. Polycystic ovary syndrome was diagnosed in 32 (25%) adolescents, hypothyroidism in 6 (4.7%), uterine structural anomalies in 3 (2.3%), and hyperprolactinemia in 3 (2.3%), 2 of whom had microprolactinoma. One adolescent was diagnosed with von Willebrand disease following a hematological evaluation.

Conclusion: Primary care providers should understand normal menstrual cycle patterns and thus be adept at identifying HMB. Early recognition of the underlying etiology in adolescents facilitates timely diagnosis, helping to prevent severe anemia and potential hospitalization.

Keywords: Heavy menstrual bleeding, adolescent, abnormal uterine bleeding

Introduction

Heavy menstrual bleeding (HMB) is defined by both the American College of Obstetricians and Gynecologists (ACOG) and the International Federation of Gynecology and Obstetrics (FIGO) as excessive menstrual blood loss that negatively affects a woman's physical, emotional, social, and material quality of life (1,2). ACOG further specifies that HMB refers to menstrual bleeding lasting more than seven days and/or resulting in blood loss exceeding 80 mL per cycle (2).

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The ACOG and the American Academy of Pediatrics highlight the menstrual cycle as a "vital sign" for girls, urging clinicians to educate adolescents and caregivers about typical menstrual patterns (2). Menarche is deemed normal between the ages of 10.5 and 15.5 years (3), while a typical adolescent menstrual cycle ranges from 21 to 45 days, with periods lasting 3 to 7 days (4). Normal menstrual flow typically involves the use of three to six pads per day. However, research indicates that relying on pad counts may not accurately reflect menstrual flow, particularly in adolescents. This is due to factors such as unreliable reporting, the use of products with varying absorbency levels, or changing products before they are fully saturated (5,6).

Menstruation remains a taboo subject in some cultures, where it may not be discussed at all (7). Consequently, some young women may never have received education about menstruation. Even in high-income countries, both adolescents and their parents frequently report discomfort discussing the topic, contributing to poor menstrual health literacy (8). HMB is often under-reported among adolescents because its definition relies on subjective experiences without clear reference points and is influenced by individual perceptions of what is considered "normal". This can result in delays in identifying heavy or prolonged menstrual bleeding, increasing the risk of associated morbidity.

FIGO recommends classifying HMB according to the PALM-COEIN system, which includes polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not otherwise classified categories (1). In adolescents, non-structural causes of abnormal bleeding patterns are significantly more common than structural ones, with ovulatory dysfunction accounting for 90% of HMB cases in this population (9). HMB frequently affects adolescents, with unpredictable and prolonged periods often occurring shortly after menarche (4). Among Swedish adolescents, the prevalence of HMB was documented at 37%, representing a significant source of distress (10). HMB in adolescents often necessitates urgent medical intervention. Many adolescents, both with and without underlying bleeding disorders, present to emergency departments with HMB. However, limited information is available about the management decisions made for these patients (11). While several reports address the treatment of HMB, there remains a lack of robust evidence-based guidance for its diagnosis and management (7,12,13).

In our single-center retrospective study, we analyzed the clinical characteristics and management options of adolescent patients referred to a pediatric endocrinologist for the evaluation and treatment of their HMB, with or without associated iron deficiency anemia.

Methods

A retrospective chart review was conducted to identify eligible patients, defined as girls younger than 18 years who were referred to a tertiary care hospital for HMB between 8 February 2021 and 30 June 2024. The study was approved by the Non-Interventional Clinical Research Ethics Committee of Samsun University (approval no: 2024/4/15, date: 14/02/2024).

Data collected for analysis included patient demographics, age at referral, age at menarche, average duration of bleeding, laboratory workup results, ultrasound findings, the presence of other medical conditions or medication use, and family history of HMB or thrombosis. The selected treatment and final diagnosis were also documented. In addition, for patients with hemoglobin (Hb) levels of <10 g/dL, the time to recovery of the Hb and ferritin levels was recorded. Patients were excluded from the study if they had a pre-existing diagnosis of a coagulation or bleeding disorder or had not yet reached menarche.

The parameters defining HMB included a menstrual duration of at least seven days, with patients reporting either "flooding," bleeding through a pad in ≤2 hours during most periods, or the use of highly absorbent products (2).

Laboratory tests were performed for all patients to evaluate the severity of bleeding and to identify potential underlying causes of HMB. At our institution, patients presenting with HMB undergo a first tier of laboratory investigations, which includes a complete blood count, ferritin level, prothrombin time, activated partial thromboplastin time, bleeding time, thyroid function tests (including free thyroxine and thyroid-stimulating hormone), prolactin, progesterone, total testosterone, and beta human chorionic gonadotropin. For patients in the present study with a significant bleeding history or those on oral hormone therapy where initial laboratory tests appear normal, the hematologist repeated the von Willebrand disease (vWD) panel. Any abnormal laboratory results were retested at least twice for confirmation.

The definition of anovulation was based on the following two criteria: menstrual bleeding occurring more frequently than every 21 days or being excessive in nature, and a serum progesterone level of <0.5 ng/mL at the time of diagnosis and/or the exclusion of other identified causes of HMB (9,14).

All adolescents were classified according to the degree of anemia. Group 1 included patients with Hb levels

of <8 g/dL (severe anemia), while Group 2 consisted of those with Hb levels of 8-10 g/dL (serious anemia). Group 3 included patients with Hb levels of 10-12 g/dL (moderate anemia), and Group 4 comprised patients with Hb levels of ≥12 g/dL (mild or no anemia). Admission and follow-up characteristics were compared across the four groups.

The primary clinical goal in managing HMB was to restore hemodynamic stability by addressing anemia while determining the underlying cause. Patients with Hb levels of <7 g/dL or those with Hb levels of <10 g/dL accompanied by active bleeding were admitted to the hospital.

Patients with hemodynamic instability were transfused with erythrocyte suspension. For those treated with combined oral contraceptives (COCs), pills containing at least 30 mcg of ethinyl estradiol were preferred and administered every 6 to 8 hours until the bleeding ceased. Once the bleeding stopped, the dosage was gradually reduced to once daily and continued until Hb levels exceeded 10 g/dL. Cyclic treatment was then initiated. For patients with Hb levels of 10-12 g/dL, iron supplementation with 100 mg of elemental iron per day was prescribed to address persistent blood loss. Patients with regular menstrual cycles but heavy bleeding episodes each month were treated with oral tranexamic acid (10 mg/kg/day) to reduce menstrual flow.

Descriptive statistics were used to analyze the data. Selection bias was minimized by including all adolescents referred to our institution for the evaluation of HMB during the study period.

Statistical Analysis

All statistical analyses were performed using SPSS, version 25 (IBM Corp., Armonk, NY, USA). Data are expressed as mean ± standard deviation or median (25^{th}-75^{th} percentile). The Kolmogorov-Smirnov test was used to assess the normality of the variables. Descriptive analyses are presented as mean ± standard deviation for variables with a normal distribution. Student's *t*-test was used to compare the means of continuous variables with a normal distribution. The Mann-Whitney U test, with appropriate confidence intervals, was used for non-parametric measurements. A p-value of <0.05 was considered statistically significant in all analyses.

Results

In total, 122 patients met the study criteria. The mean age at the time of referral was 13.7 ± 1.9 years, and the median body mass index (BMI) standard deviation score was 0.5 (-0.7 to 1.47). The mean age at menarche was 11.9 ± 1.1 years. From the onset of menarche, HMB was observed in 42% of patients. The prevalence of HMB from the onset of menarche in Groups 1, 2, 3, and 4 was 23%, 41%, 46.7%, and 48%, respectively, although the differences in proportion were not significant. Moreover, HMB occurring within the first two years after menarche was reported by 68% of patients.

The median duration of bleeding was 16 (10-30) days. In the whole cohort, the mean Hb level was 11.07 ± 2.18 g/dL, while the median ferritin level was 12 (5.9-20) ng/dL. In addition, 18% (n = 23) required hospitalization for the acute management of HMB. Excluding transfused patients, the recovery times for Hb and ferritin were 2.0 ± 1.18 months and 3.96 ± 1.77 (2-6) months, respectively. However, no significant differences were observed between the groups stratified by degree of anemia. Clinical and laboratory characteristics of patients with HMB are shown in Table 1.

Taking all groups together, anovulation was identified as the primary cause of HMB in 57.8% of patients. In the study cohort, 32 (25%) adolescents were diagnosed with polycystic ovary syndrome (PCOS), 6 (4.7%) with hypothyroidism, and 3 (2.3%) with uterine structural anomalies (uterus didelphys). Furthermore, three (2.3%) adolescents were diagnosed with hyperprolactinemia, two of whom had microprolactinoma. One girl was diagnosed with vWD following a hematological evaluation. No cases of other factor deficiencies or platelet dysfunction/structure were identified. Two patients had a family history of thrombosis; genetic testing in one of these patients revealed a homozygous *plasminogen activator inhibitor* (*PAI*) gene mutation.

The distribution of diagnoses across groups is detailed in Table 2.

Across the full cohort, 28 (21%) adolescents were found to have a comorbidity. These included euthyroid chronic lymphocytic thyroiditis (n = 10), autism (n = 4), hearing impairment (n = 2), cystic fibrosis (n = 1), asthma (n = 1), epilepsy (n = 1), and gastritis (n = 1). Four (3.1%) adolescents were using COCs prescribed for hirsutism. Moreover, four were taking levothyroxine, two were taking metformin, one was using an inhaled steroid, one was taking levetiracetam, and one was using a proton pump inhibitor. None of these medications were found to contribute to bleeding. All serum beta human chorionic gonadotropin levels were <0.1 IU/L. No adolescents had a history of anorexia or bulimia.

Treatment Procedures

Management of HMB was tailored to the underlying etiology and the severity of bleeding. When all groups were analyzed together, 10 (8%) adolescents received transfusions with

Table 1. Clinical and laboratory features of cases with heavy menstrual bleeding

	Total	Group 1 (Hb < 8 g/dL) (n = 13)	Group 2 (Hb = 8-10 g/dL) (n = 18)	Group 3 (Hb = 10-12 g/dL (n = 30)	Group 4 (Hb > 12 g/dL) (n = 61)	p value
Age (years)	13.7 ± 1.9	13.9 ± 2.03	14.2 ± 1.8	13.8 ± 1.9	13.37 ± 2.1	0.33
Menarcheal age	11.9 ± 1.1	11.4 ± 1.04	12 ± 0.8	12 ± 0.9	11.6 ± 1.19	0.25
HMB from menarche (%)	42.7 (n = 56)	23.1 (n = 3)	33.3 (n = 6)	46.7 (n = 14)	48.4 (n = 30)	
Irregularity after menarche > 2 years (%)	32 (n = 41)	46.2 (n = 6)	38.9 (n = 7)	23.3 (n = 7)	29.5 (n = 18)	
BMI-SDS	0.5 (-0.7-1.55)	0.6 (-1.17-2.4)	0.5 (-1.1-1.4)	1.1 (-0.57-1.9)	0.6 (-0.75-1.45)	0.72
Bleeding duration (days)	16 (10-30)	21.5 (13-40.2)	17 (10-21)	15 (8.5-27)	17.5 (10-30.7)	0.26
Hemoglobin (g/dL)	11.1.06 ± 2.18	6.67 ± 0.9[a]	8.8 ± 0.56[b]	11 ± 0.6[c]	12.7 ± 0.73[d]	**< 0.001***
Platelets (per µL)	315.9 ± 72.2	358 ± 79.0[a]	324 ± 96[ab]	340.4 ± 57.4[ab]	297.7 ± 63.4[b]	**0.02***
Ferritin (ng/dL)	12 (5.9-20)	4 (2-7)[ac]	5 (3.7-10.1)[c]	11 (6.2-17)[b]	16 (9-23)	**< 0.001***
Progesterone (ng/mL)	0.37 (0.1-1.95)	0.35 (0.17-1.8)	0.4 (0.3-1.75)	0.2 (0.09-1.8)	0.4 (0.14-2.2)	0.6
Hb recovery time (months)	2 ± 1.18 (2-3)	2 ± 0.81 (1.25-2.75)	2.1 ± 0.7 (2-3)	2.1 ± 1.34 (1-2.5)		0.24
Ferritin recovery time (months)	3.96 ± 1.77 (2-6)	2 ± 2 (2-5)	4 ± 1.7 (2.7-6)	3 ± 1.9 (2.25-6)		0.45
Polycystic ovarian morphology (%)	18 (n = 22)	7.7 (n = 1)	16.7 (n = 3)	23.3 (n = 7)	17.7 (n = 11)	
Endometrial thickness (mm)	7 (5-10.2)	6 (5-10)	10 (6.7-12.2)	6 (5-7.6)	8 (4-12)	**0.092***

[a,b,c,d]: in the same row, groups marked with different supercript letters differ significantly from each other ($p < 0.05$). Groups sharing the same letter are not significantly different. Post-hoc analyses were performed to determine pairwise differences.
*: $p < 0.05$.
HMB: heavy menstrual bleeding, BMI-SDS: body mass index-standard deviation score, Hb: hemoglobin

Table 2. Differential diagnosis of cases with heavy menstrual bleeding

Diagnosis	Total	Group 1 (Hb < 8 g/dL) (n = 13)	Group 2 (Hb = 8-10 g/dL) (n = 18)	Group 3 (Hb = 10-12 g/dL (n = 30)	Group 4 (Hb > 12 g/dL) (n = 61)
Anovulatory cycle (%)	57.8 (n = 74)	76.9 (n = 10)	55.6 (n = 10)	46.7 (n = 14)	57.4 (n = 35)
PCOS (%)	25 (n = 32)	7.7 (n = 1)	27.8 (n = 5)	30 (n = 9)	26.2 (n = 16)
Hypothyroidism (%)	4.7 (n = 6)			10 (n = 3)	4.9 (n = 3)
Iatrogenic	3.1 (n = 4)		5.6 (n = 1)	6.7 (n = 2)	1.6 (n = 1)
Hyperprolactinemia	2.3 (n = 3)		5.6 (n = 1)		3.3 (n = 2)
Uterine anomaly	2.3 (n = 3)			3.3 (n = 1)	3.3 (n = 2)
Others	2.3 (n = 3)	7.7 (n = 1)	5.6 (n = 1)	3.3 (n = 1)	
Endometrial causes	0.8 (n = 1)	7.7 (n = 1)			
Bleeding disorder	0.8 (n = 1)				1.6 (n = 1)

PCOS: polycystic ovary syndrome, Hb: hemoglobin

erythrocyte suspension, 100 (76%) were treated with iron supplementation, 62 (53%) received COCs, and 56 (42%) were treated with tranexamic acid. Sixteen (12%) patients were monitored without any specific treatment. One patient, who presented at the age of 10.1 years, had menarche before the age of 10 years and had experienced continuous bleeding since menarche; this patient was treated with leuprolide acetate. Table 3 outlines the treatment differences across the groups.

Two adolescents with normal pelvic ultrasound (PUS) findings did not respond to a combination of COCs and tranexamic acid therapy. Pelvic magnetic resonance imaging was performed for these patients, and the findings were normal.

Discussion

Ensuring timely and adequate access to appropriate care is important when managing HMB, as delays in treatment may lead to severe anemia, reduced quality of life, and increased rates of depression and anxiety. In a population-based study of 1,000 healthy Swedish girls, 73% reported menstrual problems, with 37% experiencing HMB (10). Similarly, other population-based studies reported that 12.1% and 17.9%

of girls in Nigeria and Hong Kong, respectively, experienced HMB (14,15).

An immature hypothalamic-pituitary-ovarian axis during the peri-menarchal period can result in anovulatory cycles and heavy, irregular menstrual bleeding. Within the first two years after menarche, anovulatory cycles are common and are considered part of normal physiological development (4). Studies have shown that 60% to 80% of adolescents have regular cycles within three years after menarche, while it may take up to 5 to 6 years for 95% of women to achieve normal cycles (12). The findings of the present study align with existing evidence, demonstrating that anovulation is the most common cause of HMB in adolescents (2).

Endocrine disorders that can cause anovulation include PCOS, thyroid dysfunction, adrenal insufficiency, Cushing syndrome, hyperprolactinemia, and diabetes mellitus (4). In our cohort, PCOS was identified in 32% of participants. By comparison, a study of Turkish adolescents with abnormal uterine bleeding reported a PCOS prevalence of 16% (9). In addition, long-term studies indicate that up to 59% of adolescents with abnormal uterine bleeding meet the diagnostic criteria for PCOS (16). The higher detection rate of PCOS in our cohort may be attributed to the large sample size and the routine use of PUS and testosterone measurements for all patients with HMB. Furthermore, the increasing prevalence of obesity in our society may contribute to a rise in PCOS cases, making it a more common cause of HMB.

In the present study, hypothyroidism was identified in six (4.7%) patients. This frequency aligns closely with existing literature (12). Both hypothyroidism and hyperthyroidism may contribute to HMB and so thyroid function tests should be included in the initial evaluation of patients with HMB.

Hyperprolactinemia was identified in three (2.3%) patients in our cohort, two of whom were treated with cabergoline following a diagnosis of prolactinoma. By contrast, two previous studies from Türkiye with sample sizes of 22 and 79 patients, respectively, reported no cases of hyperprolactinemia (9,12). The higher rate observed in our study may be attributable to the larger number of patients included. We recommend that prolactin levels be monitored in all patients presenting with HMB, ideally before initiating treatment with COCs.

Structural causes of HMB, such as endometrial and cervical polyps, adenomyosis, and uterine abnormalities, are uncommon in adolescents (4). One study reported that structural causes were found in only 1.3% of adolescents who underwent PUS for HMB evaluation (17). In the present study, three (2.3%) cases of uterine abnormalities were identified, a rate consistent with the literature. Endometrial causes of HMB in adolescents are also rare, accounting for <10% of HMB cases (6). Endometritis due to pelvic inflammatory disease is the most common cause of endometrial bleeding in adolescents (4). In our cohort one case of an endometrial polyp was found, but no cases of pelvic inflammatory disease were observed, aligning with the findings reported in the literature.

Iatrogenic causes of HMB include anticoagulants, hormonal contraception, and other drugs that affect ovulation, such as antipsychotics (18). Hormone therapy is the most common iatrogenic cause of HMB. Both COCs and progesterone-only pills may contribute to HMB, with irregular bleeding being more frequent in patients using progesterone-only

Table 3. Treatment of cases with heavy menstrual bleeding

Treatment	Total	Group 1 (Hb < 8 g/dL) (n = 13)	Group 2 (Hb = 8-10 g/dL) (n = 18)	Group 3 (Hb = 10-12 g/dL (n = 30)	Group 4 (Hb > 12 g/dL) (n = 61)
I (%)	75.8 (n = 97)	100 (n = 13)	100 (n = 18)	100 (n = 30)	49.2 (n = 30)
COCs therapy (%)	51.6 (n = 66)	100 (n = 13)	100 (n = 18)	50 (n = 15)	27.9 (n = 17)
T (%)	43 (n = 55)	69.2 (n = 9)	55 (n = 11)	36.7 (n = 11)	36.1 (n = 22)
Erythrocyte suspension therapy (%)	7.8 (n = 10)	38.5 (n = 5)	22.2 (n = 4)	0	0
Only I (%)	15.6 (n = 20)	0	0	33.3 (n = 10)	14.8 (n = 9)
I + COCs (%)	26.6 (n = 34)	30.8 (n = 4)	44.4 (n = 8)	30 (n = 9)	18 (n = 11)
I + COCs + T (%)	22.7 (n = 29)	69.2 (n = 9)	55.6 (n = 10)	20 (n = 6)	4.9 (n = 3)
I + T (%)	11.7 (n = 15)	0	0	16.7 (n = 5)	13.1 (n = 8)
Only T (%)	7.8 (n = 10)	0	0	0	16.4 (n = 10)
COCs + T (%)	0.8 (n = 1)	0	0	0	1.6 (n = 1)
Untreated follow-up	12.5 (n = 15)	0	0	0	26.2 (n = 15)

COCs: combined oral contraceptives, T: tranexamic acid therapy, I: iron therapy, Hb: hemoglobin

pills (5,7). In the present study, four (3.1%) cases of prolonged menstrual bleeding were associated with the use of COCs prescribed for hirsutism. Proper administration of COCs, such as taking the pill consistently at the same time daily, avoiding missed doses, and refraining from concurrent use of drugs that alter estrogen metabolism, may help reduce or prevent HMB.

The prevalence of bleeding disorders in the general population is 1% to 2%, but this rate increases significantly to 20% to 33% in adolescents with HMB (19). In our study, one adolescent was diagnosed with vWD, with HMB as her first presenting symptom. vWD, the most common inherited bleeding disorder in women with HMB, is caused by a quantitative or functional defect in von Willebrand factor and affects approximately 1% of the general population (20). While the severity of vWD varies, nearly all affected women experience HMB (3). The literature indicates that bleeding disorders are the second most common cause of HMB in adolescents after anovulation and are particularly prevalent in females presenting with HMB at menarche (19). Coagulopathy may be suspected as the etiology if bleeding is cyclical, but excessive in volume or duration (4). However, in the present study, the patient with vWD experienced prolonged menstrual bleeding that began after menarche, and her anemia was not severe. These findings suggest that any patient with prolonged menstrual bleeding should be evaluated for a bleeding diathesis, even if there is no family history of severe anemia or coagulopathy.

Treatment of HMB frequently involves hormone therapy, and it is important to evaluate for contraindications to COCs, including a family history of thromboembolic events (21). The prevalence of homozygous *methylenetetrahydrofolate reductase* (*MTHFR*) gene mutation, which alters B vitamin metabolism, in the Turkish population reportedly ranges from 3% to 6% (22). In the present study, no cases of homozygous *MTHFR* mutation were identified among patients with a family history of thrombosis. However, a homozygous *PAI* gene mutation was detected in one adolescent. These findings underscore the importance of screening for thrombophilic gene mutations in patients with a family history of thromboembolic events before initiating hormone therapy.

The initial approach to treating HMB involves medical management using hormonal therapy, hemostatic agents, or a combination of both. Treatment options include COCs, oral progestins, antifibrinolytics, non-steroidal anti-inflammatory drugs (NSAIDs), gonadotropin-releasing hormone analogs, and, where possible, addressing the underlying pathology (18). Although various hormonal therapies have been shown to effectively stop menstrual bleeding, there is limited evidence to suggest the superiority of one option over another (4). In our cohort, treatment decisions were primarily guided by the degree, duration, and pattern of anemia. Except for patients in Group 4, all others received COCs and iron supplementation. Two patients with prolactinoma were treated with cabergoline, while a gonadotropin-releasing hormone analog was used for a patient with early menarche and heavy uterine bleeding. NSAIDs were not used as a first-line treatment in any patient because NSAIDs can affect platelet function (23). Thus, they were not administered before completing a comprehensive hematological evaluation.

Ferritin levels serve as a key indicator of the body's iron status, with low serum ferritin levels being predictive of excessive menstrual blood loss. The threshold for low ferritin is typically defined as <15 µg/L (3). In the present study, the mean ferritin level was 12 µg/L. Iron deficiency, even without anemia, has been associated with increased muscle fatigue, impaired memory, and learning difficulties in adolescents, while fatigue is commonly reported by young women with HMB (24). Iron supplementation should continue until anemia resolves and for an additional three months thereafter to replenish iron stores (3). A review of clinical guidelines for managing iron deficiency and iron-deficiency anemia in HMB, although not specifically focused on adolescents, recommends oral iron therapy as the preferred treatment for individuals with mild anemia or non-anemic iron deficiency (indicated by low ferritin levels). This approach is also suggested for patients at high risk of developing iron deficiency (25). Adolescents with severe uterine bleeding should be monitored for iron status even after bleeding has ceased. In our study, the overall ferritin recovery time (to 20 µg/L) across the whole cohort was 3.96 ± 1.77 (2-6) months, emphasizing the importance of long-term follow-up and the prevention of recurrent bleeding.

Tranexamic acid therapy was used in combination with iron or COCs in 44% of patients in the present study and as monotherapy in 16% of patients within Group 4. No side effects related to tranexamic acid were observed. Tranexamic acid therapy is particularly suitable for patients with regular cycles and long or heavy bleeding. It is also a preferred option for those where concerns about potential impacts on height from COCs treatment exist. Tranexamic acid, an antifibrinolytic agent, is a viable option for non-hormonal treatment or as an adjunct to hormonal therapy for HMB when monotherapy is ineffective (21). The medication is approved for use in patients with HMB and is typically administered orally every 8 hours for 5 days during menstruation, regardless of whether the patient has

a bleeding disorder. Although tranexamic acid has been associated with a potentially increased risk of thrombosis, clinical studies indicate that the incidence of thrombosis in women treated with tranexamic acid is comparable to the spontaneous incidence in untreated women (23,26). One study evaluated the efficacy of tranexamic acid in adolescents with HMB through an open-label, prospective, multicenter trial involving 32 adolescents aged 10 to 19 years. Participants were treated with 1,300 mg of tranexamic acid orally three times daily for the first five days of their menstrual cycle and were followed for four months. The study demonstrated a reduction in mean blood loss and an improvement in quality-of-life scores (27). Consistent with the literature, patients with severe uterine bleeding but no anemia were successfully treated with tranexamic acid monotherapy in our cohort.

Many existing guidelines recommend PUS as a first-line diagnostic tool for assessing HMB (28). ACOG also states that the decision to order a PUS for abnormal or heavy bleeding is at the provider's discretion (23).

In our clinical experience, PUS is typically sufficient for imaging pelvic structures and assessing endometrial thickness. In the present study, uterine abnormalities were identified in three patients, and endometrial polyps were found in one patient. Similar findings were reported in the study by Kızılcan et al. (9). Two patients were further evaluated with magnetic resonance imaging because of a lack of response to treatment and normal findings on ultrasound. Given that structural causes are uncommon in the etiology of severe uterine bleeding in adolescents, more invasive imaging options may be reserved for selected cases. Surgical treatment of HMB in adolescents should be avoided unless absolutely necessary for life-saving interventions because it poses a significant risk to future fertility (18).

Study Limitations

Due to the retrospective nature of the study, reliance on information documented in medical records was necessary, which may have introduced limitations in data accuracy and completeness. Larger studies are needed to provide more robust and generalized results.

Conclusion

Primary care providers should be well-informed about the characteristics of a normal menstrual cycle and capable of identifying HMB, especially in adolescent girls. Early recognition of the etiology of HMB in adolescents is very important because it facilitates timely intervention, potentially preventing severe anemia, hospitalization, and prolonged school absences. Early detection also helps reduce psychological impacts associated with HMB. For adolescents, anovulatory cycles are the most common cause of HMB, but other potential causes should be thoroughly investigated. Hormonal and hemostatic therapies are the primary treatment options for managing adolescent HMB. Effective management of HMB in adolescents requires a personalized approach, including a thorough evaluation of the underlying cause, prompt acute treatment when needed, and a long-term plan to promote regular menstrual cycles and overall well-being.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Samsun University (approval number: 2024/4/15, date: 14/02/2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Tuğba Kontbay Çetin, Zuhal Keskin Sarılar, Concept: Tuğba Kontbay Çetin, Design: Tuğba Kontbay Çetin, Zuhal Keskin Sarılar, Data Collection or Processing: Tuğba Kontbay Çetin, Zuhal Keskin Sarılar, Analysis or Interpretation: Tuğba Kontbay Çetin, Zuhal Keskin Sarılar, Literature Search: Tuğba Kontbay Çetin, Writing: Tuğba Kontbay Çetin.

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ORIGINAL ARTICLE

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What is the Most Effective Method for Predicting Adult Height in Boys with Constitutional Delay of Growth and Puberty?

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What is already known on this topic?

Predicted adult height can be calculated using methods, such as the Bayley-Pinneau, Roche-Wainer-Thissen (RWT), and BoneXpert, which rely on bone age assessment. However, as these methods were originally developed for healthy children, their predictive accuracy has shown variability when applied to different patient groups.

What this study adds?

This study demonstrated that the RWT method was more effective than other methods for estimating adult height in boys with delayed bone age, irrespective of whether the delay was ≤2 years or >2 years.

Abstract

Objective: Predicted adult height (PAH) can be calculated using methods such as Bayley-Pinneau (BP), Roche-Wainer-Thissen (RWT), and BoneXpert based on bone age (BA) assessment. Since these methods were developed for healthy children, varying results have been reported regarding their efficacy across different patient groups. Our aim was to determine the most accurate method for PAH by comparing the BP, RWT, and BoneXpert methods in boys with constitutional delay of growth and puberty (CDGP).

Methods: Male patients with CDGP who had reached their final height (FH) were included in the study. Two experienced clinicians reassessed left-hand and wrist radiographs taken at the time of diagnosis using the Greulich-Pyle (GP) atlas to manually determine BA. Among the methods used for PAH, the GP atlas was used for BP and RWT, while we used the intrinsic GP-based application with BoneXpert.

Results: For the 62 boys included, the mean age at diagnosis was 14.2 ± 0.8 years, with 58.1% (n = 36) having a similar family history. The mean height standard deviation (SD) score was -2.1 ± 0.9, and 24.2% (n = 15) of patients received low-dose testosterone induction therapy. The median (range) BAs were 12.5 (11.5-13.0) years using the GP atlas and 12.6 (11.8-13.4) years with BoneXpert ($p < 0.001$). Boys who were or were not treated with testosterone therapy had similar mean height SD scores, median testicular volumes, and median BAs assessed by both methods. The mean target height and FH SD scores were -0.6 ± 0.6 and -0.6 ± 0.9, respectively ($p = 0.8$). Almost all patients (n = 60, 97%) achieved adult height within the target range, with no significant difference in the FH SD score between boys who received testosterone and those who did not ($p = 0.1$). There was no significant difference between the FH and PAH when estimated by the BP and RWT methods ($p = 0.2$ and $p = 0.6$, respectively), while the BoneXpert method underestimated the FH ($p < 0.001$). The BP and RWT methods provided better predictions in patients with BA ≤2 years compared to BoneXpert ($p = 0.3$ and $p = 0.4$ vs. $p < 0.001$,

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respectively). Conversely, RWT and BoneXpert methods were more accurate in PAH in boys with delayed BA >2 years (p=0.1 and p=0.1, respectively), while the BP method resulted in overestimation (p=0.003).

Conclusion: The RWT method was found to be a better predictor of FH compared to the BP or BoneXpert methods in boys with delayed BA ≤2 years and >2 years.

Keywords: Adult height estimation, final height, constitutional delay of growth and puberty

Introduction

Constitutional delay of growth and puberty (CDGP) is classified as the most prevalent cause of short stature and delayed puberty, primarily in boys. This temporary condition is considered a normal growth spectrum, characterized by a slowdown in linear growth, retarded bone maturation, and delayed onset of puberty and, consequently, the pubertal growth spurt. The exact etiology of CDGP remains unclear, but about 50-75% of patients have a family history of delayed puberty, often following an autosomal dominant inheritance pattern. Typically, these children are expected to reach normal adult height after experiencing delayed but otherwise normal puberty (1,2,3).

In the management of boys with CDGP, reassurance and watchful waiting are generally adequate. However, for adolescents experiencing psychological challenges and low self-esteem, medical therapy with low-dose testosterone and psychological counseling may be necessary (1,2,3,4). Clinicians often use predicted adult height (PAH) based on bone age (BA) assessments to inform patients and their parents about future growth potential. In these patients, PAH can be calculated using several methods, including the Bayley-Pinneau (BP), Roche-Wainer-Thissen (RWT), and BoneXpert application, which were originally developed for healthy children (5,6,7,8,9,10). In addition, delayed BA is a known factor that can limit the accuracy of adult height prediction. So far, only a few studies have evaluated prediction methods in patients with CDGP, and there is limited and conflicting information about their accuracy (5,7,8,9,10,11).

In the present study, we aimed to assess the accuracy of the BP, RWT, and BoneXpert methods for estimating adult height in boys with CDGP to provide them with realistic and more accurate information about their future height potential.

Methods

Patients

Boys diagnosed with CDGP who were referred to pediatric endocrinology units for evaluation of short stature or delayed puberty between 2010 and 2018 and who had achieved their final height (FH) were included. To increase the sample size, extended criteria for delayed puberty were applied (12,13). The inclusion criteria were: (i) boys aged 13 years or older with a testicular volume less than 6 mL, as measured by a Prader orchidometer, who exhibited spontaneous pubertal development before the age of 18 or after pubertal induction with low-dose testosterone; (ii) absence of any endocrine or chronic medical condition; and/or (iii) a familial history of pubertal delay. Male subjects who were born small for gestational age, had received any medication, or had systemic diseases, dysmorphic syndromes, skeletal abnormalities, or pituitary hormone deficiencies were excluded.

FH was defined based on the following criteria: (i) fused epiphyses; (ii) a growth velocity of less than 1.0 cm in the preceding year; and (iii) completed secondary sexual characteristics. Boys were considered to have achieved their target height if their FH was within the 1.5 standard deviation (SD) score of the target height.

Clinical Assessment

Data were retrospectively gathered on age, anthropometric measurements, physical examination findings, and parental height, as well as laboratory and radiological findings from patient medical records. Height was measured to the nearest millimeter using a Harpenden stadiometer, and weight was measured with a SECA scale (Hamburg, Germany) to an accuracy of 0.1 kg, with patients wearing only underwear and no shoes. SD scores for height, weight, and body mass index (BMI) were calculated using an online calculator (child metrics) based on Turkish standards published by Neyzi et al. (14). The pubertal stage was assessed using Tanner's standards (15). The genetic target height was calculated by adding 6.5 cm to the average parental height, following the Tanner formula (16). The levels of luteinizing hormone (LH), follicle-stimulating hormone, serum total testosterone (ng/mL) obtained at 8:00 am were recorded, together with the gonadotropin-releasing hormone-stimulated LH levels from the patient files.

Bone Age Assessment and Adult Height Prediction Methods

The BAs of boys with CDGP were reassessed using both manual and automated methods. Initially, BAs were independently re-evaluated by two experienced clinicians

(AA and GAK) using left-hand and wrist radiographs, according to the Greulich-Pyle (GP) atlas (17). The manual BA for each patient was subsequently calculated by averaging these independent assessments. Radiographs were stored on a PACS workstation, and all images were uploaded in DICOM format before being analyzed by BoneXpert software. Subsequently, the same radiographs were evaluated using the automated BA assessment method provided by BoneXpert Standalone, based on the GP atlas (Visiana, Holte, Denmark, www.boneXpert.com) (18).

Adult height predictions were made using the BP, RWT, and BoneXpert methods. The GP atlas was used for both the BP and RWT methods. For the BoneXpert method, two approaches were employed: (1) PAH was calculated using the BA automatically generated by the BoneXpert software, which is based on the GP atlas, after uploading left-hand X-rays; and (2) PAH was calculated by entering the BA manually assessed using the GP atlas into the BoneXpert's web page. Manually assessing BA using the GP atlas and applying it in the BoneXpert method for PAH calculation is routine practice in our clinics.

The estimated adult height for the BP and RWT methods was calculated using the online calculator (child metrics, www.childmetrics.org) (19). For the BP method, this calculator uses tables mentioned in the study by Post and Richman (20), which provide decimal fractions indicating the proportion of adult height attained at various BAs. These fractions are categorized based on whether the BA is average (within one year), delayed, or advanced relative to chronological age. PAH is determined by dividing the current height by the corresponding decimal fraction for the patient's BA.

The RWT method calculates PAH based on the child's height (standing height was used instead of recumbent length due to the retrospective nature of data collection in this study), weight, and BA, incorporating mid-parental height and using sex- and age-specific coefficients (21). While recumbent length is generally recommended for younger children, standing height is more practical and is commonly measured in clinical practice for children older than two years. According to the World Health Organization Child Growth Standards, recumbent length is, on average, 0.7 cm greater than standing height (22). Although this small difference could theoretically affect PAH calculations, given the retrospective design of our study and the minimal variation between standing height and recumbent length, the impact on RWT prediction accuracy is expected to be negligible.

The BoneXpert method, available as a free online calculator at http://www.boneXpert.com/adult-height-predictor, is based on BA, chronological age, gender, height, father's height, mother's height, and ethnicity. For the ethnicity parameter, we selected the Caucasian European South population, as it most closely matches the Turkish population (23,24). In Türkiye, the average height is reported as 163.1 cm for females and 176.2 cm for males, whereas in the Caucasian European South population, the corresponding averages are 162 cm for females and 175 cm for males (14,25).

Ethics

This study was approved by the Local Ethics Committee of Dokuz Eylül University Faculty of Medicine (approval number: 2024/05-21, date: 07.02.2024) and performed in line with the principles of the Declaration of Helsinki. An informed written consent form was not obtained due to the retrospective nature of the study.

Statistical Analysis

Statistical analyses were conducted using Statistical Package for the Social Sciences for Windows, version 24.0 (IBM Co., Armonk, NY, USA). The normality of the data was assessed with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Clinical data were reported as numbers (%) for categorical variables, mean ± SD for continuous variables with a normal distribution, and medians with the respective 25th-75th percentile values for non-normally distributed variables. Comparisons between categorical variables were performed using the Pearson chi-square test or Fisher's exact test, as appropriate. For continuous variables, the Student's t-test was used to compare normally distributed data between the two groups, while the Mann-Whitney U test was applied for non-normally distributed data.

The interclass correlation coefficient (ICC) was used to evaluate interobserver agreement, with ICC values interpreted as follows: excellent (greater than 0.9), good (0.75 to 0.9), moderate (0.5 to 0.75), and poor (less than 0.5). The Wilcoxon signed-rank test was employed to compare two related samples, with a p value of <0.05 considered statistically significant.

Friedman's two-way analysis of variance was employed to compare differences between predicted heights and FHs. If a significant difference was found, the Bonferroni post-hoc test was conducted for pairwise comparisons, with a p value of <0.0167 considered significant, calculated using the formula $p = 0.05 \times 2/k\ (k-1)$, where k is the number of comparisons.

Results

Baseline Characteristics of Study Subjects

This study included sixty-two patients, with a mean age at diagnosis of 14.2 ± 0.8 years. Fifty-six subjects (90.3%) were born with normal birth weights, while the remaining subjects were born large for gestational age. Thirty-six patients (58.1%) had a family history of CDGP. The main reasons for presenting to pediatric endocrinology clinics were short stature (n = 56, 90.3%) and delayed puberty (n = 5, 8.1%).

The baseline characteristics of the study subjects are presented in Table 1. The mean SD scores for height and BMI were -2.1 ± 0.9 [(-3.5) - (0.3)] and -0.8 ± 1.5 [(-4.3) - (2.6)], respectively. According to their age and sex, 36 subjects (58.1%) exhibited short stature, and 12 patients (19.4%) had a low BMI at the first evaluation.

Fifteen patients (24.2%) received low-dose testosterone therapy. Patients who underwent testosterone induction therapy were older, taller, and had a higher BMI SD score compared to those who did not ($p = 0.02$, $p = 0.04$, and $p = 0.01$, respectively). However, the treated and untreated groups were similar in terms of height SD score, and testicular volume at presentation ($p = 0.4$ and $p = 0.5$, respectively) (Table 1).

Bone Age Assessment

The median BAs evaluated using the GP atlas and the BoneXpert method were 12.5 (11.5-13.0) and 12.6 (11.8-13.4) years, respectively ($p < 0.001$). For the GP atlas when determining BAs, the interobserver coefficient of variation was 0.964 (95% confidence interval 0.941-0.979). The median BA retardation was 2.0 (1.3-2.6) years when BA was assessed by the GP atlas and 1.6 (1.0-2.3) years when determined by the BoneXpert method ($p < 0.001$). The median BAs of boys, whether they were treated or not treated with testosterone, were found to be similar ($p = 0.09$ for the GP atlas and $p = 0.1$ for the BoneXpert method).

Evaluation at 12 Months of Follow-up

We had first-year data available for 36 (58.1%) patients. After a year, the mean age of these patients was 15.2 ± 0.9 years. Of these 36 patients, 13 (36.1%) received low dose testosterone treatment. The mean height SD score was -2.0 ± 1.1, while the height velocity was 7.3 ± 2.6 cm/year. The height velocity was not significantly different in boys who received testosterone treatment and those who did not (8.1 ± 2.3 cm/year vs. 6.8 ± 2.7 cm/year, $p = 0.6$). The median testicular volume was 10 (8-12) mL for all the patients. The median testicular volume in the treated and untreated groups at 12 months of follow-up was also similar ($p = 0.4$).

Characteristics of Boys at Final Height

The median age of the patients at their FH was 19.4 (18.5 to 20.3) years. They had mean target height and FH SD scores of -0.6 ± 0.6 [(-2.1) - (1.0)] and -0.6 ± 0.9 [(-2.5) - (1.4)], respectively ($p = 0.8$). The difference in SD scores between the target height and the FH was -0.04 ± 0.8 [(-2.2) - (2.0)]. Ninety-seven percent of the patients (n = 60) reached an adult height within the target height range. Adult height was less than 165 cm in only four boys (6.5%). Furthermore, there was no significant difference in the FH SD score between boys who received testosterone and those who did not ($p = 0.1$). No significant difference in target height was found between the two groups ($p = 0.5$).

Comparison of Adult Height Prediction Methods

The median PAH SD scores calculated using the BP, RWT, and BoneXpert methods were -0.5 [(-1.3) - (-0.1)], -0.6 [(-1.0) - (0.0)], and -1.1. [(-1.6) - (-0.4)], respectively. Among the PAH methods, there was no significant difference between the FH and the PAH estimated by the BP and RWT methods ($p = 0.2$ and $p = 0.6$, respectively) (Table 2). Consequently, the BP and RWT methods provided more accurate predictions for boys with CDGP. Notably, the BoneXpert method underestimated the PAH in these patients ($p < 0.001$) (Figure 1). For the BP, RWT, and BoneXpert methods, the differences between the SD scores of PAH and FH were 0.2 [(-0.4) - (0.7)], 0.03 [(-0.5) - (0.5)] and -0.4 [(-0.9) - (0.1)], respectively (Table 3). The median difference between PAH and FH for the BP and RWT methods was similar ($p = 0.2$). However, the median differences between PAH and FH for the BP and RWT methods were also significantly higher than the BoneXpert method ($p < 0.001$ and $p < 0.001$, respectively).

In the subgroup analysis of boys with delayed BA ≤2 years or >2 years, the BP and RWT methods gave better predictions in patients with delayed BA ≤2 years ($p = 0.3$ and $p = 0.4$, respectively). In this subgroup, the BoneXpert method underestimated the PAH. Furthermore, the RWT and BoneXpert methods were more accurate in predicting PAH in boys with delayed BA >2 years ($p = 0.1$ and $p = 0.1$, respectively). However, the BP method resulted in overestimation in the same subgroup (Table 4). Consequently, the RWT method was the best predictor of FH among the three different methods in boys with delayed BA of both ≤2 years and >2 years.

Table 1. The clinical and laboratory characteristics of the patients with CDGP at presentation

Clinical features	All patients (n = 62)	Patients who received testosterone induction therapy (n = 15)	Patients who did not receive testosterone induction therapy (n = 47)	p
Chronological age, years	14.2 ± 0.8	14.4 (14.1-15.2)	14.0 (13.7-14.6)	0.02[a]
Bone age by GP atlas, years	12.5 (11.5-13.0)	13.0 (11.5-13.5)	12.3 (11.5-13.0)	0.09[a]
Bone age by the BoneXpert method, years	12.6 (11.8-13.4)	13.4 (11.9-13.7)	12.4 (11.8-13.2)	0.1[a]
Height, cm	149.2 ± 7.0	152.5 ± 9.5	148.1 ± 5.8	0.04[b]
Height, SD score	-2.1 ± 0.9	-1.9 ± 1.2	-2.2 ± 0.7	0.4[b]
Body mass index, SD score	-0.8 ± 1.5	0.1 ± 1.7	-1.0 ± 1.4	0.01[b]
Target height, cm	172.3 ± 4.2	173.0 ± 4.0	172.1 ± 4.3	0.5[b]
Target height, SD score	-0.6 ± 0.6	-0.5 ± 0.6	-0.6 ± 0.7	0.5[b]
Age at final height, years	19.4 (18.5-20.3)	20.4 (19.5-22.0)	19.1 (18.3-19.8)	0.001[a]
Final height, cm	172.7 ± 5.8	174.6 ± 6.8	172.1 ± 5.3	0.1[b]
Final height, SD score	-0.6 ± 0.9	-0.3 ± 1.1	-0.7 ± 0.9	0.1[b]
Testicular volume, mL	4 (3-6)	4 (3-6)	4 (3-6)	0.5[a]
< 4 mL, [n (%)]	34 (54.8%)	5 (33.3%)	24 (51.1%)	0.3[c]
4-6 mL, [n (%)]	28 (45.2%)	10 (66.7%)	23 (48.9%)	
Tanner stage (pubic hair)				
Stage 1 [n (%)]	24 (38.7%)	5 (33.3%)	19 (40.4%)	0.8[c]
Stage 2 [n (%)]	37 (59.7%)	10 (66.7%)	27 (57.4%)	
Stage 3 [n (%)]	1 (1.6%)	0 (0%)	1 (2.1%)	
Stage 4 [n (%)]	0 (0%)	0 (0%)	0 (0%)	
Stage 5 [n (%)]	0 (0%)	0 (0%)	0 (0%)	
Laboratory				
FSH, mIU/mL	2.3 (1.6-2.9) **n = 42**	1.9 (1.2-2.8) **n = 15**	2.5 (1.7-3.3) **n = 27**	-[d]
LH, mIU/mL	0.8 (0.6-1.0) **n = 42**	0.7 (0.4-0.8) **n = 15**	0.8 (0.7-1.5) **n = 27**	-[d]
Total testosterone, ng/dL	19.4 (14.2-25.9) **n = 42**	19.4 (15.0-31.0) **n = 15**	19.2 (12.5-24.9) **n = 27**	-[d]
Peak LH, mIU/mL	13.0 (9.7-21.4) **n = 12**	14.8 (9.1-21.7) **n = 10**	11.8* **n = 2**	-[d]

Data are presented as mean ± standard deviation for normal distribution and median (25^{th}-75^{th} percentile) for those not distributed normally. [a]Mann-Whitney U test, [b]Student's t-test, [c]Pearson chi-square test; $p < 0.05$.
[d]Statistical comparisons could not be performed due to missing data.
*For peak LH, only two patients were included; therefore, only the mean value is presented.
GP: Greulich-Pyle, SD score: standard deviation score, FSH: follicle-stimulating hormone, LH: luteinizing hormone, CDGP: constitutional delay of growth and puberty

Discussion

In the literature, there is uncertainty about whether boys with CDGP can achieve their target height, regardless of whether they receive low-dose testosterone induction therapy or not. Moreover, studies evaluating adult height prediction methods for this population often show conflicting results, partly due to limited patient numbers. To address this issue, we collected data from a relatively large group of patients and compared the accuracy of the BP, RWT, and BoneXpert methods. Our findings indicated that the mean FH SD scores of boys with and without pubertal induction were similar, and the majority of patients were able to reach their target heights. Furthermore, this study demonstrated that the RWT method was more effective than other methods for estimating adult height in boys with delayed BA, regardless of whether the delay was ≤2 years or > 2 years.

Pharmacological induction of puberty to accelerate the pubertal growth spurt and enhance statural outcomes in boys with CDGP remains contentious. While some researchers suggest that this therapy negatively impacts FH (25), other studies indicate no significant effect of testosterone treatment on FH or PAH in boys with CDGP (8,26,27,28). For instance, Arrigo et al. (8) found no significant difference in FH between boys with CDGP who received low-dose testosterone therapy and those who did not, with similar height SD scores at diagnosis. Similarly, Kelly et al. (28) observed no significant difference in FH

Table 2. Comparison of final heights and predicted heights in boys with CDGP

	Final height	PAH (bone age assessed by the GP atlas)			PAH (bone age assessed by BoneXpert)
		BP	RWT	BoneXpert	BoneXpert
Height, cm	172.0 (168.0-177.0)[a,b]	173.4 (168.5-177.7)	172.4 (169.5-176.2)	170.7 (168.0-175.4)[a]	169.4 (166.6-174.0)[b]
Height, SD score	-0.7 [(-1.3)-(0.1)][c,d]	-0.5 [(-1.3)-(-0.1)]	-0.6 [(-1.0)-(0.0)]	-0.9 [(-1.3)-(-0.1)][c]	-1.1. [(-1.6)-(-0.4)][d]

Data are given as median (25th-75th percentile)

[a-d] values with the same letter designation were different in the Wilcoxon signed-rank test, at a p value of < 0.05.
Height, cm: Final height vs PAH (BoneXpert; bone age assessed by GP atlas), [a]$p = 0.01$; Final height vs PAH (BoneXpert; bone age assessed by BoneXpert), [b]$p < 0.001$.
Height, SD score: Final height vs PAH (BoneXpert; bone age assessed by GP atlas), [c]$p = 0.01$; Final height vs PAH (BoneXpert; bone age assessed by BoneXpert), [d]$p < 0.001$.
PAH: predicted adult height, GP: Greulich-Pyle, BP: Bayley-Pinneau, RWT: Roche-Wainer-Thissen, SD score: standard deviation score, CDGP: constitutional delay of growth and puberty

Table 3. Comparison of the difference between predicted heights and final heights

	Bone age assessed by the GP atlas			Bone age assessed by BoneXpert	
	BP	RWT	BoneXpert	BoneXpert	p*
PAH-FH difference, cm	1.3 [(-2.5)-(4.3)][a,b]	0.2 [(-2.9)-(2.6)][c,d]	-1.6 [(-4.4)-(2.0)][a,c,e]	-2.7 [(-5.7)-(0.6)][b,d,e]	< 0.001
PAH-FH difference, SD score	0.2 [(-0.4)-(0.7)][f,g]	0.03 [(-0.5)-(0.5)][h,i]	-0.3 [(-0.7)-(0.3)][f,h,j]	-0.4 [(-0.9)-(0.1)][g,i,j]	< 0.001

Data are given as median (25th-75th percentile). *Friedman's two-way analysis of variance.
[a-u]Values with the same letter designation were different in the post-hoc analysis of pairwise groups, at a p value of < 0.008. [a]$p = 0.001$, [b]$p < 0.001$, [c]$p = 0.001$, [d-j]$p < 0.001$.
FH: final height, PAH: predicted adult height, GP: Greulich-Pyle, BP: Bayley-Pinneau, RWT: Roche-Wainer-Thissen, SD score: standard deviation score

between the treated and untreated groups; however, they noted that the FHs of treated boys were closer to their genetic target heights compared to untreated boys, whose FHs were below their target heights. Consistent with these findings, our study also demonstrated no significant difference in FH SD scores between treated and untreated boys, suggesting that testosterone therapy neither improves nor impairs FH outcomes in boys with CDGP. Notably, even high-dose testosterone therapy has been reported to have no significant effect on the height-for-BA SD score, as shown by Büyükgebiz (29), further supporting the conclusion that testosterone therapy does not significantly influence FH outcomes in boys with CDGP.

Several studies have demonstrated that patients with CDGP may not reach their genetic target height (7,30,31). Poyrazoğlu et al. (7) reported that the FH of patients with CDGP was below their target height, with 46.3% of patients unable to attain their target height. Similarly, in a study of 15 boys, Rohani et al. (30) found that the FHs of the subjects were considerably less than their target heights (165.7 ± 2.89 cm vs. 171.8 ± 4.65 cm). In contrast, von Kalckreuth et al. (6) noted that their patients achieved their genetic target height without needing growth-stimulating therapy. In another retrospective study evaluating boys with CDGP, it was reported that the FHs of the patients were similar to their target heights. In addition, among those who did not undergo testosterone therapy, 3 out of 27 patients did not reach their target height, while only 1 out of 22 treated patients failed to reach their target height (8). In the present

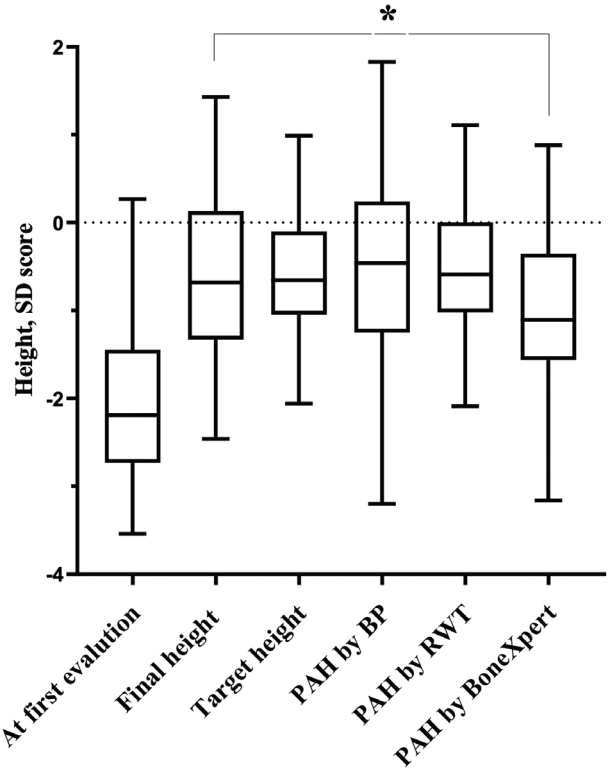

Figure 1. Comparison of predicted adult heights, target heights, and final heights in boys with CDGP

**Wilcoxon signed-rank test, $p < 0.05$.*

PAH: predicted adult height, BP: Bayley-Pinneau, RWT: Roche-Wainer-Thissen, SD score: standard deviation score, CDGP: constitutional delay of growth and puberty

Table 4. Comparison of predicted heights and final heights based on the bone age delay

	Bone age assessed by the GP atlas				Bone age assessed by BoneXpert	
	Final height (n = 31)	**BP (n = 31)**	**RWT (n = 31)**	**BoneXpert (n = 31)**	**Final height (n = 39)**	**BoneXpert (n = 39)**
Delayed bone age ≤2 years						
Height, cm	175.0 (168.5-175.7)[a]	172.4 (167.4-177.5)	172.7 (170.1-177.3)	171.0 (168.2-175.7)[a]	174.0 (168.5-178.5)[c]	169.8 (166.3-174.8)[c]
Height, SD score	-0.2 [(-1.3)-(-0.1)][b]	-0.6 [(-1.4)-(0.2)]	-0.6 [(-1.0)-(0.2)]	-0.8 [(-1.3)-(-0.1)][b]	-0.4 [(-1.3)-(0.4)][d]	-1.0 [(-1.6)-(-0.2)][d]
	Final height (n = 31)	**BP (n = 31)**	**RWT (n = 31)**	**BoneXpert (n = 31)**	**Final height (n = 23)**	**BoneXpert (n = 23)**
Delayed bone age >2 years						
Height, cm	170.0 (167.6-175.0)[e]	173.5 (170.5-179.0)[e]	171.6 (169.0-175.2)	170.4 (167.5-174.2)	170.0 (167.1-174.0)	168.7 (166.8-173.9)
Height, SD score	-1.0 [(-1.4)-(-0.2)][f]	-0.4 [(-0.9)-(-0.5)][f]	-0.6 [(-1.1)-(-0.2)]	-0.9 [(-1.4)-(-0.3)]	-1.0 [(-1.5)-(-0.4)]	-1.2 [(-1.5)-(-0.4)]

Data are given as median (25th-75th percentile).
[a-d]Values with the same letter designation were different in the Wilcoxon signed-rank test, at a p value of < 0.05.
[a]$p = 0.02$, [b]$p = 0.02$, [c]$p < 0.001$, [d]$p < 0.001$, [e]$p = 0.003$, [f]$p = 0.003$.
GP: Greulich-Pyle, BP: Bayley-Pinneau, RWT: Roche-Wainer-Thissen, SD score: standard deviation score

study and consistent with previous research, we found no significant difference between the FH and the target height. Most of our cohort reached an adult height within their expected target range. Only four boys had an adult height below 165 cm, reflecting familial height characteristics and influences.

There are published data comparing adult height prediction methods for boys with CDGP (5,6,7,8,9,11,28). For instance, a study involving 14 male patients with CDGP found that height predictions using the BP method (173.9 ± 7.5 cm) were highly accurate when compared to the FH (171.3 ± 5.3 cm) (6). In the study by Arrigo et al. (8), no significant differences were found between the final adult height and the PAH calculated using the BP method in both testosterone-induced and non-induced groups. However, they observed discrepancies greater than ± 5 cm between FH and PAH in 33% of non-induced subjects and 23% of induced subjects. Kelly et al. (28) suggested that the Tanner and Whitehouse RUS (TW2) method is useful and accurate. They observed that the FHs of boys with CDGP were closely related to the estimated heights, with only three patients having FHs below the predicted range. According to Poyrazoğlu et al. (7), the BP method provided a very reliable estimation of adult height compared to the TW method.

Our findings indicated that the RWT method outperformed other methods in estimating adult height for boys with delayed BA, irrespective of whether the delay was ≤2 years or >2 years. Consistent with this, Brämswig et al. (9) concluded that the RWT method was the most accurate, while the BP method overestimated adult height in their cohort of 37 boys with untreated short stature and CDGP. Similarly, Reinehr et al. (11) reported that the BP method overestimated adult height, particularly in boys with a delayed BA of 2 years or more. To address this, they developed a new prediction model specifically for patients with CDGP, which they stated had a good predictive capability for subjects with retarded BA.

In contrast, Unrath et al. (5) found that the BoneXpert method, which incorporates parents' heights, was more accurate in predicting FHs than the BP method in a cohort including boys with CDGP. Their study compared automated BA assessments using the BoneXpert software with manual BA assessments performed with the GP method. When the mean of BAs, blindly re-evaluated by three experienced pediatric endocrinologists, was considered the 'Reference' BA, it was found to be closer to the manual BA than the automated BA. The automated BA slightly overestimated BA, while the manual BA values were generally lower than the reference BA. Furthermore, using manual BA instead of automated BA in the BoneXpert adult height prediction calculator resulted in a slightly weaker, but still good, performance.

These studies have shown varying results for height prediction models in boys with CDGP. In the present study, the PAH estimated using both the BP and RWT methods was very closely aligned with, and was not significantly different from, the FH. In contrast, the BoneXpert method, whether using manual or automated BA assessments, underestimated the PAH in these patients. This underestimation may be attributed to several factors. First, BoneXpert relies on generalized growth models that may not fully account for the dynamic and individualized growth patterns of boys with CDGP, particularly those with delayed bone maturation and pubertal onset (5). Second, as observed in both our study and the findings of Unrath et al. (5), automated methods like BoneXpert tend to slightly overestimate BA compared to manual assessments, leading to discrepancies in adult height predictions. Furthermore,

our study found a significant difference between the median BAs obtained through manual and automated methods, with the automated BA consistently being more advanced. This discrepancy highlights that automated systems like BoneXpert may have inherent margins of error, despite their standardization and efficiency, raising questions about their reliability. Future studies with larger sample sizes are needed to refine these models and enhance their predictive accuracy and clinical applicability.

BA retardation may result in inaccuracies in adult height predictions. Notably, in the studies cited above, the commonly used BP method tends to overestimate adult height in boys with CDGP (9,11). In the present study, the BP and RWT methods were found to be more accurate for individuals with a delayed BA of less than two years. However, for boys with a BA delayed by more than two years, the BP method tended to overestimate, consistent with findings from previous studies. Conversely, the RWT and BoneXpert methods were found to be more reliable for these patients. This study demonstrated that the RWT method is the most accurate predictor of adult height, regardless of the magnitude of delay in BA in boys with CDGP. Its incorporation of multiple growth parameters, including height, weight, mid-parental height, and sex- and age-specific coefficients, likely accounts for its superior performance, particularly in patients with complex and variable growth patterns. In summary, these findings highlight the clinical utility of the RWT method as a reliable and precise tool for estimating adult height in boys with CDGP, even in the presence of delayed BA.

Study Limitations

The current study has several limitations. First, the inclusion criteria for study participants were somewhat extended to increase the sample size. In addition, the patients were recruited from different centers, resulting in a heterogeneous population; some patients received testosterone therapy, while others did not. Medical therapy was administered specifically to adolescents experiencing psychological challenges. Furthermore, there is inter- and intra-observer variability in the manual assessment of BA. Nonetheless, all radiographs were re-evaluated by two experienced pediatric endocrinologists, who demonstrated excellent agreement in BA determinations. Finally, the RWT method was originally designed for calculation using recumbent length, but due to the retrospective nature of the study, we used standing height measurements instead. Standing height is approximately 0.7 cm less than the recumbent length in children over two years old, which may affect RWT-based predictions.

Conclusion

In conclusion, the present study showed that low-dose testosterone induction therapy did not negatively impact FH, and both treated and untreated boys attained heights in line with their genetic target heights. Furthermore, the RWT method appears to be more suitable for accurate height estimation, especially in conditions such as CDGP, which is characterized by delayed BA. Future research should focus on developing disease-specific prediction models that offer superior advantages over traditional methods for predicting adult height in boys with CDGP.

Ethics

Ethics Committee Approval: This research complies with the guidelines for human studies and is conducted ethically following the World Medical Association Declaration of Helsinki. Institutional approval was granted by the Ethics Committee of Dokuz Eylül University Faculty of Medicine (approval number: 2024/05-21, date: 07.02.2024).

Informed Consent: An informed written consent form was not obtained due to the retrospective nature of the study.

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Footnotes

Authorship Contributions

Concept: Gözde Akın Kağızmanlı, Ayhan Abacı, Design: Gözde Akın Kağızmanlı, Korcan Demir, Ece Böber, Ahmet Anık, Samim Özen, Ayhan Abacı, Data Collection or Processing: Gözde Akın Kağızmanlı, Deniz Özalp Kızılay, Reyhan Deveci Sevim, Kübra Yüksek Acinikli, Fulya Mete Kalaycı, Ayşegül Tekneci, Analysis or Interpretation: Gözde Akın Kağızmanlı, Korcan Demir, Ahmet Anık, Samim Özen, Ayhan Abacı, Literature Search: Gözde Akın Kağızmanlı, Korcan Demir, Ece Böber, Ayhan Abacı, Writing: Gözde Akın Kağızmanlı, Korcan Demir, Ayhan Abacı.

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The Effect of Problematic Internet Use, Internet Gaming Disorder and Cyberbullying/Victimization Levels on Self-esteem in Obese Adolescents

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What is already known on this topic?

Studies have been conducted on problematic internet use, internet gaming disorder (IGD), self-esteem, and levels of cyberbullying/victimization among obese adolescents.

What this study adds?

In the present study, cyberbullying/victimization and withdrawal symptoms of IGD may be associated with self-esteem in obese adolescents. This is the first study to investigate the relationship between problematic technology use and self-esteem in obese adolescents.

Abstract

Objectives: To compare the levels of problematic internet use, self-esteem, internet gaming disorder (IGD) and cyberbullying/victimization in adolescents diagnosed with obesity with a control group and to examine the relationship between these variables and self-esteem.

Methods: Adolescents with and without obesity were recruited. The relationship between the scales of Problematic Internet Use, Cyberbullying/Victimization, IGD and the Piers-Harris Self-Esteem Scale was analyzed using linear regression methods.

Results: The study included a total of 164 adolescents (115 females; 70.1%). Of these, 93 (56.7%) were diagnosed with obesity (female n = 64; 68.8%). Self-esteem in adolescents diagnosed with obesity was lower compared to healthy controls ($p < 0.001$), and problematic internet use was higher in obese individuals compared to healthy controls ($p = 0.011$), although no difference was found between the groups in terms of IGD ($p = 0.494$) and cyberbullying/victimization ($p = 0.706$) levels. In obese individuals, cyber forgery ($p = 0.003$; $\beta = -0.103$) and verbal cyberbullying victimization ($p = 0.032$; $\beta = -0.057$), IGD withdrawal subscales ($p = 0.03$; $\beta = -0.084$), and total scores on the cyberbullying scale ($p = 0.017$; $\beta = -0.289$) were found to negatively affect self-esteem.

Conclusion: These findings suggest that taking measures to reduce problematic internet use, IGD, and cyberbullying/victimization in obese adolescents may be a protective measure for self-esteem and, consequently, mental health.

Keywords: Obese adolescents, self-esteem, problematic internet use, internet gaming disorder, cyberbullying/victimization

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Introduction

Obesity is a significant public health problem for both developed and developing countries (1). The prevalence and severity of obesity are reported to be increasing dramatically in children and adolescents in some populations (2). Obesity in childhood is associated with cardiometabolic and psychosocial comorbidities (3). In contemporary times, the increased use of technology has led to adolescents spending a proportion of their time online, thereby exposing them to environmental factors that undermine their self-esteem. Specifically, problematic internet use, cyberbullying, cyber victimization, and internet gaming addiction may pose significant issues that adversely affect the self-esteem of obese individuals.

Self-esteem refers to the way individuals perceive and value themselves (4). Specifically, it is the extent to which a person believes in their own talents, significance, success, and worth. The relationship between obesity and low self-esteem has been demonstrated in various studies (5,6,7). Low self-esteem in overweight adolescents may play an important role in the development of a range of mental disorders, such as inappropriate eating and dieting behaviors, depression, anorexia nervosa, bulimia nervosa, anxiety, violent behavior, and substance abuse (8,9). These findings suggest that maintaining self-esteem may help prevent the onset of psychopathology in individuals diagnosed with obesity.

A negative self-concept may trigger problematic internet use and internet gaming disorder (IGD). Problematic internet use is generally defined as the problematic, compulsive use of the internet, which in turn causes significant dysfunction in various life domains of the individual over a long period of time (10). There is a negative relationship between self-esteem and internet addiction (11). It has been reported that for every unit increase in self-esteem, the likelihood of internet addiction decreases by 11 % (12). Moreover, it has been demonstrated that individuals with low self-esteem spend more time on the internet compared to others (13,14). Furthermore, research examining the relationship between body weight and internet use has reported that adolescents with problematic internet use are more likely to be obese or overweight (15,16,17).

Digital game addiction is described as children's continuous playing of games, associating the game with real life, preferring gaming over other activities, and avoiding their real-life responsibilities (18). Low self-esteem has been commonly reported to be associated with gaming and other internet-related disorders (19,20,21). Individuals with IGD are attracted to games because gaming fosters experiences of power and autonomy, thereby enhancing self-esteem (22). Furthermore, pathological gamers tend to overvalue game rewards, activities, identities (avatars), or other elements, which promotes increased gaming engagement and a diminished interest in less appealing, real-life activities (22). Avatars (simulated identities within a game) can amplify feelings of power and strength and facilitate an escape from real-life problems (22). A recent review of self-esteem in gaming disorders has shown a negative relationship between gaming disorders and physical and academic self-esteem (23).

Young people are spending increasing amounts of time using digital technology and, as such, are at great risk of being involved in cyber bullying as a victim, bully, or bully/victim (24). Cyberbullying is the use of information and communication technology in a deliberate, repetitive, and hostile manner to harass and harm (25). Cyberbullying actions include threatening and spreading rumors, sharing other people's private information, and promoting social isolation and exclusion (26). Studies examining the relationship between cyberbullying and obesity have reported contradictory findings (27,28). However, the negative association between cyberbullying victimization and self-esteem has been reported in various studies (29,30).

The aim of this study was to evaluate self-esteem, problematic internet use, IGD, and cyberbullying/victimization levels in adolescents with obesity and to compare them with a control group. In addition, a further aim was to evaluate the relationship between these variables (problematic internet use, cyberbullying/victimization, IGD and self-esteem. We hypothesize that adolescents with obesity will have higher levels of problematic internet use, IGD, and cyberbullying/victimization, compared to controls, and that their self-esteem will be lower compared to controls, and that these variables may be independently associated with the self-esteem of obese adolescents.

Methods

Subjects

Between March 2022 and September 2022, the eligibility of adolescents diagnosed with obesity who attended the Pediatric Endocrinology Clinic of Süleyman Demirel University Faculty of Medicine Hospital was assessed according to inclusion and exclusion criteria.

The inclusion criteria for the obesity group were: (1) aged between 12 and 18 years; (2) a body mass index (BMI) percentile value ≥95th; and (3) informed consent given by the adolescent and parent. According to reference curves for Turkish children and adolescents, patients with a BMI of

≥95th percentile were accepted as obese (31). All participants were evaluated by a pediatric endocrinology specialist and a child psychiatry specialist. Patients with obesity due to syndromic and endocrinological causes and those taking medications that can cause obesity (e.g., glucocorticoids, anticonvulsants such as carbamazepine and valproate, antidepressants, antipsychotics, or antihistamines) were excluded from the study. In addition, patients with a major psychiatric disorder, such as intellectual disability, autism spectrum disorder, bipolar disorder, or schizophrenia and/or a history of psychiatric drug use were excluded from the present study.

The healthy control group was formed from the children who applied to our outpatient clinic for consultancy services and who did not have any psychiatric complaints or history. The inclusion criteria for the healthy control group were: (1) aged 12-18 years; (2) BMI ≥5th to <85th percentile; and (3) informed consent given by the adolescent and parent. The exclusion and inclusion criteria were the same for the control group, except for the presence of obesity. Similarly to the obesity group, all participants in the healthy control group were evaluated by both a pediatric endocrinology specialist and a child psychiatry specialist.

The study was approved by the Ethics Committee of Süleyman Demirel University Faculty of Medicine (protocol no: 72867572.050.01.04-216193, date: 11.02.2022). Written informed consent was obtained from the participants and their families.

Procedures

Measures/Instrumentation

The sociodemographic characteristics of all participants were assessed using a sociodemographic data form developed by the authors. In addition, using this form, the authors recorded information on internet and social media use duration, total internet connection time, parental online control, and the use of a filtering program. In this single-center, cross-sectional study, data was collected using the Turkish language versions of the Piers-Harris Self-Esteem Scale (PHCSES) (32), Problematic Internet Use Scale (PIUS) (33), Cyber Victim and Bullying Scale (34), and the Internet Gaming Disorder Scale (IGDS) (35). These scales were administered to adolescents in both the patient and control groups, and the data between the groups were compared.

Piers-Harris Children's Self-Esteem Scale: PHCSES is also referred to as "Thoughts About Myself". A high score indicates a positive self-concept, while a low score indicates a negative self-concept. The scale consists of six sub-scales. The sub-scales are as follows: 1. Happiness-satisfaction, 2. Anxiety, 3. Popularity, social approval, and being favored, 4. Conduct and compliance, 5. Physical appearance, 6. Mental and school status. The Turkish validity-reliability study of the scale was conducted by Öner (32,36).

Problematic Internet Use Scale-Adolescent: PIUS-A consists of three subscales: negative consequences of internet (NCI), social benefit/social comfort and excessive usage (EU). High scores from the scale indicate a high level of PIU. The validity-reliability study of the scale was conducted by Ceyhan and Ceyhan (33).

Cyber Victim and Bullying Scale: The cyberbullying and victimization form consists of three sub-dimensions: Cyber Forgery (CF-10 items), Cyber Verbal Bullying (CVB-7 items), and Hiding Identity (HI-5 items). The validity and reliability study of the scale developed by Çetin et al. (34) has been conducted on adolescents.

Internet Gaming Disorder Scale: The IGDS was developed by Pontes et al. (37). In this scale, (1) salience, (2) mood modification, (3) tolerance, (4) withdrawal symptoms, (5) conflict, and (6) relapse are assessed with 20 items. Cases scoring 69 or above are defined as having a disorder, while those scoring 60 or above are classified as being at risk. The Turkish validity and reliability of the scale was conducted by Çakıroğlu and Soylu (35).

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normality of data distribution. Continuous variables were compared between groups using the Student's t-test or Mann-Whitney U test based on the distribution characteristics of the data. The chi-square test was employed to compare categorical variables. Descriptive statistics for categorical variables are presented as frequencies (n), while continuous variables were summarized using means and standard deviations for normally distributed data or medians and interquartile ranges, defined as the range between the 25th percentile (p25) and the 75th percentile (p75), for non-normally distributed data. Linear regression analysis was used to examine associations between clinical variables and self-esteem. The significance level was set at $p < 0.05$ for all analyses.

A post-hoc power analysis was performed using G*Power 3.1.9.7 to assess the statistical power of the study for comparing two independent groups ($\alpha = 0.05$, Cohen's $d = 0.50$, group 1 sample size = 93, group 2 sample size = 71). The analysis indicated that the study had approximately 88% statistical power based on the Student's t-test.

Results

A total of 164 adolescents aged 12-18 years, of whom 115 (70.1%) were included in the study. There were 93 patients in the obesity group (64 females; 68.8%), the average age was 15.2 ± 1.5 years, while in the control group consisting of 71 adolescents (51 female; 71.8%), the mean age was 15.6 ± 1.6 years. There was no difference between gender and age in these groups. The mean BMI percentile for the obese group was 98.8 ± 1.5, while that of the control group was 29.4 ± 26.4. The demographic characteristics of obese adolescents and controls are given in Table 1.

The total PHCSES score of the obesity group was significantly lower than that of the healthy control group (Table 2). The obesity group scored lower than the control group for the PHCSES sub-scales of physical appearance, behavior, popularity, anxiety, and happiness satisfaction (Table 2). In the obesity group, the total PIUS score and the PIUS sub-scale scores NCI and EU were significantlyt worse than in the healthy control (Table 2). No difference was found between the groups in the total scores of IGDS, CVBS, and their sub-scale scores (Table 2).

Compared to the healthy control group, the obesity group spent significantly more time on the internet and using social media (Table 3). Internet use at night was more prevalent in the obese group (30.1%; n = 28) than in the control group (16.9%; n = 12) (Table 3).

When comparing the monitoring of internet use by family members and the use of filtering programs for internet access between the obesity and control groups, no significant difference was found between the groups (Table 3).

Table 4 shows the results of linear regression analysis of psychiatric scale scores that are thought to be effective on self-esteem in the obesity group. The PHCSES was used as the dependent variable while PIUS-A, IGD, CV, CB scale sub-scores, BMI percentiles, gender, and time spent on the internet were taken as independent variables. The analysis showed that the CV-CF sub-scale (p = 0.003; β = -0.103), CV-CVB sub-scale (p = 0.032; β = -0.057), and the IGD-withdrawal sub-scale (p = 0.03; β = -0.084) were identified as factors that decrease self-esteem in the obesity group.

Table 5 presents the results of the linear regression analysis using the Enter method for the total scores of psychiatric scales that we hypothesized could have an effect on self-esteem in the obesity group. While the PHCSES was taken as the dependent variable, the total scores of the scale were taken as the independent variable. The analysis indicated that the total CB score (p = 0.017; β = -0.289) was a negative predictor of self-esteem in the obesity group.

Table 1. Demographic features of adolescents with obesity and control subjects

	Obesity (n = 93)	Controls (n = 71)	x^2, t, z	p value
BMI percentile (mean ± SD)	98.82 ± 1.54	29.45 ± 26.48	6.345[b]	< 0.001
Age, years (mean ± SD)	15.2 ± 1.5	15.6 ± 1.6	-1.803[b]	0.073
Gender (M/F)	29/64	20/51	0.175[a]	0.676

[a]Chi-square test; [b]Student's t-test; Mann-Whitney-U test.
BMI: body mass index, SD: standard deviation, M: male, F: female

Table 2. Clinical characteristics of the groups

	Obesity (n = 93)	Controls (n = 71)	t/z	p value
PHCSES				
Total (IQR; median [p25-p75])	49 [40-58.5]	59 [48-64]	-3.660[a]	< 0.001
Mental state (mean ± SD)	3.81 ± 1.75	4.28 ± 1.73	-1.691[b]	0.093
Physical appearance (IQR; median [p25-p75])	5 [3-7]	7 [4-8]	-2.660[a]	0.009
Behaviour (mean ± SD)	10.66 ± 3.06	12.05 ± 2.41	-3.125[b]	0.002
Popularity (IQR; median [p25-p75])	8 [5.5-10]	9 [7-11]	-2.916[a]	0.004
Anxiety (mean ± SD)	5.52 ± 2.80	6.73 ± 3.10	-2.603[b]	0.011
Happiness satisfaction (IQR; median [p25-p75])	8 [4-10]	9 [6-11]	-2.539[a]	0.012
PIUS-A				
Total (IQR; median [p25-p75])	41 [25.5-50.5]	36 [26-47]	-2.551[a]	0.011
NCI (IQR; median [p25-p75])	28 [20-38]	24 [18-30]	-2.267[a]	0.023
EU (IQR; median [p25-p75])	21 [16-24]	18 [15-22]	-2.359[a]	0.018
SB/SC (mean ± SD)	15.95 ± 6.73	14.52 ± 6.12	1.407[b]	0.161

Table 2. Continued

	Obesity (n = 93)	Controls (n = 71)	t/z	p value
IGDS				
Total (mean ± SD)	41.29 ± 16.11	39.52 ± 16.73	0.685[b]	0.494
Salience (mean ± SD)	5.80 ± 3.05	5.54 ± 3.18	0.524[b]	0.601
Mood (mean ± SD)	7.98 ± 3.11	7.49 ± 3.10	1.012[b]	0.313
Tolerance (mean ± SD)	5.81 ± 2.96	5.81 ± 3.05	0.001[b]	0.999
Withdrawal (mean ± SD)	5.46 ± 3.09	5.28 ± 2.87	0.382[b]	0.703
Conflict (mean ± SD)	10.32 ± 4.17	10.02 ± 4.18	0.449[b]	0.654
Recurrence (mean ± SD)	5.89 ± 3.00	5.35 ± 2.79	1.175[b]	0.242
CVBS				
CB-total (mean ± SD)	25.76 ± 6.45	25.40 ± 5.25	0.378[b]	0.706
CV-total (mean ± SD)	28.18 ± 11.1	27.35 ± 7.6	0.263[b]	0.592
CVB-CB (mean ± SD)	8.52 ± 2.97	8.46 ± 2.77	0.136[b]	0.892
CVB-CV (mean ± SD)	9.33 ± 4.25	9.14 ± 3.37	0.313[b]	0.755
HI-CB (mean ± SD)	6.31 ± 2.03	6.36 ± 2.07	-0.867[b]	0.867
HI-CV (mean ± SD)	6.7 ± 3.3	6.5 ± 2.4	0.436[b]	0.663
CF-CB (mean ± SD)	10.92 ± 2.96	10.57 ± 1.40	0.913[b]	0.363
CF-CV (Mean ± SD)	12.13 ± 5.06	11.7 ± 3.40	0.625[b]	0.533

[a]Mann-Whitney U test; [b]Student's t-test.
Interquartile ranges (IQR), defined as the range between the 25th percentile (p25) and the 75th percentile (p75). Bold values represent significant results.
PHCSES: Piers-Harris Children's Self-Esteem Scale, PIUS-A: Problematic Internet Use Scale-Adolescent, NCI: negative consequences of internet, SB/SC: social benefit/social comfort, EU: excessive usage, IGDS: Internet Gaming Disorder Scale, CVCB: Cyber Victim and Bullying Scale, CF: cyber forgery, CVB: cyber verbal bullying, HI: hiding identity, SD: standard deviation

Table 3. Comparison of the obesity and control groups internet and social media usage times, internet connection times, and supervision of internet use by family members

		Obesity (n = 93)	Controls (n = 71)	x²	p value
Internet usage time	Less than 1 hour (%)	1 (1)	4 (5)	37,410	< 0.001
	1-3 hours (%)	21 (22.5)	42 (59.1)		
	More than 3 hours (%)	71 (76.3)	25 (35.2)		
Social media usage time	Less than 1 hour (%)	24 (25.8)	25 (35.2)	11.610	0.021
	1-3 hours (%)	33 (35.4)	35 (49.2)		
	More than 3 hours (%)	36 (38.7)	11 (15.4)		
Internet connection time	Morning (%)	3 (3.2)	2 (2.8)	9.689	0.021
	Mid day (%)	23 (24.7)	10 (14)		
	Evening (%)	39 (41.9)	47 (66.1)		
	Night (%)	28 (30.1)	12 (16.9)		
Family control online	Yes (%)	32 (34.4)	31 (43.6)	1.457	0.227
	No (%)	61 (65.5)	40 (56.3)		
Filter program entity	Yes (%)	13 (13.9)	17 (23.9)	2.675	0.102
	No (%)	80 (86)	54 (76)		

Chi-square test. Bold values represent significant results

Table 4. Regression analyses of factors affecting Piers-Harris Self-Esteem Scale in obese adolescents

	Unstandardized coefficients	Standardized coefficients		95% confidence interval for B	
	B	Beta	p	Lower bound	Upper bound
CV-CF	-0.270	-0.103	0.003	-0.441	-0.099
CV-CVB	-0.177	-0.057	0.032	-0.336	-0.018
IGD-withdrawal	-0.358	-0.084	0.030	-0.674	-0.042

$F = 176.836$, $df = 28$, $p < 0.001$, adjusted $R^2 = 0.982$.
CV: cyber victim, CF: cyber forgery, CVB: cyber verbal bullying, IGD: internet gaming disorder

Table 5. Regression analyses of the total scores of scales affecting Piers-Harris Self-Esteem Scale in obese adolescents

	Unstandardized coefficients	Standardized coefficients		95% confidence interval for B	
	B	Beta	p	Lower bound	Upper bound
CB total	-0.589	-0.289	0.017	-1.063	-0.115
CV total	-0.069	-0.059	0.642	-0.359	0.221
PIUS total	-0.122	-0.188	0.270	-0.338	0.094
IGDS total	-0.066	-0.079	0.493	-0.254	0.122

$F = 2.927$, $df = 16$, $p < 0.001$, adjusted $R^2 = 0.630$.
CV: cyber victim, CF: cyber forgery, PIUS: Problematic Internet Use Scale, IGDS: Internet Gaming Disorder Scale

Discussion

The present study showed that adolescents diagnosed with obesity exhibited lower self-esteem compared to healthy controls, while problematic internet use was higher among obese individuals relative to healthy controls. However, no differences were found between groups regarding IGD and cyberbullying/victimization levels. To the best of our knowledge, this study is the first to examine the relationship between problematic internet use, IGD, and cyberbullying/victimization with self-esteem in obese adolescents. Significant findings were identified that both confirm and extend existing research in this area. In obese individuals, CF and verbal cyberbullying victimization, IGD withdrawal subscales, and total scores on the cyberbullying scale were found to be factors negatively affecting self-esteem.

Self-esteem refers to a person's self-evaluation or attitude towards themselves and is a fundamental aspect of mental health (8,38). In a study of 2,813 Australian children (average age: 11.3 years), obese children showed significantly lower athletic competence, physical appearance, and overall self-esteem compared to their normal-weight peers (39). A review of the literature reveals that self-esteem is impaired in obese adolescents in nearly all studies (40). In the present study, similar to the existing literature, it was found that obese adolescents had significantly lower scores in physical appearance, behavior, popularity, anxiety, happiness satisfaction sub-scales, and overall self-esteem compared to the control group. Overweight/obese children tend to encounter more social pressure and negative events, such as peer aggression, teasing, and bullying outside of their homes (41,42). These experiences can often lead to the development of low self-esteem in children with obesity.

IGD prevalence rates vary between 0.6% to 50% across studies conducted in different countries (43,44). Başdaş and Özbey (45) found that adolescents diagnosed with obesity have higher digital game addiction scores compared to a control group. These authors suggested that adolescents who allocate more time to digital games sit for longer periods and thus are less physically active. Being male has been shown to be a risk factor for IGD in various studies. In a study conducted with 1,556 students in Korea, it was shown that males play online games three times more than females (46). In the present study, no significant difference was found between adolescents diagnosed with obesity and the control group in terms of IGD. In the obese group 15% of the adolescents and 14% in the control group showed symptoms of risky internet gaming, with IGD being identified in 0.4% of the adolescents in the obesity group. In the present study, the prevalence of IGD was found to be lower than in other studies in the literature. This may have been because more than 2/3 of the sample group in our study was composed of girls, and that IGD was more commonly seen in boys, may have resulted in no significant difference being found between the groups in our study and the apparently low prevalence of IGD. We found that withdrawal symptoms of IGD were found to be a negative predictor of self-esteem in obese adolescents. Withdrawal symptoms are the negative emotions and/or physical effects that arise when gaming is suddenly stopped or reduced (47). It has also been found that low self-esteem triggers pathological gaming behavior (22). Excessive gamers are attracted to games because gaming stimulates the experience of power and autonomy, and strengthens self-esteem (22). Considering the relationship between IGD and self-esteem, monitoring internet gaming in adolescents could be a protective approach for self-esteem.

In the online world, individuals who are overweight and obese may frequently encounter aggressive messages. A systematic assessment of comments on a video-sharing website has reported that weight stigma can 'go viral' on the internet (48). In a study conducted among 4,364 children in the Netherlands, it was found that children diagnosed with obesity were more likely to be both victims and perpetrators of bullying compared to the control group (49). Sergentanis et al. (50) hypothesized that, due to the increasing prevalence of obesity, overweight/obesity has become normalized among adolescents. According to data from the Turkish Statistical Institute, the prevalence of obesity is increasing and being overweight or obese may have also become normalized in Türkiye, which could explain the lack of a

difference between the groups. Nocentini et al. (51) have reported that parental monitoring of online internet use is a protective factor against cyberbullying. In the present study, no difference was found between the groups in terms of parental monitoring of internet use. Thus, another reason for the lack of differences between the groups in terms of cyberbullying and victimization may be the similar levels of parental internet monitoring.

We found that exposure to CF and verbal cyberbullying victimization could be factors negatively affecting self-esteem in adolescents diagnosed with obesity. Adolescents diagnosed with obesity are often more affected by negative emotional experiences and generally have lower self-esteem compared to their peers (7,39,52). Therefore, cyberbullying victimization may further reduce self-esteem in obese adolescents. Self-esteem becomes increasingly important during adolescence, as this period heightens the significance of peer relationships, peer acceptance, and physical appearance, which can make adolescents more aggressive towards events that may threaten their self-esteem (53). Social relations theory posits that individuals with low self-esteem have weaker social relationships with others and that their lower conformity to social norms increases the risk of aggression (54). Individuals with low self-esteem may exhibit aggressive behavior to gain power and achieve a higher level of self-esteem (55). According to our findings, cyberbullying is another factor negatively affecting self-esteem. Obese adolescents might be exhibiting aggressive behaviors as a means of self-expression due to their low self-esteem, which could further diminish their sense of self-worth. When these findings are considered together, preventing cyberbullying/victimization in obese individuals may be a protective approach for the self-esteem of these individuals.

Study Limitations

Our study has several limitations. The most significant limitation is the cross-sectional design of our study. The cross-sectional design complicates the determination of the direction of the relationships between the variables assessed in individuals with obesity, as well as the establishment of causal relationships. Longitudinal studies are needed to provide more evidence for these relationships. Moreover, only self-report measures were used. Employing a multi-method approach (for example, integrating self-report measures with interviews) could be a strategy to overcome the limitations associated with collecting self-reported data. At the same time, we selected study samples from patients referred to pediatric endocrinology clinics, and nearly two-thirds of the adolescents in our study were girls. These factors limit the generalizability of our findings.

Conclusion

Our findings indicated that obesity was associated with low self-esteem and problematic internet use during adolescence. It was also shown that risky online behavior may be associated with self-esteem. In light of this, taking preventive measures to reduce problematic online behavior in obese adolescents may be a protective measure for self-esteem of obese adolescents. For the variables in our study to gain clarity in individuals diagnosed with obesity, longitudinal studies in a more homogeneous and larger sample are needed.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Süleyman Demirel University Faculty of Medicine (protocol no: 72867572.050.01.04-216193, date: 11.02.2022).

Informed Consent: Written informed consent was obtained from the participants and their families.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Havvanur Eroğlu Doğan, Concept: Havvanur Eroğlu Doğan, Evrim Aktepe, Design: Havvanur Eroğlu Doğan, Evrim Aktepe, Ümit Işık, Mustafa Özgür Pirgon, Data Collection or Processing: Havvanur Eroğlu Doğan, Ümit Işık, Mustafa Özgür Pirgon, Analysis or Interpretation: Havvanur Eroğlu Doğan, Ümit Işık, Literature Search: Havvanur Eroğlu Doğan, Evrim Aktepe, Writing: Havvanur Eroğlu Doğan, Evrim Aktepe, Ümit Işık, Mustafa Özgür Pirgon.

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What to Do for Atypia of Undetermined Significance in Pediatric Thyroid Nodules?

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What is already known on this topic?

Thyroid nodules in children and adolescents are less common than in adults but the likelihood of malignancy is higher. The American Thyroid Association pediatric guidelines recommend surgery while the European Thyroid Association guidelines recommend fine-needle aspiration biopsy repetition after six months for thyroid nodules with a cytological finding of atypia of undetermined significance.

What this study adds?

Lobectomy appears to be a more appropriate approach in cases of atypia of undetermined significance, but only when nuclear atypia is present, to avoid diagnostic leap and unnecessary surgery.

Abstract

Objective: International guidelines recommend different approaches for the management of pediatric thyroid nodules with a finding of atypia of undetermined significance (AUS) on cytology. The American Thyroid Association (ATA) pediatric guidelines recommend surgery whereas the European Thyroid Association (ETA) guidelines recommend repeat fine-needle aspiration biopsy after six months. Our objective was to identify markers of malignancy in AUS cases and to discuss the management of pediatric AUS nodules.

Methods: Specimens from pediatric patients who underwent surgery due to AUS cytology were re-evaluated and subcategorized according to the 2023 Bethesda classification.

Results: Of the 20 cases included, 11 (55%) were histologically benign, while 9 (45%) were malignant. On the subcategorization of AUS, nuclear atypia was present in 14 patients (70%), and other atypia in 6 patients (30%). Of the cases with nuclear atypia, 64.3% were malignant (n=9), whereas no malignancy was detected in cases with other atypia (p=0.012). Among the cytopathological features, chromatin clearing, nuclear enlargement, and irregular margins were significantly associated with malignancy (p=0.035, p=0.003, and p=0.012, respectively). Adhering to ETA recommendations would delay diagnosis by at least 6 months in 45% of our malignant cases. Conversely, performing lobectomy according to ATA recommendations may lead to unnecessary surgery in 55% of our cases.

Conclusion: Based on our findings, lobectomy appears to be a more appropriate approach in AUS cases but only when nuclear atypia is

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present, to avoid diagnostic delay and unnecessary surgery. Guidelines should be updated according to the latest Bethesda classification.
Keywords: Pediatric thyroid nodules, rate of thyroid malignancy, thyroid fine needle aspiration biopsy, the Bethesda System for Reporting Thyroid Cytopathology Classification, atypia of undetermined significance, nuclear atypia

Introduction

Thyroid nodules in children and adolescents are less common than in adults (0.2-5% vs. 19-35%), although the likelihood of malignancy is higher in children and adolescents than adults (up to 20-26% vs. 7-15%) (1,2,3,4,5,6). Key ultrasonographic features of thyroid nodules—such as hypoechogenicity, solid composition, microcalcifications, irregular margins, increased intranodular vascularity, and a taller-than-wide shape—are significant indicators of thyroid malignancy. (7,8,9). The American Thyroid Association (ATA) adult guidelines recommend ultrasound (US)-guided fine-needle aspiration biopsy (FNAB) for solid or partially cystic thyroid nodules ≥1 cm or nodules with suspicious ultrasonographic findings in a patient without risk factors for thyroid malignancy, which is similar to the European Thyroid Association (ETA) guidelines that recommend FNAB for suspicious nodules based on multiple US characteristics (5,6). FNAB results are reported according to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). The TBSRTC was updated in 2023. The latest edition simplifies the terminology of the six categories and recommends dropping the terms "unsatisfactory," "follicular lesion of undetermined significance," and "suspicious for a follicular neoplasm" for TBSRTC categories 1, 3, and 4, respectively. The new categories are: (1) non-diagnostic; (2) benign; (3) atypia of undetermined significance (AUS); (4) follicular neoplasm; (5) suspicious for malignancy; and (6) malignant (11). Furthermore, in the 2023 TBSRTC, the AUS subcategories are newly divided into two groups—nuclear and other (including architectural, oncocytic, and lymphocytic atypia)—whereas in the 2017 TBSRTC they were divided into five subcategories: cytologic, architectural, cytologic and architectural atypia, Hürthle cell AUS, and atypia not otherwise specified (11).

AUS is the most indeterminate category, as it is neither benign nor clearly malignant and can progress to malignancy or to a "suspicious for malignancy" category. The rate of malignancy (ROM) of AUS nodules in adults is approximately 22% (range, 13–30%), whereas it is higher—28% (range, 11–54%)—in the pediatric population. (11). The management of adult thyroid nodules with AUS cytology includes some combination of repeat FNAB, molecular testing, and surgery, depending on risk factors, patient history, clinical features, sonographic patterns, and patient preference. Guidelines provide different recommendations for the management of thyroid nodules with AUS cytology in children. In the management of the pediatric thyroid nodules with AUS cytology, the ATA pediatric guidelines recommend surgery (mostly lobectomy and isthmusectomy) whereas the ETA guidelines recommend repeat FNAB after six months (5,6). This discrepancy in the guidelines is attributed to the lack of data and limited research on this subject.

The aim of this study was therefore to determine the ROM and markers of malignancy in pediatric AUS cases and to discuss the approach to managing pediatric thyroid nodules with AUS cytology.

Methods

Records of children and adolescents who were followed up for thyroid nodules with AUS cytology in the Pediatric Endocrinology Division of the University of Health Sciences Türkiye, Ankara Dr. Sami Ulus Child Health and Diseases Training and Research Hospital, were retrospectively evaluated. Since the first edition of TBSRTC was published in 2009, patients were screened from 2009 to 2023. Age at diagnosis, gender, thyroid stimulating hormone (TSH) levels at diagnosis (in μIU/mL), patient history, thyroid US findings, FNAB cytopathology, and histopathological results were recorded.

Experienced radiologists performed US and FNAB procedures on the patients using high-frequency linear-array transducers (Toshiba Aplio 500, Toshiba Medical Systems, Tokyo, Japan). The US results were evaluated for composition (solid, semisolid, cystic), echogenicity (isoechoic, hypoechoic), margin characteristics (regular, irregular), and the presence of microcalcifications. Sampling was performed with 22-gauge needles attached to 10-mL syringes. Five or six samples were prepared on slides for each patient. For patients with multiple nodules, the most suspicious nodule was selected. Surgery decisions for children with AUS cytology were made by an experienced multidisciplinary thyroid team, including experts in pediatric endocrinology, radiology, pathology, oncology, and surgery, following ATA guidelines.

Within the scope of this study, FNAB samples were re-evaluated by the same experienced pathologist and subcategorized into two groups by type of atypia, nuclear

and other, as described in the new TBSRTC criteria. Nuclear atypia was defined as focal nuclear changes such as chromatin clearing, nuclear enlargement, and irregular nuclear contour.

In the literature, the terms "malignancy rate" and "risk of malignancy" are used interchangeably to describe the percentage of malignant cases in each TBSRTC category. In most studies, the number of malignant cases is divided by the number of cases with a histopathological diagnosis. However, due to variations in surgical selection rates, determining the actual ROM is challenging. In the present study, two different methods were used to estimate the most accurate ROM. The first method (ROM-H: ROM of nodules with AUS cytology based on histopathological diagnosis) was calculated by dividing the number of malignant cases by the number of AUS cases that underwent surgery and had a histopathological diagnosis. The second method (ROM-O: Overall ROM) was calculated by dividing the number of malignant cases by the overall number of AUS cases.

Approval was obtained from the Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (decision no: 2012-KAEK-15/2767, date: 23.08.2023).

Statistical Analysis

Statistical Package for the Social Sciences, version 22 (IBM Inc., Chicago, IL, USA) software was used for statistical analysis. In descriptive statistics, qualitative variables are expressed as frequency (n), and percentage (%); quantitative variables as mean ± standard deviation for normally distributed data and as median (minimum-maximum) for non-normally distributed data. Normality was assessed using the Shapiro-Wilk test. The χ^2 test was used in the analysis of categorical variables. The Student's t-test was used for comparisons of normally distributed continuous variables, and Mann-Whitney U test for non-normally distributed variables. A $p < 0.05$ was considered statistically significant.

Results

Among 312 children and adolescents who underwent FNAB for thyroid nodule(s) in our outpatient clinic, 28 (9%) had AUS cytology. These patients were recommended to undergo lobectomy in accordance with ATA guidelines. Five patients (17.8%) refused surgery, and three patients (10.7%) were transferred to adult clinics upon turning 18 years old and were subsequently followed according to adult guidelines. Twenty patients who underwent surgical evaluation were included.

The mean age of cases was 14.3 ± 3 years (range: 7.7-18 years); the female/male ratio was 4:1. Backgrounds, complaints on admission, and final diagnoses of the patients are presented in Table 1. Six patients (30%) had Hashimoto thyroiditis, two (10%) had congenital hypothyroidism, and one patient each (5%) had a thyroglossal duct cyst, Turner syndrome, insulin-dependent diabetes mellitus, precocious puberty, or epilepsy. On admission, 45% of the patients (n = 9) had no symptoms. Among the remaining patients 25% (n = 5) had swelling in the neck, 25% (n = 5) had abnormal thyroid function tests, and 5% (n = 1) had breathing difficulty. Three patients (15%) had a *DICER1* mutation (Table 1).

In terms of thyroid US findings, 25% of the patients (n = 5) had parenchymal heterogeneity. Sixty-five percent of the nodules (n = 13) were solid, 10% (n = 2) were semisolid, and 25% (n = 5) were cystic. Thirty-five percent of the nodules (n = 7) were hypoechoic, and 65% of the nodules (n = 13) were isoechoic. Microcalcifications were observed in 35% of the nodules (n = 7), irregular margins in 15% (n = 3), and increased intranodular vascularity in 15% (n = 3).

When the FNAB slides were re-evaluated by the same pathologist, nuclear atypia findings revealed chromatin clearing in 50% (n = 10), nuclear enlargement in 50% (n = 10), irregular nuclear contours in 70% (n = 14), and histiocytoid cells in 5% (n = 1). Among other atypia findings, three-dimensional groups were present in 10% (n = 2) and microfollicles in 30% (n = 6). Using the newly recommended subcategorization of AUS, nuclear atypia was found in 14 (70%), and other atypia in 6 (30%).

Histological diagnosis included neoplasia in 18 patients (90%). Of these, 11 (55%) were benign [follicular adenoma 9.1% (n = 1), nodular hyperplasia in 72.7% (n = 8), and chronic lymphocytic thyroiditis in 18.2% (n = 2)], while nine were malignant (45%) [papillary thyroid carcinoma (PTC) in 44.5% (n = 4), follicular variant-PTC in 22.2% (n = 2), and papillary microcarcinoma in 33.3% (n = 3)]. The ROM-H of nodules with AUS cytology was 45% (9/20), and when all aspirated AUS nodules were included, the ROM-O was 32.1% (9/28). In the benign and malignant groups, no significant differences were found in terms of age, gender, pubertal status, genetic predisposition, or serum TSH levels (Table 2). There were no significant difference in the US findings between malignant and benign nodules (Table 3) with the exception of the benign nodules being significantly larger in diameter ($p = 0.036$) (Table 3). The mean diameter of cystic nodules was 25.8 ± 22.2 mm, while the non-cystic nodules had a mean diameter of 13.4 ± 5.5 mm ($p = 0.003$). Eighty percent (n = 4) of the cystic nodules were benign, while 20% (n = 1) were malignant. The ROM-H was higher

Table 1. The characteristics of AUS cases

Patient no	Background	Complaint	Nuclear atypia	Histological diagnosis
1	N/A	Alterations in thyroid function tests	+	PTC
2	N/A	Swelling in the neck	-	Follicular adenoma
3	Hashimoto's thyroiditis	Alterations in thyroid function tests	+	PTC
4	N/A	Swelling in the neck	-	Nodular hyperplasia
5	*DICER1* mutation	Swelling in the neck	-	Nodular hyperplasia
6	Hashimoto's thyroiditis	N/A	+	FV-PTC
7	Thyroglossal duct cyst	Swelling in the neck	+	FV-PTC
8	Hashimoto's thyroiditis	Alterations in thyroid function tests	+	Papillary microcarcinoma
9	Hashimoto's thyroiditis	Difficulty breathing	+	Papillary microcarcinoma
10	Hashimoto's thyroiditis	Alterations in thyroid function tests	+	Chronic lymphocytic thyroiditis
11	Insulin depended diabetes mellitus	N/A	+	PTC
12	Turner syndrome	N/A	+	Chronic lymphocytic thyroiditis
13	Congenital hypothyroidism	N/A	-	Nodular hyperplasia
14	N/A	Swelling in the neck	+	Nodular hyperplasia
15	*DICER1* mutation	N/A	+	PTC
16	Epilepsy	N/A	+	Papillary microcarcinoma
17	Hashimoto's thyroiditis	N/A	+	Nodular hyperplasia
18	Precocious puberty	Alterations in thyroid function tests	-	Nodular hyperplasia
19	*DICER1* mutation	N/A	+	Nodular hyperplasia
20	Congenital hypothyroidism	N/A	-	Nodular hyperplasia

AUS: atypia of undetermined significance, PTC: papillary thyroid cancer, FV-PTC: follicular variant-papillary thyroid cancer, N/A: not applicable

Table 2. Clinical and laboratory characteristics of benign and malignant cases with AUS cytology

	Total (n = 20)	Benign (n = 11)	Malignant (n = 9)	p
Age, y, mean ± SD	14.3 ± 3	13.9 ± 3.2	14.6 ± 2.8	0.5
Gender, n (%)				0.62
Female	16 (80)	9 (56.3)	7 (43.8)	
Male	4 (20)	2 (50)	2 (50)	
Puberty, n (%)				0.65
Prepubertal	9 (45)	5 (55.6)	4 (44.4)	
Pubertal	11 (55)	6 (54.5)	5 (45.5)	
TSH (μIU/mL), median (min-max)	1.73 (0.02-6.98)	1.59 (1-3.59)	1.77 (1.09-3.80)	0.11
Genetic predisposition (*DICER1*), n (%)				0.57
Absent	17 (85)	9 (52.9)	8 (47.1)	
Present	3 (15)	2 (66.7)	1 (33.3)	

min-max: minimum-maximum, TSH: thyroid stimulating hormone, AUS: atypia of undetermined significance, SD: standard deviation

in patients with nuclear atypia features, such as chromatin clearing, nuclear enlargement, and irregular nuclear contours (p = 0.035, p = 0.003, p = 0.012, respectively) (Table 4). All nodules with microfollicles were benign (p = 0.012) (Table 4). Of the cases with nuclear atypia, 64.3% were malignant (9/14) whereas no malignancy was detected in the "other atypia" group (p = 0.012) (Table 5).

In the present study, patients with *DICER1* mutations were examined separately due to their predisposition to malignancy. We found that only one of the patients with a DICER1 mutation had malignant histology (PTC), whereas the other two had nodular hyperplasia. So, the ROM-H of the patients with *DICER1* mutation was found to be 33.3% whereas it was 47% for those without the mutation (p = 0.57) (Table 2).

Table 3. Ultrasonographic features of benign and malignant cases with AUS cytology

	Total (n = 20)	Benign (n = 11)	Malignant (n = 9)	p
Echotexture, n (%)				0.98
Homogeneous	15 (75)	10 (66.7)	5 (33.3)	
Heterogeneous	5 (25)	1 (20)	4 (80)	
Composition, n (%)				0.47
Solid	13 (65)	6 (46.2)	7 (53.8)	
Semisolid	2 (10)	1 (50)	1 (50)	
Cystic	5 (25)	4 (80)	1 (20)	
Echogenicity, n (%)				0.63
Isoechoic	13 (65)	7 (53.8)	6 (46.2)	
Hypoechoic	7 (35)	4 (57.1)	3 (42.9)	
Microcalcification, n (%)				0.63
Absent	13 (65)	7 (53.8)	6 (46.2)	
Present	7 (35)	4 (57.1)	3 (42.9)	
Margin, n (%)				0.42
Regular	17 (85)	10 (58.8)	7 (41.2)	
Irregular	3 (15)	1 (33.3)	2 (66.7)	
Intranodular vascularization, n (%)				0.57
Absent	17 (85)	9 (52.9)	8 (47.1)	
Present	3 (15)	2 (66.7)	1 (33.3)	
Thyroid volume SDS, median (min-max)	1.29 [(-2)-(9.21)]	1.17 [(-2)-(9.21)]	1.39 [(-0.93)-(8.61)]	0.73
Diameter of the thyroid nodules (mm), mean ± SD	16.51 ± 12.54	20.84 ± 15.71	11.22 ± 2.82	0.036

min-max: minimum-maximum, AUS: atypia of undetermined significance, SD: standard deviation, SDS: standard deviation score

Table 4. Cytopathological features of benign and malignant cases with AUS cytology

	Total n (%)	Benign n (%)	Malignant n (%)	p
Findings of nuclear atypia				
Chromatin clearing				0.035
Absent	10 (50)	8 (80)	2 (20)	
Present	10 (50)	3 (30)	7 (70)	
Nuclear enlargement				0.003
Absent	10 (50)	9 (90)	1 (10)	
Present	10 (50)	2 (20)	8 (80)	
Irregular nuclear contour				0.012
Absent	6 (30)	6 (100)	0 (0)	
Present	14 (70)	5 (35.7)	9 (64.3)	
Histiocytoid cells				0.45
Absent	19 (95)	13 (59.1)	8 (36.4)	
Present	1 (5)	0 (0)	1 (4.5)	
Findings of other atypia				
Three-dimensional groups				0.71
Absent	18 (90)	10 (55.6)	8 (44.4)	
Present	2 (10)	1 (50)	1 (50)	
Microfollicles				0.012
Absent	14 (70)	5 (35.7)	9 (64.3)	
Present	6 (30)	6 (100)	0 (0)	

AUS: atypia of undetermined significance

Table 5. Rate of malignancy of pediatric thyroid nodules with AUS cytology

Atypia subcategory	Total n (%)	Benign, n (%)	Malignant, n (%)	p
Total	20 (100)	11 (55)	9 (45)	**0.012**
Nuclear atypia	14 (70)	5 (35.7)	9 (64.3)	
Other atypia	6 (30)	6 (100)	0 (0)	

AUS: atypia of undetermined significance

Discussion

In the literature, there are varying data on the ROM of pediatric AUS cases. The ROM-H was 45% while ROM-O was 32.1% in our cohort. The true ROM lies between the ROM-H and the ROM-O. Considering resection rates ranging from 52% to 100%, the ROM-H of thyroid nodules with AUS cytology in the literature has been estimated to be between 20% and 75% (12,13,14,15,16,17). In our clinic, three of the 28 AUS cases were transferred to adult clinics due to being over 18 years old, and five patients refused surgery. It was noted that the three patients transferred to adult clinics were not operated on but were followed up clinically according to adult guidelines. Therefore, since our surgery rate (80%) is relatively high compared with the literature, we believe that the ROM-H found in our study reflects a true ROM.

DICER1 syndrome is an autosomal-dominant, pleiotropic tumor-predisposition disorder, increasing the risk of non-toxic multinodular goiter, adenoma, and thyroid cancer, caused by pathogenic variants in *DICER1* (18,19,20). In our cohort, only one of the patients with *DICER1* mutation had differentiated thyroid cancer while the other two had nodular hyperplasia. In our study, the ROM-H of the patients with *DICER1* mutation was 33.3% compared to 47% for those without mutation. Contrary to the literature, *DICER1* mutation did not increase the ROM in our cohort but the low number of patients with *DICER1* mutations, which is one of the limitations of the study, may have led to this unusual finding.

In earlier studies, US findings, such as solid structure, hypoechogenicity, presence of microcalcifications, irregular margins, increased intranodular vascularity, and abnormal cervical lymph nodes, have been found to be associated with malignancy (21,22). Lee et al. (23) also found that microcalcifications and irregular margins on US were associated with malignancy in AUS cases. However, no significant relationship was found between malignancy and US findings in our study, again likely due to the small sample size. In our cohort, however, benign nodules were found to be significantly larger. Most of the cystic nodules were benign and larger, probably due to the cystic component.

The latest edition of TBSRTC divides AUS into two subcategories: AUS-nuclear and AUS-other. In our cohort, the ROM-H of cases with nuclear atypia was found to be 64.3% while ROM-H of the cases with other atypia was found to be 0%. In the literature, both in adult and pediatric studies, the ROM in nuclear atypia has been reported to be 2-4 times higher than in other atypia (24,25,26,27,28,29). Similar to our study, Smith et al. (24) in a study including 43 pediatric AUS cases, reported that the ROM-H of nuclear atypia (formerly known as cytological atypia) was 50%. Another recent pediatric study by Jin et al. (13) found ROM-H to be 52%. According to the study of Cherella et al. (16) that included 68 pediatric thyroid nodules with AUS cytology, ROM-O in the presence of nuclear atypia increased to 59%, which was 10 times higher than in the absence of nuclear atypia.

Guidelines recommend different management strategies for thyroid nodules with AUS cytology in children. The ATA pediatric guidelines recommend surgery while the ETA guidelines recommend repeating FNAB after six months (5,6). When lobectomy is performed based on ATA recommendations for AUS cases, the likelihood of missed diagnosis is minimized, yet some patients undergo unnecessary surgery. Following ETA recommendations with repeat FNAB after six months reduces the risk of unnecessary surgery but may delay diagnosis in malignant cases. Our data suggest that adhering to ETA recommendations would delay diagnosis of malignancy by at least six months in 45% of our cases, which is a considerable risk. However, when we performed lobectomy according to the ATA recommendations for our cases, 55% of children underwent unnecessary surgery. Due to the significantly higher ROM-H in cases with nuclear atypia in our study, performing lobectomy for these cases would reduce the risk of unnecessary surgery from 55% to 35.7%, while the risk of misdiagnosis remains at 0%. Based on clinical and cytological evaluations, we suggest that surgical decisions should be individualized for each patient, even in the absence of nuclear atypia. AUS cases without nuclear atypia may carry a lower risk, but surgical decisions should also take other clinical factors into consideration. Based on our findings, performing surgery

only in cases with nuclear atypia and carrying out repeat FNAB after six months for cases with other atypia would be more appropriate than the current recommendations of both the ATA and ETA guidelines.

Study Limitations

One of the limitations of our study is the small sample size. Furthermore, since not all AUS cases were operated on, we cannot calculate the true ROM. We only know that the true ROM falls between ROM-H and ROM-O. However, given our high operation rates, the ROM-H we report most likely closely reflects the true ROM.

Conclusion

The literature indicates that the ROM in AUS in children is higher than in adults. Recommending FNAB six months later for AUS cases may lead to a significant number of delayed malignancy diagnoses. However, performing surgery on every AUS case often results in unnecessary surgery. Based on our findings, it is essential to consider the subgroups in the latest TBSRTC classification for the management of AUS cases. The association between nuclear atypia and malignancy has been clearly demonstrated, and lobectomy appears to be a more appropriate approach in AUS cases with nuclear atypia to avoid diagnostic delay and unnecessary surgery. Therefore, management decisions for AUS cases should be based on the presence of nuclear atypia, and guidelines should be updated according to the latest Bethesda classification to avoid diagnostic delays or leaps and subsequent unnecessary surgery.

Ethics

Ethics Committee Approval: Approval was obtained from the Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (decision no: 2012-KAEK-15/2767, date: 23.08.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Zülal Özdemir Uslu, Nebiyye Genel, Elif Tuğçe Tunca Küçükali, Agah Akın, İbrahim Karaman, Gürses Şahin, Hasan Bulut, Semra Çetinkaya, Nursel Muratoğlu Şahin, Concept: Zülal Özdemir Uslu, Nursel Muratoğlu Şahin, Design: Zülal Özdemir Uslu, Nursel Muratoğlu Şahin, Data Collection or Processing: Zülal Özdemir Uslu, Nebiyye Genel, Elif Tuğçe Tunca Küçükali, Agah Akın, İbrahim Karaman, Gürses Şahin, Hasan Bulut, Semra Çetinkaya, Nursel Muratoğlu Şahin, Analysis or Interpretation: Zülal Özdemir Uslu, Nebiyye Genel, Elif Tuğçe Tunca Küçükali, Nursel Muratoğlu Şahin, Literature Search: Zülal Özdemir Uslu, Nursel Muratoğlu Şahin, Writing: Zülal Özdemir Uslu, Nebiyye Genel, Elif Tuğçe Tunca Küçükali, Agah Akın, İbrahim Karaman, Gürses Şahin, Hasan Bulut, Semra Çetinkaya, Nursel Muratoğlu Şahin.

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ORIGINAL ARTICLE

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Diagnostic Utility of Next-Generation Sequencing-based CNV Analysis in Eleven Patients with Peters-Plus Syndrome: A Single-Center Experience

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What is already known on this topic?

Peters-Plus syndrome (PTRPLS) is a rare genetic condition caused by biallelic pathogenic variants in the ß 1,3-glucosyltransferase gene (*B3GLCT*). Affected individuals exhibited anterior eye-chamber defects, disproportionate short stature, facial dysmorphism and developmental delay.

What this study adds?

To the best of our knowledge, this is the first report demonstrating that exonic deletions can contribute to the pathogenesis of PTRPLS. We report the smallest homozygous deletion identified on chromosome 13q12, encompassing the fifteenth exonof the *B3GLCT* gene in PTRPLS patients.

Abstract

Objective: Peters-Plus syndrome (PTRPLS) is an autosomal recessive congenital disorder of glycosylation caused by biallelic pathogenic variants in the ß 1,3-glucosyltransferase gene (*B3GLCT*). To date, homozygous or compound heterozygous splicing, truncating, missense variants, and whole gene deletions have been reported in the *B3GLCT* gene. Our aim was to investigate the role of small copy number variations (CNVs) in this condition alongside the clinical features of the patients.

Methods: The study included eleven patients from six consanguineous families originating from the same village. Clinical exome sequencing-based CNV analysis was employed across all probands to ascertain the genetic background.

Results: Using GATK-gCNV, we identified a homozygous deletion on chromosome 13q12.3, encompassing the fifteenth exon of the *B3GLCT* gene. The median age at admission was 2.74 years, ranging from 2 months to 41 years. The mean standard deviation scores for height and weight at admission were -4.4 ± 0.9 and -3.8 ± 1.8, respectively. Ophthalmological abnormalities included corneal haze, anterior synechiae, unilateral leucoma, corneal-lenticular adhesion, glaucoma, and severe visual loss. Patients under the age of five years exhibited global developmental delay, while those older than five years demonstrated varying degrees of intellectual disability, with two exceptions exhibiting normal cognitive function.

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Conclusion: Our findings highlight an important role for Next-Generation Sequencing (NGS)-based CNV analysis in improving the diagnostic accuracy in PTRPLS. CNVs represent a significant form of genomic variation and should be systematically considered in genetically unresolved Mendelian disorders. Integrating CNV detection algorithms into routine NGS diagnostic workflows has the potential to enhance the identification of pathogenic changes, ultimately facilitating a more comprehensive molecular diagnosis for affected individuals.

Keywords: Peters-Plus syndrome, copy number variation, next-generation sequencing, Mendelian disorders

Introduction

Peters-Plus syndrome (PTRPLS; OMIM #261540) is a rare autosomal recessive congenital disorder of glycosylation caused by mutations in the ß 1,3-glucosyltransferase gene (*B3GLCT*). PTRPLS typically presents with a spectrum of clinical features encompassing ocular defects, disproportionate short stature, clefting and developmental delay (1). Ocular manifestations primarily involve the anterior chamber, with the hallmark being Peters anomaly characterized by corneal clouding and adhesions between the iris, lens, and cornea (2,3,4,5). The term "Peters' Plus syndrome" was introduced in 1984 by Dutch ophthalmologist van Schooneveld et al. (6), who described 11 patients with anterior eye chamber defects, clefting, short limb dwarfism, and developmental delay. Decades later, the molecular etiology was elucidated using genome-wide 1-Mb resolution array-based comparative genomic hybridization and Sanger sequencing, which identified a ~1.5-Mb interstitial deletion on chromosome 13q12.3q13.1 encompassing the causative gene *B3GLCT*, along with the common c.660+1G>A variant on the other allele (1). To date, splicing, truncating, missense variants, and whole gene deletions have been reported in *B3GLCT* (7). *B3GLCT* plays a crucial role in the modification of proteins during glycosylation. O-fucose is added to cysteine-rich domains known as thrombospondin type 1 repeats (TSRs) by protein O-fucosyltransferase 2 (POFUT2) and is subsequently elongated with glucose by B3GLCT (8). Previous studies have indicated that O-linked fucose is crucial for the proper folding and secretion of POFUT2-modified proteins and that the extension of the disaccharide by B3GLCT is vital for only a subset of these targets. Patients with PTRPLS are affected by the reduced function of specific POFUT2/B3GLCT targets, resulting from the loss of B3GLCT activity.

In the present study, the aim was to evaluate eleven patients diagnosed with PTRPLS using Next-Generation Sequencing (NGS)-based copy number variation (CNV) analysis and to highlight novel molecular approaches that may elucidate the genetic background of rare Mendelian disorders. Traditional techniques, such as microarrays and multiplex ligation-dependent probe amplification (MLPA), have been commonly used for CNV detection. However, the introduction of NGS-based CNV analysis has revolutionized the field with its efficiency and cost-effectiveness (9).

Methods

Patients and Samples

The study received approval from the Non-invasive Clinical Research Ethical Committee of University of Health Sciences Türkiye, Diyarbakır Gazi Yaşargil Training and Research Hospital (approval number: 46, date: 10.05.2024). The molecular genetic analysis, including NGS-based CNV analysis, was performed as previously described (10,11,12,13,14). Written informed consent was obtained from their legal parents or guardians, including permission to publish clinical information and photographs of the children. One ophthalmologist and one pediatric genetic specialist evaluated all cases. After a thorough physical examination, dysmorphic features and anthropometric measurements were noted, and standard deviation scores (SDS) were calculated and recorded. SDS was calculated using a national pediatric calculator following national standards (https://www.ceddcozum.com). Demographic features, family history, and clinical and radiographic findings were all obtained from retrospective data. Ophthalmologic examinations were conducted using the following methods: Anterior segment examination was performed with slit-lamp bimicroscopy. Intraocular pressure was measured using an I-care tonometer (I-care Finland Oy, Vantaa, Finland). Pupil dilation was achieved with 1% tropicamide, followed by a detailed fundus examination. For patients whose fundus could not be visualized due to anterior segment pathology, retinal evaluation was performed using B-scan ultrasonography. The clinical diagnosis of PTRPLS was established based on dysmorphic features and molecular genetic results.

Genetic Analysis

Sample Collection: Peripheral blood samples were collected from patients and their family members, and genomic DNA was extracted using the MagNA Pure 96 DNA and Viral NA Small Volume Kit (Roche Diagnostics GmbH, Mannheim, Germany).

Sample Preparation: Clinical exome sequencing (CES) was performed using the HyperCap Design Share Inherited Disease Panel (covering 4,125 genes; Roche Sequencing Solutions, Pleasanton, CA, USA) for target enrichment, and libraries were prepared with the KAPA HyperExome kit (Roche Sequencing Solutions, Pleasanton, CA, USA). Samples were prepared following the respective kit protocols, which involved capturing exonic regions of interest using targeted probes.

Sequencing: The prepared libraries were sequenced on the DNBSEQ-G400 platform (MGI Tech Co., Ltd., Shenzhen, China). This process generated raw sequencing data as short reads, representing the DNA fragments.

Variant Classification and Analysis: The raw sequencing data (FASTQ files) were uploaded to the SEQ Platform (Genomize Inc., İstanbul, Türkiye). The reads were aligned to the human reference genome GRCh37 using the Burrows-Wheeler Aligner (10). Variant calling was performed using FreeBayes (11), followed by additional steps such as Polymerase Chain Reaction (PCR) deduplication and indel realignment using Genomize's proprietary algorithms. Identified variants were annotated using VEP v102 (12) to provide functional annotations. American College of Medical Genetics (ACMG) pathogenicity classification was employed, using Genomize's proprietary algorithm, based on the guideline published by Richards et al. (13).

CNV Analysis: CNV analysis was conducted using the SEQ Platform from Genomize Inc. Reads aligned to the human reference genome GRCh37 were processed with the GATK gCNV tool v4.1.8.1 (14), using optimized parameters to detect and analyze CNVs. Additional information from external sources, such as ClinVar entries, bioinformatics-based effect prediction tool scores, and variant frequency values in the SEQ cohort, were considered during the analysis to assess variant significance and frequency further.

PCR: Long-range PCR was performed using LongAmp® Taq 2X Master Mix (M0287L, New England Biolabs, NEB) following the manufacturer's protocol. The reaction mixture was prepared in a final volume of 25 µL, containing 13.0 µL LongAmp® Taq 2X Master Mix, 1.0 µL 50 mM $MgCl_2$, 1.0 µL forward primer (*B3GLCT*-LONG-Y15F: CAACCTCAGCACTTTGGGAG), 1.0 µL reverse primer (*B3GLCT*-LONG-Y15R: CCCCGGTATCAGTAGAAGGC), 5.0 µL nuclease-free water (ddH_2O), and 80 ng genomic DNA. Thermal cycling conditions included an initial denaturation at 95 °C for 5 minutes, followed by 35 cycles of 94 °C for 30 seconds (denaturation), 60 °C for 1 minute (annealing), and 65 °C for 3 minutes (extension), with a final extension at 65 °C for 10 minutes and an indefinite hold at 4 °C. PCR products were analyzed by agarose gel electrophoresis and visualized under UV light.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows (SPSS, Inc., Chicago, IL). Descriptive statistics for quantitative data are presented as arithmetic mean, SD, median, and minimum-maximum values.

Results

Clinical Findings

Eleven patients (seven male, four female) from six families with a mean age at diagnosis of 11.1 ± 12.5 years were included. Five families had first- and/or second-degree consanguineous marriages, and all the families included in the study originated from the same village. Four family pedigrees (F3, F4, F5, F6) were remarkable due to the presence of multiple affected individuals, and five pedigrees (F1, F2, F3, F4, F6) were noteworthy in terms of recurrent abortus and intrauterine termination due to multiple congenital abnormalities, including cleft lip and/-or palate and hydrocephaly (Table 1, Supplementary Data 1). All patients were referred to our department due to short stature, facial dysmorphism, and severe brachydactyly. Except for patients 7, 8, 10, and 11, all others exhibited "happy" facial appearance and muscular body build. The median age at admission was 2.74 years, ranging from 2 months to 41 years. The mean SDS for height and weight at admission were -4.4 ± 0.9 and -3.8 ± 1.8, respectively. The median age at the last evaluation was 5.4 years, with ages ranging from 0.8 to 42 years. At this evaluation, the mean SDS of height, weight, and head circumference were -4.1 ± 1.1, -3.1 ± 1.1, -1.9 ± 0.9, respectively. On first examination, all patients displayed similar facial gestalt (Figure 1a-k). Three patients (P5, P8 and P9) had cleft lip/palate, which was operated on during infancy (Figures 1e, g, j). Interestingly, P9 displayed gingival hypertrophy on the upper incisors (Figure 1n). Echocardiography and abdominal ultrasonography were performed in all patients except P11, who had severe joint contractures and intellectual disability, which prevented us from conducting a comprehensive evaluation. Six patients (P3, P5, P6, P7, P9 and P10) exhibited genitourinary abnormalities, including an anterior-placed anus, deep sacral dimple, and bilateral cryptorchidism. Urinary ultrasonography revealed a duplex collecting system in the left kidney of P10, who subsequently underwent surgery for nephrolithiasis. A skeletal survey was performed in all cases, which revealed no significant findings

Table 1. Demographic, clinical, and radiological features of the patients in the present study

Family	**1**	**2**	**3**		4				**5**	**6**	
Patient No	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Consanguinity	Same village	First cousin	Second cousin	First cousin	First cousin	First cousin	First cousin	First cousin	Second cousin	First cousin	
Sex	M	M	F	F	M	M	F	M	M	F	M
Gestational age (weeks)	32	Full term	32	35	39	Full term	36	N/A	35	38	N/A
Birth weight (g/SDS)	1750/-0.0	2300/-2.6	1530/-0.7	1750/-1.7	2390/-2.9	2200/-2.9	1850/-2.6	N/A	1300/-4.0	3200/-0.1	N/A
Birth length (cm/SDS)	43/-0.0	N/A	42/-0.2	44/-0.8	47/-1.6	46/-1.7	40/-3.1	N/A	43/-1.45	49/-3.0	N/A
IUGR	-	+	+	+	+	+	-	N/A	+	N/A	N/A
Antenatal US	Short extremities at third trimester	Short extremities at third trimester	IUGR	Short extremities at third trimester	IUGR	Short extremities at third trimester	Short extremities at third trimester, macrocephaly	N/A	Hydrocephaly	N/A	N/A
Oligo/polyhydramnios	-/-	-/+	-/-	-/+	-/-	-/-	-/-	N/A	-/-	N/A	N/A
Neonatal ICU requirement	Respiratory distress	-	Respiratory distress	Respiratory distress	Feeding difficulties, cleft lip/palate	Respiratory distress	Respiratory distress	-	Respiratory distress, feeding difficulties, cleft lip/palate, hydrocephalus	-	-
Family history	Recurrent abortus										
Age at admission (years)	$1^{4/12}$	$10^{5/12}$	$5^{4/12}$	$0^{2/12}$	$1^{7/12}$	$2^{8/12}$	$0^{2/12}$	$41^{5/12}$	$0^{6/12}$	$15^{3/12}$	$26^{3/12}$
Height at admission (cm/SDS)	64.5/-4.9	115/-4.1	94/-3.7	47/-4.8	72.5/-3.2	77/-4.6	48.3/-3.9	145.3/-5.0	51/-6.5	141/-3.4	150/-4.2
Weight at admission (kg/SDS)	7.4/-3.3	19.7/-3.5	12.5/-3.1	2.9/-3.9	7.6/-3.6	6.9/-7.1	4/-1.8	59.5/-1.4	2.3/-7.3	37/-3.5	46/-3.5
OFC at admission (cm/SDS)	N/A	50.5/-2.2	N/A	N/A	46/-1.7	47.5/-1.5	39/-0.1	56/-1.1	N/A	53/-2.0	55/-1.8
Age at diagnosis (years)	$3^{4/12}$	$10^{7/12}$	$9^{1/12}$	$5^{5/12}$	$2^{9/12}$	$2^{10/12}$	$0^{9/12}$	$41^{5/12}$	$4^{3/12}$	$15^{9/12}$	$26^{10/12}$
Current age (years)	$3^{8/12}$	$12^{0/12}$	$10^{1/12}$	$5^{5/12}$	$3^{2/12}$	$3^{7/12}$	$0^{9/12}$	$41^{5/12}$	$4^{9/12}$	$15^{9/12}$	$26^{10/12}$
Current height (cm/SDS)	82/-4.8	124.1/-3.7	127/-1.8	83.5/-6.0	85/-3.3	85/-3.9	60/-4.4	145.3/-5.0	90/-4.3	141.7/-3.5	150/-4.5
Current weight (kg/SDS)	11.0/-3.3	28.1/-2.2	27.5/-1.0	10.3/-4.7	10.1/-3.6	10.0/-4.1	6.0/-3.0	59.5/-1.4	11.7/-3.7	37.7/-3.4	46.0/-3.5
Current OFC (cm/SDS)	47/-2.6	52/-1.8	51/-1.3	47/-2.7	47/-2.2	47/-2.5	45/0.1	56/-1.1	48/-2.4	53/-2.1	55/-1.8
Dysmorphic features											
Round face	+	+	-	+	+	+	+	+	-	+	+
Long face	-	-	+	-	-	-	-	-	+	+	-
Prominent forehead	+	-	+	+	+	+	+	-	+	-	-
High anterior hairline	+	-	+	+	+	+	+	+	+	+	+

Table 1. Continued

Widows peak	+	+	-	-	+	+	-	-	-	+	-
Hypertelorism	+	+	+	+	+	+	+	+	+	+	+
Upslanting palpebral fissures	-	+	+	+	+	+	+	+	+	-	-
Long philtrum	+	+	+	+	+	+	+	+	+	+	+ (tented)
Cupid bow upper lip	+	+	+	+	+	+	+	+	+	+	+
Thin upper vermillion	+	+	+	+	+	+	+	+	+	+	+
Cleft lip/palate	-	-	-	-	+ / +	-	-	+ /-	+ / +	-	-
Widely spaced teeth	+	-	-	-	-	-	-	-	+	-	+
Gingival hypertrophy	-	-	-	-	-	-	-	-	+	-	-
Short neck	+	+	+	+	+	+	+	+	+	+	+
Low set ears	+	+	-	+	+	+	+	-	+	+	+
Preauricular pit/cyst	-	-	-	-	-	+	+ Unilateral	-	+	-	-
Double whorl	-	-	-	-	-	+	-	-	-	-	-
Single palmar crease	-	-	+	-	-	+	+	-	+	+	-
Hearing loss	-	-	-	-	-	-	-	-	-	-	N/A
Ocular defects											
Peters anomaly	-	+	-	+	-	+	-	+	+	+	+
Anterior chamber anomaly	-	+	-	+	-	+	-	+	+	+	+
Cataract	+	-	-	Bilateral	-	-	+	-	+ Left	-	N/A
Iris atrophy	-	-	-	+	-	-	-	-	+	-	N/A
Retinal atrophy	+	-	+	+	+	+	-	+	-	-	-
Glaucoma	-	+	-	-	-	-	-	+	+	-	N/A
Iris coloboma	-	-	-	+	-	+	-	-	-	-	-
Retinal coloboma	-	-	-	+	-	+	-	-	-	-	N/A
Optic disc	Pale	-	Pale	-	Pale	-	-	Pale	-	-	N/A
Cardiac defects											
ASD	-	+	-	-	-	-	+	-	+	-	N/A
VSD	-	-	-	-	-	-	-	-	+	-	N/A
Pulmonary stenosis	-	-	-	-	-	-	+	-	-	-	N/A
Bicuspid aorta	-	+	-	-	-	-	-	-	-	-	N/A
PFO	-	-	-	-	+	-	-	-	-	-	N/A
Genitourinary abnormalities											
Hydronephrosis	-	-	-	-	-	-	-	-	-	-	N/A
Renal duplication	-	-	-	-	-	-	-	-	-	+	N/A
Cryptorchidism	-	-	-	-	Bilateral	Bilateral	-	-	Bilateral	-	-
Inguinal hernia	-	-	-	-	-	-	-	-	+	-	-
Hypoplastic clitoris/ labia majora	-	-	-	-	-	-	-	-	-	-	-
Nephrolithiasis	-	-	-	-	-	-	-	-	-	+	-
Anterior placed anus	-	-	+	-	-	-	+	-	+	-	-
Sacral dimple	-	-	+	-	-	-	-	-	+	-	-

Table 1. Continued

Skeletal findings																									
Rhizomelic shortening	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brachydactyly	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Broad hands/feet	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fifth finger clinodactyly	+	-	+	+	+	+	+	+	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+
Vertebral defects	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurologic impairment																									
DD/ID	+	-	-	+	+	+	+	+	-	+ (mild)	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADHD	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CC hypoplasia/ agenesis	-	-	-	?	-	-	-	-	+	-	-	+	+	+	+	+	+	+	+	+	-	-	-	-	N/A
Enlarged ventricules/ hydrocephaly	-	-	-	-	-	-	-	+	+	-	-	+	+	+	+	+	+	+	+	+	-	-	-	-	N/A
Tip toe walking	+	+	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	-	-	-	-	Wheelchair-bound
Feeding difficulties	-	-	+	+	+	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	-	-	-	-	-
Other	Sludge in the gallbladder	GH treatment	-	-	-	-	-	-	Epilepsy	Partial hypergonadotropic hypogonadism	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

ADHD: attention deficit hyperactivity disorder, ASD: atrial septal defect, CC: corpus callosum, DD: developmental delay, F: female, GH: growth hormone, ICU: intensive care unit, ID: intellectual disability, IUGR: intrauterine growth retardation, M: male, N/A: not available, PFO: patent foramen ovale, SD: standard deviation, USG: ultrasonography, VSD: ventricular septal defect SDS: standard deviation score, US: ultrasonography, N/A: not applicable

of skeletal dysplasia apart from severe brachydactyly. P2 was diagnosed with growth hormone deficiency based on provocative GH tests (clonidine and L-dopa stimulation) and has been receiving growth hormone treatment for one year, leading to a height increase of 9.5 cm during this period. The Turkish version of the Denver Developmental Screening Test was used for patients under five years old, while the Porteus Maze Test and Kent EGY test assessed performance and verbal IQ in older patients. Five individuals (P1, P4, P5, P6, P7) exhibited mild developmental delays across fine motor, gross motor, personal-social, and language skills. In contrast, P9 demonstrated a profound global developmental delay in all domains. In addition, P4 exhibited attention deficit hyperactivity disorder (ADHD) requiring medical treatment. P2 and P3 exhibited normal intelligence, yet P3 presented with ADHD. P10 showed mild intellectual disability, while her brother, P11, was compatible with severe intellectual disability. Moreover, P7 had experienced afebrile seizures from three months of age. Cranial magnetic resonance imaging (MRI) revealed a thin corpus callosum and hydrocephalus in both P7 and P9 (Figures 2a, b). P9 required a ventriculoperitoneal shunt during the neonatal period. P8, the oldest patient in the cohort, had mild hepatosteatosis and lobulation in the right kidney. Cranial tomography showed enlargement of the third and lateral ventricles, along with atrophy of the hemispheric sulci and fissures. In addition, a diffuse decrease in the density of the periventricular white matter was noted, which was evaluated as being consistent with chronic ischemic changes (Figures 2c, d). He exhibited mild intellectual disability, as he was unable to learn to read or perform simple mathematical calculations. Moreover, he had been married for six years without having children, suggesting infertility. Elevated follicle-stimulating hormone (FSH) (13.76 mIU/mL) and luteinizing hormone (LH) (10.0 mIU/mL) levels were detected, along with low testosterone (1.59 ng/mL) and anti-Müllerian hormone (1.60 ng/mL). These findings suggest partial hypergonadotropic hypogonadism. Unfortunately, a spermiogram could not be performed to assess sperm parameters.

Ophtalmologic Findings

P10 had bilateral central corneal haze with mild to moderate decreased visual acuity and was considered to be mild (Figure 3a). P4 had central corneal leucoma covering the pupil and anterior synechiae in the left eye and iris, and retinal coloboma in the right eye (Figure 3b). The right eye had cataract surgery and was pseudophakic. P6 displayed right corneal leucoma, prominent iris papillae, and iris and retinal coloboma in the same eye (Figure 3c). Both P4 and P6 were classified as having a moderate form. P2 and

Figure 1. Photographs of older patients in the study. **a)** P2 (11 years and 8 months), **b)** P3 (10 years), **c)** P10 (15 years and 9 months), **d)** P11 (26 years), and **e)** P8 (41 years). Common dysmorphic features include hypertelorism, a high anterior hairline, a thin vermillion border with a Cupid's bow-shaped upper lip, and a long philtrum. Additionally, P2, P10 and P11 displayed low-set ears **(a, c, d)**, while P3 exhibited up-slanting palpebral fissures **(b)**. Second row: Photographs of patients under six years old. **f)** P1 (3 years and 8 months), **g)** P5 (3 years and 2 months), **h)** P4 (5 years and 5 months), **i)** P6 (3 years and 7 months), **j)** P9 (4 years and 9 months), and P7 (2 months). All patients exhibit nearly identical facial features, including hypertelorism, a long philtrum, low-set ears, and a thin vermillion border. Note the short neck and muscular body build, which overlap with features of geleophysic dysplasia. Hands are notably short with brachydactyly. P5 and P9 had cleft lip/palate repair surgery **(g, j)**. Third row: Characteristic findings of PTRPLS in the present study. P4 had corneal clouding in the left eye **(l)**. P9 exhibited severe glaucoma in the left eye, resulting in vision loss, and underwent surgeries for both glaucoma and cleft lip/palate **(m)**. Additionally, P9 displayed remarkable gingival hypertrophy, an uncommon feature of PTRPLS **(n)**. P6 had an ear pit and low-set, posteriorly rotated ears **(o)**

PTRPLS: Peters-Plus syndrome

P9 had unilateral corneal leucoma with severe visual loss, corneo-lenticular adhesion, and glaucoma (Figure 3d). P9 underwent diode laser treatment twice for glaucoma and is currently on topical latanoprost and dorzolamide-timolol as part of the treatment regimen. P10 and P11, who are siblings, presented with bilateral corneal involvement. However, P11 had more severe involvement in the left eye, leading to vision loss. P1 and P7 exhibited posterior subcapsular opacification, which caused mild visual impairment. P1, P3, and P5 exhibited no corneal opacity but presented with a pale optic disc and chorioretinal atrophy. Moreover, P1 was diagnosed with crystalline fibrils in the vitreous. P8 had mild corneal haze in one eye, high myopia (-20 diopters), and glaucoma in both eyes. He was using travoprost drops bilaterally. P2, P4, and P5 displayed uni–and/ or bilateral microcornea.

Molecular Analysis

P1 had previously undergone karyotype and chromosomal microarray before presenting to our clinic. We conducted a CES due to the presence of syndromic features and family history suggestive of autosomal recessive inheritance. No pathogenic or likely pathogenic variant related to the phenotype could be detected. However, in all patients, CNV detection algorithms identified a 690 bp homozygous deletion in the 13q12.3 region (hg19: chr13:31903374-31904064),

encompassing exon 15 of *B3GLCT* (NM_194318.4) (Figure 4a, c). There were no other morbid OMIM genes except for *B3GLCT* in the deleted region on chromosome 13q12.3. This alteration was found to be haploinsufficient by Franklin. However, the ClinGen database did not provide reliable data about the haploinsufficiency (HI) score. According to the ACMG criteria, the pathogenicity of this CNV alteration is uncertain and has not been reported in public databases, including Database of Genomic Variants and GnomAD. Analysis of BAM files using the Integrative Genomics Viewer

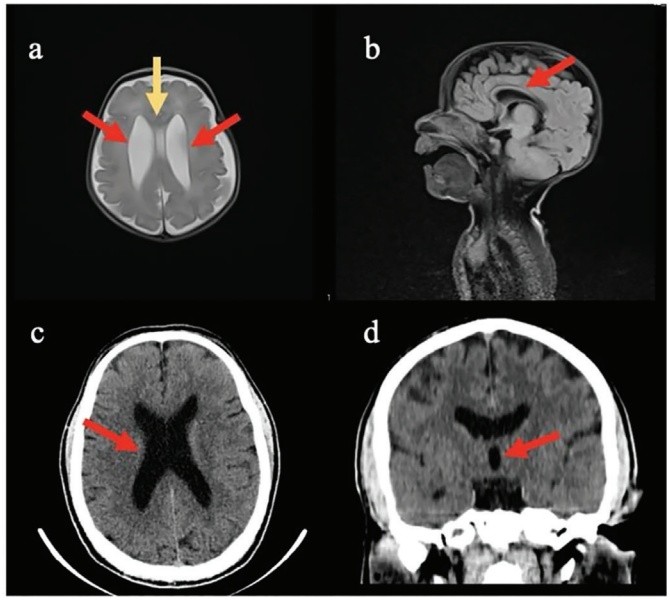

Figure 2. MRI findings of Patient 7. Widened lateral ventricles (indicated by red arrows) and a cavum septum pellucidum vergae variant (highlighted by a yellow arrow) were observed **(a)**. Corpus callosum hypoplasia (red arrow) was seen in the sagittal section **(b)**. CT imaging of Patient 8. The ventricular system and sulci appeared widened (red arrows), indicating cerebral atrophy **(c, d)**. Additionally, a diffuse decrease in periventricular white matter density was observed, consistent with chronic ischemic changes **(d)**

MRI: magnetic resonance imaging, CT: computed tomography

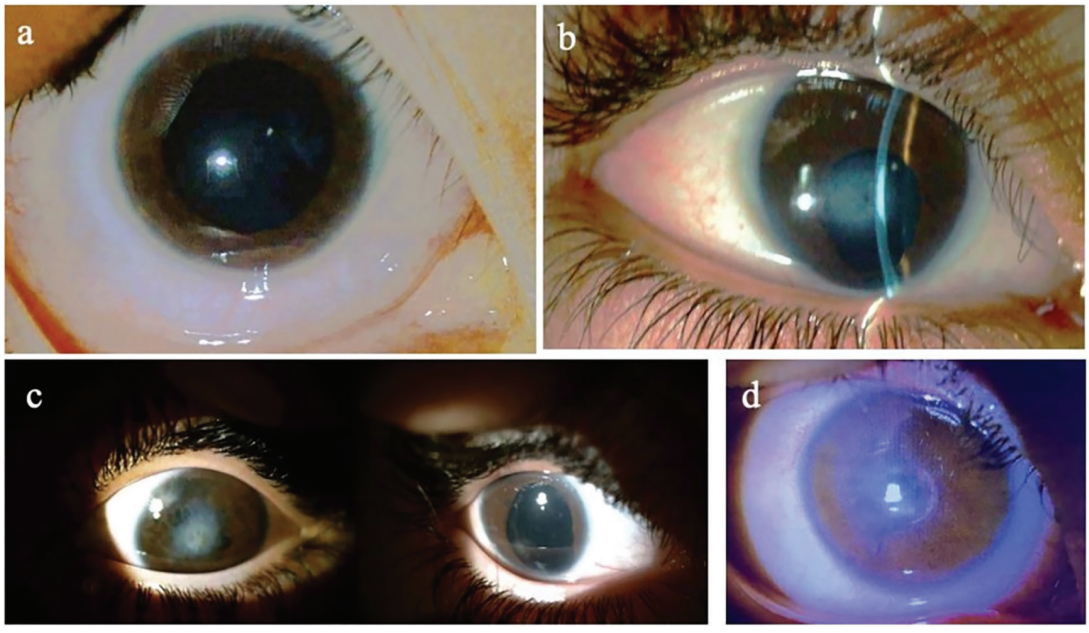

Figure 3. Ophthalmologic abnormalities detected in the study **a)** Patient 10; corneal haze, **b)** Patient 4; central corneal leucoma covering the pupil and anterior synechiae (left photo) and iris coloboma and pseudophakic (right photo). **c)** Patient 6; central corneal leucoma and iris coloboma. **d)** Patient 2; central and nasal paracentral corneal leucoma with corneo-lenticular adhesion

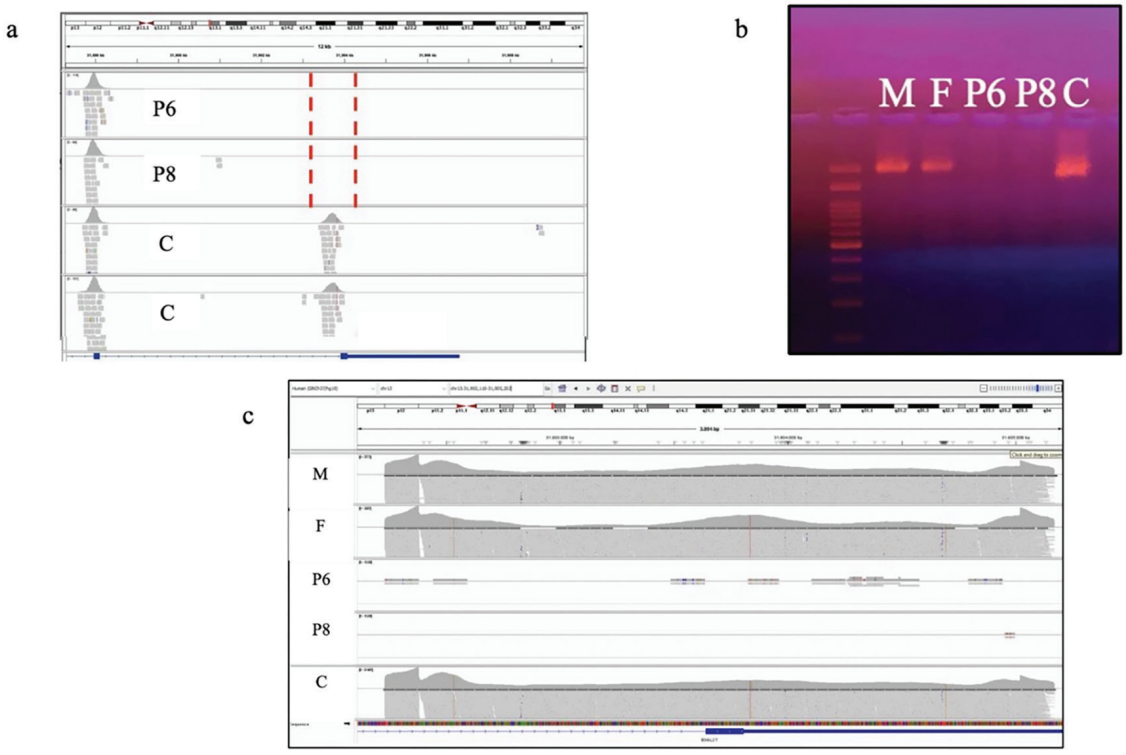

Figure 4. NGS-based CNV analysis. **a)** CNV alteration of the two probands on the IGV vizulation. While controls demonstrated no alteration of CNV, the first and second rows show the O copy number of the 15th exons of the *B3GLCT* gene. **b)** Given that the parents are known to be first cousins and predicted to be obligatory heterozygous carriers of the deletion, the detected amplicons in their PCR reactions are likely derived from their non-deleted, healthy alleles. This assumption is supported by the fact that the healthy control, possessing two non-deleted alleles, also showed similar amplification. **c)** NGS-based CNV analysis through CES revealed a decreased read depth in the parental samples, indicative of a potential heterozygous deletion

C: control, F: father, M: mother, P6: patient 6, P8: patient 8, NGS: Next-Generation Sequencing, CNV: copy number variation, IGV: Integrative Genomics Viewer, CES: clinical exome sequencing

(IGV) revealed zero read depth at exon 15 of *B3GLCT*, despite adequate read depth in control samples sequenced within the same run. Confirmation analysis was planned but no specific MLPA probe for *B3GLCT* was available. Chromosomal microarray analysis had previously failed to identify the deletion. Long-range PCR was considered for confirmation. The nearest exons with sufficient read depth upstream and downstream of exon 15 of *B3GLCT* were exon 14 of *B3GLCT* and exon 1 of *RXFP2*, respectively. Since the exact breakpoints could not be predicted, two long-range PCR reactions using different primer pairs were conducted. NGS-based CNV analysis revealed a decreased read depth in the parents, which indicates a reduced number of sequencing reads aligning with the region of interest. This suggests that the parents are heterozygous carriers of the deletion, as the decreased read depth corresponds to a loss of one copy of the affected genomic region. To demonstrate the carrier status of the patients, primers were designed for the region of interest. We used control, maternal, paternal, and patient samples. The observed PCR amplification in the parents and healthy control indicates the presence of at least one intact allele containing the primer-binding sites, leading to successful amplification. In contrast, no amplification in the patients suggests a homozygous deletion of the target region (Figure 4b).

Discussion

Over the past decade, employing NGS analysis to uncover inherited disorders has significantly expanded our understanding of the genetic basis of Mendelian disorders. NGS enables analysis of multiple regions of the genome in a single reaction and has proven to be both cost-effective and clinically effective for the investigation of patients with genetic conditions (15). Unfortunately, it has limitations in its ability to detect CNVs, such as single or multiple exon deletions, which are known to be important contributors to genetic disorders. The application of CNV detection

algorithms in NGS diagnostic services may facilitate immediate improvements in the clinical care of individuals with heterogeneous Mendelian disorders (16,17). P1, the proband of our study, presented with disproportionate short stature and facial dysmorphism and was evaluated for a possible genetic condition. However, despite extensive molecular analyses, including karyotype, microarray, and targeted gene panels, a definitive diagnosis could not be established. Subsequently, ten additional patients, all presenting with nearly identical symptoms, visited our clinic, albeit with varying degrees of clinical severity. NGS-based CNV analysis was subsequently employed to identify significant CNVs that could potentially explain the genetic basis of the condition. All patients were found to harbor a 690 bp homozygous deletion in the 13q12.3 region, covering the fifteenth exon of the *B3GLCT* gene. The consistent homozygous deletion in exon 15 of the *B3GLCT* gene across all unrelated patients likely results from a founder effect, as they originate from the same village, indicating a shared common ancestor. This group represents the first report of a homozygous which is also the smallest exonic deletion in the 13q12.3 region, only encompassing the *B3GLCT* gene. Other reports have shown that CNV alterations in the same region are causative for PTRPLS, with gene-targeted deletion/duplication analysis identifying four individuals with PTRPLS in the published literature (1,18,19). The first deletion was identified by Lesnik Oberstein et al. (1) using array-based comparative genomic hybridization, revealing a 1.5 Mb interstitial deletion in the 13q12 region of chromosome 13, containing the *B3GLCT* gene, along with the common c.660 + 1G > A variant on the other allele in two siblings. Similarly, Haldeman-Englert et al. (19) reported a heterozygous 781 kb deletion alongside the common c.660 + 1G > A variant in a male patient with typical PTRPLS features. Comparison of the deletion identified in our study with previous reports reveals a common overlapping region confined to the smallest area of 13q12.3, which includes exon 15 of the *B3GLCT* gene. Furthermore, while the other two reports documented heterozygous deletions encompassing multiple morbid OMIM genes, this deletion is particularly significant as it is homozygous and represents the smallest deletion reported to date, affecting only the *B3GLCT* gene. In the literature, documented pathogenic alleles consist of 86% splicing mutations, 6% truncating mutations, 4% missense mutations, and 4% whole gene deletions (7). Therefore, based on our findings and previous studies, we believe that NGS-based CNV analysis can play an important role in the diagnosis of genetic variations, including small deletions and duplications associated with inherited Mendelian disorders.

TSRs are present in over 60 human proteins but only 49 of these have the required consensus sequence for fucosylation and subsequent modification by *B3GLCT*, including secreted matrix proteins like thrombospondin 1 (TSP1) and TSP2, as well as all members of the ADAMTS and ADAMTSL families (20). Previous studies have demonstrated that HI of ADAMTS9 and ADAMTS20 is responsible for anterior segment dysgenesis and cardiac anomalies in animal models (21,22,23). Moreover, both ADAMTS9 and ADAMTS20 play a role in palatal closure, which is the definitive mechanism underlying the observed cleft palate phenotype (21). Furthermore, ADAMTS20-null mice exhibit a white spotting defect and a high degree of hydrocephalus (24). Mouse *B3GLCT* knockout models exhibit craniofacial and skeletal abnormalities similar to those observed in PTRPLS patients (24). These independent observations collectively suggest that PTRPLS specifically results from secretion defects in certain target proteins of *B3GLCT* (25). In addition, loss of *B3GLCT* significantly reduces the secretion of ADAMTSL2 (25). Geleophysic dysplasia (GD), caused by mutations in *ADAMTSL2* leading to reduced secretion of the mutant protein compared to the wild-type protein, shares several common symptoms with PTRPLS (25,26). In our cohort, P1, P2, P3, and P5 were initially diagnosed with GD based on severe brachydactyly, muscular body build, and a characteristic “happy” facial appearance. However, severe cardiac involvement in GD and distinct ocular findings in PTRPLS may provide valuable clinical clues for distinguishing between the two phenotypes. Consequently, comprehensive evaluation of both systems is essential, and we recommend considering PTRPLS in individuals who test negative for GD mutations.

Affected individuals present with similar phenotypes and complaints, yet there is significant intra- and inter-familial variability (1,19). In the present study, we noted phenotypic variability consistent with previous reports on PTRPLS. The study by Lesnik Oberstein et al. (1) highlighted that even within a genetically homogeneous group (homozygous for c.1020-1G > A), cognitive outcomes ranged from normal secondary education to severe cognitive impairment, suggesting the influence of additional genetic or environmental modifiers. Similarly, Haldeman-Englert et al. (19) proposed that the variable phenotypes in patients with deletions involving *B3GLCT* may result from the multisystemic effects of glycosylation defects or the involvement of other genes within the deleted region. Furthermore, no clear genotype-phenotype correlation has been established to date, and the cause of intra- and inter-familial variability remains unknown. It is likely that factors beyond the primary genetic variant, such as modifier genes, epigenetic influences, or environmental factors, contribute to the phenotypic heterogeneity observed in PTRPLS. Ophthalmological anomalies, which can provide clues for

an accurate diagnosis, have emerged as another feature that demonstrates this variability in this study. Four patients (P1, P3, P5, and P7) did not exhibit anterior segment dysgenesis or Peters anomaly. However, three of the four presented with retinal atrophy, except for P7. Ocular involvement is generally bilateral but unilateral cases have also been reported (27). Consistent with the literature, Peters anomaly was observed bilaterally in five of our patients and unilaterally in two. Cataract and glaucoma, common features that can also occur later in life, were observed in six of 11 patients in our cohort. Interestingly, unusual eye symptoms, including severe myopia, iris coloboma, retinal coloboma, optic atrophy, and microcornea, were noted in nine patients. Cardiac involvement is another systemic feature that varies among affected individuals. Congenital heart defects occur in approximately 30% of cases (1). Consistent with the literature, we observed bicuspid aorta, atrial septal defect, ventricular septal defect, patent foramen ovale, and pulmonary stenosis in 4 of 11 patients (36%).

Despite severe short stature, the skeletal survey showed no definitive evidence of skeletal dysplasia, apart from brachydactyly. Our observations suggest that brachydactyly was more pronounced in patients under five years of age than in older individuals. In the context of PTPRLS, GH therapy has been shown to yield positive results in a limited number of cases. Three reports in the literature have described patients with PTRPLS who demonstrated a good response to GH therapy. In these cases, GH deficiency was identified, which may have contributed to the patients' short stature. However, in all three studies, the molecular diagnoses of the patients were not established; instead, the diagnosis of PTRPLS was based on clinical findings. One of these reports also highlighted that pituitary dysfunction is well known to be associated with midline defects, encompassing a broad spectrum of congenital midline anomalies. These range from severe, nonviable conditions to milder presentations, such as isolated cleft lip or palate, as observed in PTRPLS. Notably, the prevalence of GH deficiency is reported to be 40 times higher in children with cleft lip and palate or isolated cleft palate compared to those without such anomalies. This strong correlation between pituitary dysfunction and congenital craniofacial malformations suggests that every child with midline facial defects should undergo a pituitary evaluation (2,28,29). Another study reported two siblings diagnosed with PTRPLS who also had GH deficiency and a small pituitary gland, yet no variants were detected in the *B3GLCT* gene (29). This reinforces the importance of performing cranial MRI in patients with GH deficiency and underscores the need to investigate CNVs in cases negative for *B3GLCT* variants. In our cohort, only P2 exhibited GH deficiency. Treatment with recombinant GH resulted in an increased growth velocity (9.5 cm/year), improving height from -4.0 to -3.3 SDS over one year of therapy, indicating a promising outcome. Interestingly, he had no clefting, and cranial MRI revealed no abnormalities. However, as demonstrated by previous reports of GH deficiency in children with PTRPLS, a pituitary evaluation should be considered, particularly in the presence of midline facial defects, and the growth hormone/insulin-like growth factor axis should be assessed. Further studies with larger cohorts are needed to better understand the prevalence of GH deficiency in PTRPLS, the long-term benefits of GH therapy, and its potential role in managing growth impairments in this population.

In our cohort, four patients were over the age of 10, and only one of them, P8 (40 years old), was diagnosed with partial hypergonadotropic hypogonadism. This diagnosis was based on elevated gonadotropin levels (FSH and LH) alongside low testosterone and anti-Müllerian hormone levels. To the best of our knowledge, hypergonadotropic hypogonadism has not been previously reported in patients with PTRPLS. This raises the question of whether it represents an unrecognized feature of the syndrome or an unrelated coexisting condition. Further studies involving additional patients are needed to clarify this association. However, we recommend monitoring patients for hypogonadism as they age.

Study Limitations

A limitation of the study is the inability to determine the exact breakpoints of the suspected deletion using an alternative method. However, the amplification failure of LR-PCR indirectly indicated the deletion. Furthermore, the suspected deletion was identified in all patients and their parents through NGS-based CNV analysis.

Conclusion

Previous studies have demonstrated that CNVs can contribute to the pathogenesis of PTRPLS. Deletions involving the *B3GLCT* gene can result in a clinical phenotype similar to that caused by point mutations within the gene. The findings reported herein highlight the importance of CNVs, especially in cases where standard genetic testing fails to detect small deletions/duplications. The accurate detection of CNVs using NGS-based CNV analysis highlights its value as a powerful tool in genetic diagnostics. Consequently, our study emphasizes the importance of incorporating NGS-based CNV analysis into routine genetic testing, which may lead to better clinical outcomes and personalized management for individuals with Mendelian disorders.

Ethics

Ethics Committee Approval: The study received approval from the Non-invasive Clinical Research Ethical Committee of University of Health Sciences Türkiye, Diyarbakır Gazi Yaşargil Training and Research Hospital (approval number: 46, date: 10.05.2024).

Informed Consent: Written informed consent was obtained from the parents.

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Footnotes

Authorship Contributions

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Neurodevelopmental Disorders, Cognitive Function, and Quality of Life in Children with Congenital Hypothyroidism in a Portuguese Population

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What is already known on this topic?

Neonatal screening programs have largely eliminated severe intellectual disability in congenital hypothyroidism (CH). Subtle neurodevelopmental deficits and a higher prevalence of attention deficit hyperactivity disorder and learning disabilities remain, even with early intervention.

What this study adds?

Delayed treatment initiation more than 15 days after birth negatively impacts cognitive outcomes, particularly in non-verbal domains, and lowers emotional and social QoL. This study highlights the importance of continuous monitoring and targeted interventions to address neurodevelopmental and QoL challenges in children with CH.

Abstract

Objective: Although neonatal screening programs have reduced severe intellectual disability, children with congenital hypothyroidism (CH) are still at risk for neurodevelopmental deficits and a lower quality of life (QoL). The aim of this study was to evaluate cognitive profiles, prevalence of neurodevelopmental disorders, and QoL in children with CH.

Methods: A longitudinal study was conducted at the northern reference endocrinology unit for CH in Portugal. Cognitive assessments were performed at four time points using standardized intelligence scales. Diagnoses of attention deficit hyperactivity disorder (ADHD), learning disorders, and intellectual disability were based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-DSM-V criteria. QoL was measured using the Pediatric Quality of Life Inventory-PedsQL™.

Results: Forty-six children (mean age 9.1 years, 58.7% female) were included. While overall intelligence quotients (IQ) scores were normal, later treatment was associated with significantly lower performance IQ ($r = -0.50$, $p = 0.028$) and perceptual organization index ($r = -0.57$, $p = 0.022$). ADHD was present in 26%, and affected children showed lower verbal IQ (90.2 vs. 106.8, $p = 0.022$), perceptual organization index (79.9 vs. 95.2, $p = 0.041$), and school-related QoL (63.3 vs. 81.6, $p = 0.002$). QoL scores were comparable to the Portuguese pediatric population, but treatment delays were linked to lower total QoL ($r = -0.45$, $p = 0.002$), particularly in emotional and social domains.

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Conclusion: Early thyroid hormone therapy is essential to mitigate neurocognitive deficits and improve QoL in CH. While severe intellectual disabilities are rare, non-verbal deficits persist, emphasizing the need for timely treatment and continuous monitoring.
Keywords: Adolescent development, attention deficit disorder with hyperactivity, child development, congenital hypothyroidism, learning disabilities, neurodevelopmental disorders, quality of life

Introduction

Congenital hypothyroidism (CH), affecting nearly 1 in 2000 newborns, is a chronic disease characterized by a congenital deficiency in thyroid hormone production. Primary CH arises from either thyroid gland dysgenesis or dyshormonogenesis. While thyroid gland dysgenesis has historically been the most common cause of primary CH, the widespread implementation of neonatal screening programs and lower thyroid-stimulating hormone (TSH) cut-off values have increased the detection of mild cases and cases of dyshormonogenesis, leading to a shift in etiological distribution (1,2,3).

Thyroid hormone is crucial for normal brain development, both pre- and post-natally. Untreated CH may result in irreversible intellectual and motor disabilities (4). Early diagnosis and intervention have dramatically improved outcomes. In developed countries, universal newborn screening conducted within the first days of life has virtually eradicated severe intellectual disabilities related to untreated CH (1,2).

Despite the success of these screening programs, emerging evidence indicates that even with early treatment, children with CH remain at risk for subtle neurodevelopmental deficits. Research exploring the long-term cognitive and developmental outcomes in children with CH has highlighted the importance of treatment timing, as delays are associated with more pronounced cognitive challenges (2,5). Furthermore, neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) and learning disabilities (LD) are more prevalent among children with CH compared to the general population, particularly in cases of severe neonatal hypothyroidism or maternal thyroid dysfunction during pregnancy (6,7,8,9,10,11,12). These deficits can significantly affect academic performance and overall well-being. However, findings on the impact of CH on quality of life (QoL) remain inconsistent, with some studies reporting similar or even better QoL compared to healthy peers (13,14,15,16,17) while others suggest poorer outcomes (18).

While early detection and treatment have greatly reduced the risk of severe intellectual disability, ongoing monitoring and interventions may be necessary to address the subtler but significant neurodevelopmental challenges that can persist into childhood and adolescence. Previous studies suggest that neuropsychological impairment may continue despite early treatment, yet few studies have comprehensively assessed both neurodevelopmental outcomes and QoL, particularly with long-term follow-up.

The aim of this study was to address these gaps by evaluating cognitive profiles, the prevalence of neurodevelopmental disorders, and QoL in children with CH, providing a more comprehensive understanding of the long-term challenges faced by this population.

Methods

A longitudinal study was carried out in the pediatric endocrinology unit of a tertiary hospital, the northern reference center for CH in Portugal.

Participants

Patients diagnosed with permanent primary CH between 2006 and 2023 were included. All diagnoses were established through the national newborn screening program within the first days of life. Exclusion criteria included refusal to participate, inability to respond to the questionnaire, and syndromic CH. Delayed treatment was defined as initiation of levothyroxine therapy more than 15 days after birth. Four patients were excluded due to missed appointments or unsuccessful contact.

The study was approved by the Unidade Local de Saúde de São João Ethical Committee (approval no: 202-2023, date: 23/10/2023). All eligible participants and their parents provided informed consent.

Patient Diagnosis and Follow-up

In Portugal, CH was included in the Newborn Screening Program in 1981. It primarily uses TSH as a marker, analyzing dried blood samples collected ideally between the 3rd and 6th day of life. Initially, the program employed a high TSH cut-off level of 90 µU/L, which meant that only severe cases of CH were identified. In 1996, the cut-off level was lowered to 20 µU/L, and in 2006, it was further reduced to 10 µU/L. Since our study includes patients diagnosed from 2006 onwards, this last cut-off was applied, enabling the detection of milder cases. Elevated TSH levels (above 40 µU/mL) prompt immediate referral to a reference center.

TSH values falling within the range of 20 to 40 µU/mL are considered suspicious, prompting ongoing observation of newborns until values normalize. For cases where TSH values range from 10 to 20 µU/mL, total T4 levels are assessed; if higher than 9.5 µg/dL, continued observation is the chosen strategy; if less than 9.5 µg/dL, values are considered within the normal range. In confirmed cases of CH, early referral to a reference center is implemented to initiate therapy with levothyroxine as early as possible (19). All cases are initiated on the same weight-adjusted levothyroxine dose (10-15 µg/kg/day), adjusted subsequently to maintain serum T4 concentrations at the upper limit of normal and TSH levels below 3.8 µU/L.

All patients diagnosed with CH at our center were followed by a multidisciplinary team, including a pediatric endocrinologist, a psychologist, and a specialized nurse. Routine assessments occurred every 4-6 months, with increased frequency during the initial treatment phase. Levothyroxine dosages were adjusted to maintain target thyroid hormone levels. Growth parameters, medication-related symptoms, and associated malformations were routinely monitored. Psychomotor development was assessed regularly by the same psychologist affiliated with the pediatric endocrinology unit.

Study Assessments

Psychomotor Development

Standardized assessments were conducted at specific time points. Results were expressed as intelligence quotients (IQ) with a normal distribution [mean 100, standard deviation (SD) 15]. Four formal psychometric assessments were performed: the first (IQ1) at 24 months of age, and the second (IQ2) at 4 years of age, both using the Griffiths Mental Development Scales. The third assessment (IQ3) was performed before school entry (5 to 6 years of age), using the Wechsler Preschool and Primary Scale of Intelligence. A fourth assessment (IQ4) was conducted during primary school, using the Wechsler Intelligence Scale for Children (WISC-III). This evaluation generated scores for Verbal, Performance, and Full-Scale IQ, along with index scores for the verbal comprehension index, perceptual organization index, and Processing Speed Index (the Freedom from Distractibility Index is not available in the Portuguese version) (20).

Neurodevelopmental Disorders

If neurodevelopmental disorders were suspected, children were referred to our neurodevelopment unit for clinical evaluation. Diagnoses of intellectual disability, LD, and ADHD were made based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-DSM-V criteria. School support, therapy (occupational, speech, and psychotherapy), and medications were provided as indicated.

Quality of Life

The Portuguese version of the Pediatric Quality of Life Inventory (PedsQL™ 4.0) was used for parent-reported QoL assessments. The questionnaire was administered during a school-age medical visit. The instrument, validated for Portuguese children, consists of 23 items across four domains: Physical, Emotional, Social, and School Functioning. Scores range from 0 to 100, with higher values indicating better QoL (21,22). Healthy individuals from the instrument's validation studies served as the control group (22).The control group was derived from a sample of 381 Portuguese children aged 8 to 12 years, recruited from schools in northern Portugal, as part of the PedsQL™ validation study. This sample provided normative QoL data for comparison and was not specifically age- and sex-matched to the study population. However, it is broadly representative of the general pediatric population within the specified age range (22).

Statistical Analysis

Statistical analysis was performed using SPSS, version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables are expressed as frequencies and percentages, while continuous variables are presented as means and SDs. Normality of continuous variables was assessed using the Shapiro-Wilk test. One-sample t-test was used to compare QoL scores of our study group with the Portuguese pediatric population (22). Pearson's correlation coefficients were used to assess associations between continuous variables. The strength of the relationship was interpreted based on the following r values: very weak (<0.25), weak (0.26 to 0.49), medium (0.50 to 0.69), high (0.70 to 0.89), and very high (0.90 to 1.0). A p value <0.05 was considered statistically significant.

Results

Characterization of the Population

The population analyzed is described in Table 1. Forty-six children were included in the study, 58.7% of whom were female. The mean age was 9.1 ± 0.6 years. The diagnosis was established at a mean of 12.9 ± 2.2 days of age, and treatment initiation at 14.5 ± 2.1 days. Treatment was initiated within the first 15 days of life in 37 out of 47 (78.7%) patients, between 15 and 45 days in eight (17.0%) patients, and at three months in one (2.1%). The mean venous TSH level at diagnosis was 177 ± 28.3 IU/mL. Thyroid dysgenesis was the predominant condition (82.6%) (18).

Neurodevelopment Assessments

Cognitive function was assessed longitudinally at four time points, at a mean age of: 2.4 years (mean IQ = 100.1 ± 10.4); 4.8 years (mean IQ = 100.1 ± 8.9); 5.6 years (mean IQ = 100.2 ± 15.9); and 9.1 years (mean IQ = 93.6 ± 19.5). At the final assessment, five children scored below average (IQ < 80), including two (4.3%) with scores more than two SDs below the average (IQ < 70).

Throughout the longitudinal follow-up, 26.1% of the children were diagnosed with ADHD, and 19.6% with LD. One child (2.2%) met criteria for intellectual disability.

QoL Assessments

Table 1. Demographic, clinical characteristics, and cognitive assessment of the study population

Characteristics	(n = 46)
Age, years	9.1 ± 0.6
Female sex	27 (58.7%)
Age at diagnosis, days	12.9 ± 2.2
Age at initiation of treatment, days	14.5 ± 2.1
TSH level at diagnosis, IU/mL	177.2 ± 28.3
Etiology of congenital hypothyroidism	
• Dysgenesis	38 (82.6%)
• Dyshormonogenesis	8 (17.4%)
Gestational risk	
• Gestational diabetes	7 (15.2%)
• Maternal thyroid pathology	3 (6.5%)
• In vitro fertilization	1 (2.2%)
Gestational age, weeks	39.0 ± 0.3
Birth anthropometry	
• Weight, grams	3088.3 ± 67.9
• Height, centimeters	47.8 ± 0.3
• Head circumference, centimeters	34.6 ± 0.3
Cognitive assessments, n/mean age (years)	
• First evaluation	43/2.4 ± 0.6
• Second evaluation	35/4.8 ± 0.2
• Third evaluation	13/5.6 ± 0.2
• Fourth evaluation	20/9.1 ± 0.4
Intelligence quotient scores	
• First evaluation (Griffiths)	100.1 ± 10.4
• Second evaluation (Griffiths)	100.1 ± 8.9
• Third evaluation (WPPSI)	100.2 ± 15.9
• Fourth evaluation (WISC)	93.6 ± 19.5
- Verbal IQ	99.7 ± 18.9
- Performance IQ	91.8 ± 19.3
- Perceptual organization index	88.5 ± 16.9
- Verbal comprehension index	100.4 ± 18.9
- Processing speed index	97.5 ± 17.9
Neurodevelopment disorders	
• ADHD	12 (26.1%)
• Learning disorder	9 (19.6%)
• Intellectual disability	1 (2.2%)

Data are expressed as n (%) or mean ± standard deviation.
ADHD: attention deficit hyperactivity disorder, IQ: intelligence quotient, IU: international units, TSH: thyroid stimulating hormone, WISC: Wechsler intelligence scale for children, WPPSI: Wechsler preschool and primary scale of intelligence

The QoL results are shown in Table 2. Overall, children with CH demonstrated QoL scores similar to the normative data for the Portuguese pediatric population, with a mean total QoL score of 83.0 ± 13.8. Statistically significant higher emotional QoL scores were reported for children with CH (80.6 vs. 73.3, p = 0.007). No significant differences were observed in the other domains.

Correlations Between Diagnosis, Treatment Timing, TSH, and Cognitive/QoL Scores

Table 3 presents the correlations between age at diagnosis, age at treatment initiation, TSH levels at diagnosis, and cognitive and QoL measures in our population.

Age at treatment initiation showed significant negative correlations with performance IQ (r = -0.50, p = 0.028) and perceptual organization index (r = -0.57, p = 0.022).

When assessing the impact on QoL in children with CH, significant negative correlations were found between the age at treatment initiation and multiple QoL domains. Specifically, later treatment initiation was associated with lower scores in total QoL (r = -0.45, p = 0.002), emotional QoL (r = -0.46, p = 0.001), and social QoL (r = -0.39, p = 0.007).

Neurodevelopment and QoL

The relationship between IQ and QoL is shown in Table 4. A positive correlation was observed between early psychomotor development (IQ1) and QoL outcomes, specifically in the social (r = 0.36, p = 0.017) and school (r = 0.33, p = 0.029) domains when assessed at school age. In the second preschool assessment (IQ2), a significant positive correlation was observed between IQ and total QoL (r = 0.34, p = 0.046) and physical QoL (r = 0.40, p = 0.029). By school age (IQ4), these associations strengthened: IQ showed strong positive correlations with total QoL (r = 0.78, p < 0.001), physical QoL (r = 0.66, p = 0.002), school-related QoL (r = 0.72, p < 0.001), and social QoL (r = 0.64, p = 0.002). However, emotional QoL did not demonstrate a significant correlation with IQ at any stage of development.

Table 2. Quality of Life scores of children with congenital hypothyroidism and comparison to the Portuguese pediatric population

	CH patient	Portuguese population (22)	p
Total QoL	83.0 ± 13.8	79.8 ± 12.1	0.120
Physical	87.0 ± 15.5	83.5 ± 14.8	0.138
Emotional	80.6 ± 17.6	73.3 ± 16.7	**0.007**
Social	87.6 ± 18.1	84.6 ± 15.1	0.263
Scholar	76.8 ± 18.8	78.2 ± 15.9	0.616

The data are presented as mean ± standard deviation.
CH: congenital hypothyroidism, QoL: quality of life

Cognitive and QoL Scores in Children with and without ADHD

To analyze the most common neurodevelopmental disorder diagnosed in this CH cohort, we compared the IQ and QoL scores of children with ADHD to those without this diagnosis (Table 5). Children with ADHD had lower total IQ scores (85.6 vs. 100.2, p = 0.051), with significantly lower results in verbal IQ (90.2 vs. 106.8, p = 0.022) and perceptual organization index (79.9 vs. 95.2, p = 0.041). Regarding QoL, children with ADHD demonstrated significantly lower scores in the school domain (63.3 vs. 81.6, p = 0.002), but no significant differences were found in total QoL, or in other domains.

Cognitive and QoL Scores in Children with and without LD

Similarly to the previous analysis, we compared the IQ and QoL scores of children with LD to those without this diagnosis (Table 6). Children with LD had significantly lower total IQ scores (77.5 vs. 104.3, p = 0.001), with significant differences observed in both verbal (83.9 vs. 109.5, p = 0.002) and performance IQ (78.1 vs. 100.9, p = 0.010). In addition, children with LD demonstrated lower scores in the verbal comprehension index (84.0 vs. 108.6, p = 0.010) and the perceptual organization index (79.9 vs. 97.0, p = 0.002).

Regarding QoL, children with LD had a significantly lower total QoL score (70.3 vs. 86.1, p = 0.005). Differences in specific QoL domains showed that children with LD scored lower in the school-related QoL (56.0 vs. 81.9, p < 0.001). However, no significant differences were observed in the others QoL domains.

Discussion

In this study, we assessed the prevalence of neurodevelopmental disorders and QoL in children with CH.

Table 3. Correlations between age at diagnosis, age at treatment initiation, TSH levels at diagnosis, and cognitive and quality of life scores in children with congenital hypothyroidism

	Diagnosis age (days)		Treatment initiation age (days)		TSH levels at diagnosis (IU/mL)	
	r	p	r	p	r	p
Total IQ	-0.43	0.098	-0.42	0.063	0.36	0.301
- Verbal IQ	-0.23	0.383	-0.22	0.338	0.39	0.234
- Performance IQ	-0.50	0.050	-0.50	**0.028**	0.237	0.510
Perceptual organization index	-0.54	**0.040**	-0.57	**0.022**	0.32	0.373
Verbal comprehension index	-0.14	0.597	-0.17	0.495	0.38	0.246
Processing speed index	-0.42	0.119	-0.44	0.920	0.32	0.373
Total QoL	0.41	**0.008**	-0.45	**0.002**	0.18	0.306
- Physical	-0.18	0.249	-0.27	0.075	0.17	0.333
- Emotional	-0.39	0.013	-0.46	0.001	0.30	0.087
- Social	-0.41	**0.008**	-0.39	0.007	0.07	0.713
- Scholar	-0.28	0.072	-0.29	0.053	0.07	0.707

r: Pearson correlation coefficient
TSH: thyroid-stimulating hormone, IQ: intelligence quotient, QoL: quality of life,

Table 4. Correlation between intelligence quotient scores and quality of life in children with congenital hypothyroidism

	Total QoL		Physical QoL		Emotional QoL		Social QoL		School QoL	
	r	p	r	p	r	p	r	p	r	p
IQ1 Griffiths	0.28	0.065	0.14	0.356	0.04	0.814	0.36	**0.017**	0.33	**0.029**
IQ2 Griffiths	0.34	**0.046**	0.40	0.029	0.57	**< 0.001**	0.59	**< 0.001**	0.50	**0.030**
IQ3 WPPSI	0.46	0.118	0.31	0.310	0.17	0.585	0.50	0.081	0.46	0.118
IQ4 WISC	0.78	**< 0.001**	0.66	**0.002**	0.40	0.078	0.64	**0.002**	0.72	**< 0.001**
IQ4 VIQ	0.69	**< 0.001**	0.62	**0.003**	0.32	0.160	0.52	**0.016**	0.71	**< 0.001**
IQ4 PIQ	0.74	**< 0.001**	0.66	**0.002**	0.37	0.105	0.66	**0.002**	0.61	**0.005**
IQ4 VCI	0.67	**0.002**	0.62	**0.007**	0.40	0.096	0.47	0.050	0.71	**< 0.001**
IQ4 POI	0.82	**< 0.001**	0.75	**< 0.001**	0.50	0.050	0.73	**< 0.001**	0.68	**0.004**
IQ4 PSI	0.51	**0.042**	0.47	0.070	0.29	0.285	0.52	**0.038**	0.38	0.148

r: Pearson correlation coefficient.
IQ: intelligence quotient, QoL: quality of life, WPPSI: Wechsler preschool and primary scale of intelligence; WISC: Wechsler intelligence scale for children, VIQ: verbal IQ, PIQ: performance IQ, VCI: verbal comprehension index, POI: perceptual organization index, PSI: processing speed index

ADHD and LD were prevalent, affecting 26% and 20% of the cohort, respectively. Although overall IQ scores in the cohort were within the normal range, a slight decline was observed over time, with mean IQ dropping from 100.1 in early assessments to 93.6 at school age. Notably, children treated later had lower cognitive scores, specifically in performance IQ and perceptual organization index. In addition, later diagnosis and treatment initiation was associated with lower QoL, particularly in emotional and social domains. No significant correlations were observed between TSH levels at diagnosis and IQ or QoL. ADHD and LD were linked to lower IQ and school-related QoL scores. Despite these challenges, QoL in the cohort was similar to the Portuguese pediatric population. There was a strong positive correlation between IQ and total QoL, emphasizing the relationship between cognitive function and QoL in this population.

Table 5. Comparison of intelligence quotients and quality of life scores between children with and without attention deficit hyperactivity disorder in congenital hypothyroidism

	ADHD n = 12	Non-ADHD n = 34	p
Total IQ 4	85.6 (19.9)	100.2 (17.1)	0.051
- Verbal IQ	90.2 (17.3)	106.8 (17.4)	**0.022**
- Performance IQ	85.2 (21.8)	97.2 (15.9)	0.095
Verbal comprehension index	95.6 (18.1)	104.2 (19.5)	0.175
Perceptual organization index	79.9 (17.5)	95.2 (13.8)	**0.041**
Processing speed index	92.9 (19.8)	101.1 (16.6)	0.196
Total QoL	78.0 (15.6)	84.8 (12.8)	0.096
Physical	85.8 (16.0)	87.4 (15.6)	0.387
Emotional	80.1 (18.2)	80.8 (17.7)	0.456
Social	82.7 (22.7)	89.4 (16.3)	0.180
School	63.3 (12.8)	81.6 (16.4)	**0.002**

The data is presented as mean (standard deviation).
ADHD: attention deficit hyperactivity disorder, IQ: intelligence quotient, QoL: quality of life

Table 6. Comparison of intelligence quotients and quality of life scores between children with and without learning disorders in congenital hypothyroidism

	LD n = 9	Non-LD n = 37	p
Total IQ 4	77.5 (15.0)	104.3 (14.0)	**0.001**
- Verbal IQ	83.9 (12.4)	109.5 (15.3)	**0.002**
- Performance IQ	78.1 (17.8)	100.9 (14.6)	**0.010**
Verbal comprehension index	84.0 (12.9)	108.6 (16.0)	**0.010**
Perceptual organization index	79.9 (17.5)	97.0 (11.3)	**0.002**
Processing speed index	89.8 (18.9)	102.1 (16.6)	0.163
Total QoL	70.3 (16.3)	86.1 (11.3)	**0.005**
Physical	80.4 (19.2)	88.6 (14.3)	0.197
Emotional	73.0 (25.3)	82.4 (15.1)	0.397
Social	71.9 (27.5)	91.5 (12.9)	0.063
Scholar	56.0 (13.5)	81.9 (16.4)	**< 0.001**

The data is presented as mean (standard deviation).
IQ: intelligence quotient, QoL: quality of life, LD: learning disorders

Thyroid hormone insufficiency has been linked to structural abnormalities in the brain, particularly in the corpus callosum, which connects the cerebral hemispheres and is crucial for integrated brain function (23). Abnormalities in these neural connections have been observed not only in hypothyroidism but also in autism spectrum disorders (ASD) and ADHD (24). This suggests that structural defects in the brain in CH may contribute to the neurodevelopmental issues observed in these children. The high prevalence of ADHD observed in our cohort is consistent with literature that reports elevated attention-related disorders in children with thyroid dysfunction (6,7,8,9,10), including a large Australian cohort where mildly elevated neonatal TSH levels were linked to a higher risk of ADHD and school performance issues (25). Maternal thyroid dysfunction during pregnancy has also been associated with neurodevelopmental problems, including ADHD (6,11,12). Recent studies have also reported a higher prevalence of ASD among patients with CH (9,10). Notably, one study linked the occurrence of ASD to undertreated CH, contrasting with the association of ADHD with overtreatment (9). However, no cases of ASD were observed in our cohort, indicating potential variability in neurodevelopmental outcomes associated with different treatment practices in this population.

Children with ADHD in our cohort exhibited lower total IQ, with significantly lower verbal and perceptual organization scores. Previous studies have consistently shown that, in addition to symptoms of inattention and hyperactivity-impulsivity, children with ADHD often experience distinct cognitive impairments (26,27,28). Interestingly, the pattern of subscores in our cohort differs from the typical cognitive profile seen in ADHD, where lower scores are generally observed in the processing speed index and freedom from distractibility index (not included in the Portuguese WISC-III), rather than in the verbal comprehension or perceptual organization index (27,29). The lower perceptual organization index in our cohort may be associated with and influenced by CH, as it was the lowest score in the WISC evaluation for this population and showed a decline when CH treatment was initiated later.

The lower school-related QoL scores in children with ADHD in our cohort are consistent with studies highlighting the negative impact of ADHD on academic and social functioning (30,31). These children often face difficulties with attention and executive functioning, which likely contributes to their diminished QoL in different settings (30,31). Together, these

findings highlight the need for comprehensive management of ADHD in children with CH, as both conditions appear to have a significant impact on cognitive function and QoL, particularly in academic and social settings. Early detection and tailored interventions for ADHD in this population may play a role in improving long-term neurodevelopmental outcomes.

In our cohort, 37 of 47 patients began treatment before 15 days of life, aligning with current best practices (2). However, eight patients started treatment between 15 and 45 days, and one outlier, due to an administrative error, initiated treatment at three months. This case is the only instance of an intellectual disability diagnosis in our study. This underscores the critical importance of efficient communication within screening programs to prevent delays in treatment, which can significantly impact neurocognitive development throughout life.

Numerous studies have demonstrated the importance of early treatment of CH to prevent developmental defects (5,32). Despite neonatal screening programs significantly reducing the rates of severe intellectual disability in children with CH, neurocognitive impairment, including difficulties in cognitive function, language development, motor skills, and learning achievements, remain evident into school-age and adolescence (1,33). In our cohort, the proportion of children with cognitive levels below the norm and intellectual disability aligned with expectations for the general population (20). However, the high prevalence of LD in our cohort highlights the significant academic challenges faced by children with CH. Moreover, the poorer general and school-related QoL observed in children with LD reflects its profound impact on academic functioning and daily life. The observed decline in IQ scores over time, particularly in those diagnosed and treated later, further illustrates the impact of late treatment in cognitive functions. Our results are in line with the study of Pulungan et al. (5) that also reports a negative correlation between later treatment initiation and performance IQ, with no association with verbal IQ. This suggests that non-verbal cognitive domains may be more vulnerable to treatment delays, a vulnerability that may only manifest at later developmental stages. However, some studies have found correlations between treatment timing and other IQ components, highlighting variability in how delays may affect different cognitive domains (32).

Our study found that children with CH generally had a QoL comparable to the normative Portuguese pediatric population, with significant associations between later treatment initiation and lower QoL scores in the emotional, social, and total QoL domains. Interestingly, QoL was associated only with the age of treatment initiation, not the age of diagnosis, emphasizing the critical importance of timely treatment. The literature on QoL in CH patients presents mixed findings. Some studies report similar QoL scores to those of healthy individuals (13,14,15), while others report either better (16,17), or lower QoL (18). In terms of the relationship between QoL and the timing of treatment initiation, other recent studies have also found significant negative correlations, consistent with our findings (16,17). These studies, like ours, reported no significant association between QoL and TSH levels at diagnosis, reinforcing the relevance of treatment timing over biochemical markers at diagnosis in predicting long-term outcomes. However, not all research supports these conclusions, with some studies reporting no correlation between age at treatment initiation and QoL (5,34). A recent critical review suggested that no single physiological, genetic, clinical, demographic, or behavioral factor can be definitively linked to either poor or good QoL in CH patients (35). Nevertheless, factors such as weight gain, the presence of anti-thyroid peroxidase antibodies, physical activity, and lifestyle choices may all play a role in shaping QoL (35). This range of potential influencing factors highlights the complexity of the interactions between hormone levels, hypothyroidism symptoms, and QoL.

Moreover, the clear link between IQ and QoL observed in our cohort emphasizes the broader implications of cognitive function for overall well-being. This association between cognitive function and QoL has been noted in a previous study (34), where lower IQ was linked to worse QoL, though with no clear association to later therapy initiation. In our study, parents of children with higher IQ reported better QoL, particularly in school-related domains, which underscores the importance of cognitive support for this population. These findings highlight the need for targeted interventions to improve cognitive outcomes, whether through early treatment, educational support, or ADHD management. Routine neurodevelopmental evaluations and tailored interventions should be a priority in the long-term care of children with CH, as preventing cognitive damage and addressing neuropsychological impairments must remain central goals in CH screening and treatment programs.

Study Limitations

Despite the valuable insights provided by our study, certain limitations should be acknowledged. The relatively small sample size, especially in the later cognitive assessments, may limit the generalizability of our findings. In addition, questionnaire-based assessments of QoL can be influenced by biased recall and variable interpretation. However, they

still serve as a useful tool for a general assessment of QoL in CH. While the study's longitudinal design allows for the observation of changes over time, the assessments conducted at specific intervals may not fully capture the nuances of long-term cognitive trajectories. Furthermore, the tests administered to the subjects may be influenced by various sociodemographic factors, such as family characteristics and parental education level, which were not available for analysis in this study. To confirm our results and explore the mechanisms underlying cognitive decline in children with delayed treatment initiation, future studies with larger sample sizes, and longer and more frequent follow-up periods are needed. Investigating specific interventions, such as cognitive training or behavioral therapy for ADHD, will also be important to improve outcomes for children with CH.

Conclusion

Our study reinforces the critical importance of early thyroid hormone replacement therapy, in mitigating neurocognitive deficits and improving future QoL in children with CH. Despite advances in neonatal screening that have reduced severe intellectual disability, subtle cognitive impairments, particularly in non-verbal domains, persist. Early diagnosis, timely treatment before 15 days after birth in our study, and continuous monitoring are crucial for optimizing long-term cognitive and QoL outcomes. Furthermore, addressing comorbid ADHD and LD is essential for improving both neurodevelopmental and academic outcomes in this population.

Ethics

Ethics Committee Approval: The study was approved by the Unidade Local de Saúde de São João Ethical Committee (approval no: 202-2023, date: 23/10/2023).

Informed Consent: All eligible participants and their parents provided informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Laura Leite-Almeida, Rita Curval, Inês Pais-Cunha, Bárbara Pereira-Neto, Sofia Ferreira, Rita Santos Silva, Micaela Guardiano, Paulo Almeida, Cíntia Castro-Correia, Concept: Laura Leite-Almeida, Rita Curval, Paulo Almeida, Cíntia Castro-Correia, Design: Laura Leite-Almeida, Rita Curval, Paulo Almeida, Cíntia Castro-Correia, Data Collection or Processing: Laura Leite-Almeida, Rita Curval, Inês Pais-Cunha, Bárbara Pereira-Neto, Analysis or Interpretation: Laura Leite-Almeida, Rita Curval, Inês Pais-Cunha, Bárbara Pereira-Neto, Sofia Ferreira, Rita Santos Silva, Micaela Guardiano, Paulo Almeida, Cíntia Castro-Correia, Literature Search: Laura Leite-Almeida, Rita Curval, Writing: Laura Leite-Almeida, Rita Curval.

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ORIGINAL ARTICLE

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Body Composition Changes and Catch-up Growth in Pre-pubertal Children with Short Stature: A Longitudinal Retrospective Cross-sectional Cohort Study

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What is already known on this topic?

Differentiating whether a child with pre-pubertal short stature will achieve normal height or remain short before the pubertal growth spurt is challenging. While growth hormone deficiency is associated with reduced skeletal muscle mass (SMM), longitudinal studies comparing body composition in those achieving versus failing catch-up growth are lacking.

What this study adds?

This study examined body composition changes in pre-pubertal children with short stature, distinguishing those who achieved normal height from those who remained short before the pubertal growth spurt. Differences in SMM index (SMMI) growth emerged as important, highlighting the need for possible early therapeutic intervention in cases with poorer SMMI increase.

Abstract

Objective: Predicting whether children with pre-pubertal short stature will achieve catch-up growth to a normal height or remain short remains a clinical challenge. As body composition plays a vital role in growth, we aimed to compare longitudinal body composition changes in children with short stature who either achieved normal height by the onset of the growth spurt or remained short.

Methods: This longitudinal, retrospective, cross-sectional, cohort study analyzed anthropometric and body composition data of children aged 8 and 12 years, allowing for both longitudinal tracking and cross-sectional comparisons. Participants were categorized into three groups: short-to-short statured (short stature at 8 and 12 years, n = 177), short-to-normal statured (short stature at age 8 and normal stature at 12, n = 90), and control (normal stature at both ages, n = 7,195). Height, weight, body fat mass (BFM), skeletal muscle mass (SMM), body mass index (BMI), BFM index (BFMI), and SMM index (SMMI) were assessed. Growth variations were examined using a difference-in-difference estimator.

Results: Cross-sectional analysis showed the short-to-short group had significantly lower weight, BFM, SMM, BMI, BFMI, and SMMI compared to controls at both ages. Longitudinally, the short-to-normal group exhibited significantly greater increases in height [0.87

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and 0.95 standard deviation scores (SDS) for boys and girls, respectively], weight (0.59 and 0.68 SDS), and SMMI (0.75 and 0.50 SDS) compared to the short-to-short group. However, BFMI increases were not significant.

Conclusion: Children with pre-pubertal short stature who achieved a normal height showed the most significant increase in SMMI. Children with lower increases in SMMI may require further assessment for continued short stature.

Keywords: Anthropometric data, body composition, catch-up growth, children and adolescents, short stature, skeletal muscle mass

Introduction

Short stature, defined as a height that is >2 standard deviations (SDs) below the population mean for age and sex, is a frequent reason for referral to pediatric endocrinologists (1,2). Timely evaluation and treatment of the causes of short stature are critical determinants of final adult height. In children with idiopathic short stature (ISS), early puberty or delayed treatment initiation until after puberty can lead to a shortened duration of growth hormone (GH) therapy and a reduction in final adult height (3). Similarly, starting the therapy at a younger age, before the onset of puberty, considerably increases the final adult height in individuals with ISS, GH deficiency (GHD) and Turner syndrome and those born small for gestational age (SGA) (4,5,6). Therefore, clinicians must distinguish whether a child with short stature would likely overcome this condition naturally, such as in those with constitutional delay of growth and puberty (CDGP), or will exhibit persistent short stature.

As interest in the impact of body composition on growth patterns in children and adolescents has increased, a previous cross-sectional analysis of the body composition of individuals with short stature revealed that their fat-free mass (FFM) index was considerably lower (7). However, there is a scarcity of longitudinal studies analyzing the differences in body composition between those whose pre-pubertal short stature persists into pubertal age and those with a short stature who achieved a normal height. Moreover, there is growing interest in employing bioelectrical impedance analysis (BIA) for body composition assessment in clinical settings due to its cost-effectiveness, simplicity, and non-invasiveness (7). In addition, BIA has consistently demonstrated excellent test-retest reliability and moderate to strong correlations with dual-energy X-ray absorptiometry (DXA), particularly in pediatric and adolescent cohorts, thereby establishing it as an affordable, convenient, and highly reproducible method for evaluating body composition in clinical practice (8). In the present study, we conducted a longitudinal analysis using data from Korean children and adolescents to compare the changes in body composition among those whose pre-pubertal short stature persisted into pubertal age, those who achieved a normal height and a control group with a normal height.

Methods

Study Sample

The GP Cohort Study, conducted by GP Co., Ltd. in Gwangmyeong City, Gyeonggi Province, Republic of Korea, is an ongoing mixed longitudinal research study involving Korean students. The study involves students aged 7-18 years from elementary, middle and high schools in Korea, specifically in Gyeonggi Province, with approximately 35 schools participating annually. Data collection occurs biannually in schools, where examiners use the stadiometer and octapolar multi-frequency biometric impedance analyzer (Inbody models J10 and J30, Inbody, Seoul, Korea) to measure students' height, weight and body composition following a standard protocol. Height measurements were taken using a stadiometer in accordance with the Centers for Disease Control and Prevention guidelines, whereas body composition assessments followed the manual provided by InBody Inc. (7,8,9). Participants were instructed to stand for five minutes before the examination, and the examination was conducted if at least two hours had passed since the last meal. Before the examination, participants were instructed to use the restroom, wash their hands thoroughly, and return. Examinations were preferably conducted in the morning at schools, and apart from assisting participants in adopting the standard standing posture for the examination, there was no physical contact between the subjects and the examiners during the examination.

For the original GP Cohort Study data collection, written informed consent was obtained from both the legal guardians and the students themselves prior to participation. Students eligible for physical and body composition measurements with consent from their guardians and themselves were included (8). We excluded those whose measurements could not be taken or who refused participation. Since its commencement on January 1, 2013, the study has gathered 649,330 data points from 110,648 children and adolescents (58,135 boys and 52,513 girls born between 1998 and 2020, as of December 31, 2023).

Short stature was defined as a height more than -2 SD scores (SDSs) below the population mean for age and sex, whereas normal stature was defined as a height between -2 SDS and 2 SDS for age and sex (6). The children were

categorized into the following three groups based on their stature at ages 8 and 12 years: short-to-short statured (SS) group comprising children with a short stature at both 8 and 12 years of age (177 children; 94 boys and 83 girls); short-to-normal statured (SN) group, comprising children who had a short stature at 8 years of age but achieved a normal height at 12 years of age (90 children; 47 boys and 43 girls); and control group, including children with a normal stature at both 8 and 12 years of age (7,195 children; 3,675 boys and 3,520 girls).

The present study was approved by the Institutional Review Board of Yonsei University Health System, Severance Hospital (approval no: 4-2023-1470, date: 28.12.2023), and the requirement for obtaining informed consent from the participants was waived because this investigation was a de-identified retrospective study.

Measurement of Anthropometric Parameters and Body Composition

The participants' height (cm), weight (kg), body fat mass (BFM, kg) and skeletal muscle mass (SMM, kg) were measured to determine their body mass index (BMI), BFM index (BFMI) and SMM index (SMMI), which were calculated as follows.

$$BMI\ (kg/m^2) = \frac{Weight\ (kg)}{Height\ (m)^2}$$

$$BFMI\ (kg/m^2) = \frac{BFM\ (kg)}{Height\ (m)^2}$$

$$SMMI\ (kg/m^2) = \frac{SMM\ (kg)}{Height\ (m)^2}$$

The anthropometric measurements and indices were calibrated based on the GP growth chart for Korean children and adolescents and are presented as the SDS specific to age and sex (9).

Statistical Analysis

Descriptive statistics of the SDS of height, weight, body composition and their indices are presented as mean with standard errors for age and sex. In our analysis, we examined and compared the changes in height, weight and body composition from ages 8 to 12 years between the SS, SN and control groups. Pairwise comparisons among the three groups were made using independent-sample t-tests. We used a difference-in-difference (DID) estimator to examine the growth variations among the three groups. To compute the estimator, first, we determined the mean changes in height, weight and body composition from ages 8 to 12 within one group (D_1). Second, we calculated the corresponding changes within another group (D_2). Finally, we computed the difference between these changes ($\delta_{12} = D_1 - D_2$). Statistical significance was established by estimating the DID estimator in the DID regression model.

All statistical evaluations were conducted using Python, version 3.9.7 (Python Software Foundation, Wilmington, Delaware, USA) and R, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). A p value of less than 0.05 was deemed to indicate statistical significance.

Results

Cross-sectional Analysis of Height, Weight, and Body Composition in SS, SN, and Control Group at Pre-pubertal and Early Pubertal Stages

In the cross-sectional analysis, the boys in the SS group consistently showed significantly lower weight, BFM, SMM, BMI, BFMI and SMMI at both 8 and 12 years of age than the boys in the control group (Tables 1 and 2 and Appendix Tables A1 and A2). Changes of mean height, weight, and BFM, SMM SDS at ages 8 and 12 across in both sex is described in Figure 1. To illustrate, at 8 years of age, the boys in the SS group were, on average, 12.08 cm (2.66 SDS) shorter and 7.00 kg (1.76 SDS) lighter, and their BFM and SMM were lower by 2.26 (0.83 SDS) and 2.76 (2.05 SDS) kg, respectively. In addition, their BMI, BFMI and SMMI were 1.14 (0.53 SDS), 0.75 (0.46 SDS) and 0.45 (0.86 SDS) kg/m² lower, respectively, than the boys in the control group. At 12 years of age, the boys in the SS group were, on average, 18.47 cm (2.75 SDS) shorter and 15.46 kg (1.73 SDS) lighter, and their BFM and SMM were lower by 3.34 (0.51 SDS) and 7.14 (2.17 SDS) kg, respectively. Furthermore, their BMI, BFMI and SMMI were 1.98 (0.62 SDS), 0.26 (0.07 SDS) and 1.22 (1.33 SDS) lower, respectively, than the boys in the control group.

The boys in the SN and SS groups showed a similar growth pattern and body composition at 8 years of age. Minimal non-significant differences in height (0.85 cm, 0.25 SDS), weight (0.05 kg, 0.10 SDS), BFM (-0.12 kg, 0.05 SDS), SMM (0.06 kg, 0.11 SDS), BMI (-0.19 kg/m², -0.03 SDS), BFMI (-0.12 kg/m², 0.02 SDS) and SMMI (-0.03 kg/m², -0.04 SDS) were observed between the SN and SS groups. However, by the age of 12 years, the SN and SS groups showed significant differences in most parameters. The boys in the SS group were 7.48 cm (1.12 SDS) shorter and 6.05 kg (0.70 SDS) lighter, and their BFM and SMM were lower by 0.93 (0.11

SDS) and 3.03 (0.98 SDS) kg, respectively, than those of the boys in the SN group. Moreover, the SS group had lower BMI (0.92 kg/m², 0.27 SDS) and SMMI (0.67 kg/m², 0.70 SDS) than the SN group. Interestingly, the difference in BFMI (-0.05 kg/m², -0.07 SDS) between the boys in the SS and SN groups was not significant.

In the cross-sectional analysis of the girls, those in the SS group consistently exhibited significantly lower weight, BFM, SMM, BMI, BFMI and SMMI at both 8 and 12 years of age than the girls in the control group (Tables 1 and 2 and Appendix Tables A1 and A2). To illustrate, at 8 years of age, the girls in the SS group were, on average, 12.11 cm (2.65

Table 1. Mean height, weight, and body composition SDS at ages 8 and 12 across short-to-short statured, short-to-normal statured, and control groups

Age (years)	8			12		
	Control	SN	SS	Control	SN	SS
Boys						
Height SDS (SE)	0.05 (0.88)	-2.36 (0.34)	-2.61 (0.41)	0.33 (0.86)	-1.30 (0.48)	-2.42 (0.32)
Weight SDS (SE)	0.12 (1.02)	-1.54 (0.73)	-1.64 (0.87)	0.37 (1.07)	-0.67 (0.94)	-1.36 (0.73)
BFM SDS (SE)	0.11 (1.08)	-0.67 (0.78)	-0.72 (0.90)	0.24 (1.09)	-0.16 (1.12)	-0.27 (0.98)
SMM SDS (SE)	0.14 (0.96)	-1.81 (0.59)	-1.92 (0.69)	0.33 (0.94)	-0.87 (0.62)	-1.84 (0.52)
BMI SDS (SE)	0.12 (1.06)	-0.44 (0.81)	-0.41 (0.91)	0.26 (1.09)	-0.09 (1.17)	-0.36 (1.00)
BFMI SDS (SE)	0.11 (1.09)	-0.34 (0.82)	-0.36 (0.95)	0.18 (1.09)	0.05 (1.17)	0.12 (1.06)
SMMI SDS (SE)	0.18 (1.04)	-0.72 (0.86)	-0.68 (0.96)	0.27 (1.02)	-0.35 (0.79)	-1.06 (0.73)
Girls						
Height SDS (SE)	-0.02 (0.87)	-2.34 (0.28)	-2.67 (0.47)	0.33 (0.84)	-1.37 (0.42)	-2.65 (0.49)
Weight SDS (SE)	0.02 (0.93)	-1.43 (0.69)	-1.75 (0.68)	0.20 (0.96)	-0.70 (0.79)	-1.70 (0.95)
BFM SDS (SE)	-0.00 (0.98)	-0.57 (0.81)	-0.89 (0.78)	0.10 (0.99)	-0.27 (0.91)	-0.97 (1.09)
SMM SDS (SE)	0.04 (0.89)	-1.82 (0.49)	-2.01 (0.69)	0.25 (0.93)	-0.98 (0.61)	-1.98 (0.78)
BMI SDS (SE)	0.03 (0.97)	-0.33 (0.81)	-0.53 (0.78)	0.06 (1.00)	-0.14 (0.94)	-0.66 (1.08)
BFMI SDS (SE)	0.00 (0.99)	-0.20 (0.86)	-0.50 (0.84)	0.04 (0.99)	-0.03 (0.95)	-0.56 (1.17)
SMMI SDS (SE)	0.08 (0.96)	-0.78 (0.79)	-0.82 (0.92)	0.11 (1.00)	-0.36 (0.87)	-0.90 (1.04)

SDS: standard deviation score, SN: short-to-normal statured group, SS: short-to-short statured group, BFM: body fat mass, SMM: skeletal muscle mass, BMI: body mass index, BFMI: body fat mass index, SMMI: skeletal muscle mass index, SE: standard error

Table 2. Differences of mean height, weight, and body composition SDS at ages 8 and 12 across short-to-short statured, short-to-normal statured, and control groups

Age (years)	8			12		
	Control-SN	Control-SS	SN-SS	Control-SN	Control-SS	SN-SS
Boys						
Height SDS (CI)	**2.41 (2.39-2.43)**	**2.66 (2.63-2.69)**	**0.25 (0.22-0.28)**	**1.63 (1.61-1.65)**	**2.75 (2.73-2.77)**	**1.12 (1.09-1.15)**
Weight SDS (CI)	**1.66 (1.63-1.70)**	**1.76 (1.70-1.82)**	**0.10 (0.03-0.17)**	**1.04 (0.99-1.08)**	**1.73 (1.68-1.78)**	**0.70 (0.63-0.76)**
BFM SDS (CI)	**0.77 (0.73-0.81)**	**0.83 (0.77-0.89)**	0.05^{N} (-0.02-0.13)	**0.40 (0.35-0.46)**	**0.51 (0.44-0.58)**	**0.11 (0.02-0.19)**
SMM SDS (CI)	**1.94 (1.91-1.97)**	**2.05 (2.01-2.10)**	**0.11 (0.06-0.17)**	**1.20 (1.17-1.23)**	**2.17 (2.14-2.21)**	**0.98 (0.93-1.02)**
BMI SDS (CI)	**0.56 (0.52-0.60)**	**0.53 (0.47-0.59)**	-0.03^{N} (-0.11-0.04)	**0.35 (0.29-0.41)**	**0.62 (0.55-0.68)**	**0.27 (0.18-0.35)**
BFMI SDS (CI)	**0.45 (0.41-0.49)**	**0.46 (0.40-0.53)**	0.02^{N} (-0.06-0.09)	**0.14 (0.08-0.19)**	0.07^{N} (-0.00-0.14)	-0.07^{N} (-0.16-0.02)
SMMI SDS (CI)	**0.90 (0.86-0.94)**	**0.86 (0.80-0.93)**	-0.04^{N} (-0.12-0.04)	**0.62 (0.58-0.66)**	**1.33 (1.28-1.38)**	**0.70 (0.64-0.77)**
Girls						
Height SDS (CI)	**2.31 (2.30-2.33)**	**2.64 (2.61-2.68)**	**0.33 (0.29-0.37)**	**1.70 (1.68-1.73)**	**2.98 (2.95-3.02)**	**1.28 (1.24-1.32)**
Weight SDS (CI)	**1.44 (1.41-1.48)**	**1.76 (1.72-1.81)**	**0.32 (0.26-0.38)**	**0.90 (0.86-0.94)**	**1.90 (1.83-1.97)**	**1.00 (0.92-1.08)**
BFM SDS (CI)	**0.57 (0.52-0.61)**	**0.89 (0.83-0.95)**	**0.32 (0.26-0.39)**	**0.37 (0.32-0.42)**	**1.07 (1.00-1.15)**	**0.70 (0.62-0.79)**
SMM SDS (CI)	**1.86 (1.83-1.88)**	**2.05 (2.00-2.10)**	**0.19 (0.13-0.24)**	**1.24 (1.20-1.27)**	**2.23 (2.18-2.29)**	**1.00 (0.93-1.06)**
BMI SDS (CI)	**0.36 (0.32-0.40)**	**0.56 (0.51-0.62)**	**0.20 (0.13-0.27)**	**0.19 (0.15-0.24)**	**0.72 (0.64-0.80)**	**0.52 (0.43-0.61)**
BFMI SDS (CI)	**0.21 (0.16-0.25)**	**0.51 (0.45-0.56)**	**0.30 (0.22-0.37)**	**0.07 (0.02-0.12)**	**0.60 (0.52-0.68)**	**0.53 (0.43-0.62)**
SMMI SDS (CI)	**0.87 (0.83-0.91)**	**0.90 (0.84-0.97)**	**0.03^{N} (-0.04-0.11)**	**0.47 (0.43-0.52)**	**1.01 (0.93-1.08)**	**0.53 (0.45-0.62)**

^{N}Statistically insignificant.
SDS: standard deviation score, SN: short-to-normal statured group, SS: short-to-short statured group, BFM: body fat mass, SMM: skeletal muscle mass, BMI: body mass index, BFMI: body fat mass index, SMMI: skeletal muscle mass index, CI: 95% confidence interval

SDS) shorter and their body weight, BFM and SMM were lower by 6.73 (1.77 SDS), 2.35 (0.89 SDS) and 2.61 (2.05 SDS) kg, respectively, than those of the girls in the control group. Their BMI, SMMI and BFMI were also lower by 1.19 (0.56 SDS), 0.84 (0.51 SDS) and 0.46 (0.90 SDS) kg/m² than those of the girls in the control group. At 12 years of age, the girls in the SS group were, on average, 16.34 cm (2.98 SDS) shorter, and their body weight, BFM and SMM were lower by 13.15 (1.90 SDS), 4.47 (1.07 SDS) and 5.08 (2.23 SDS) kg, respectively. In addition, their BMI, SMMI and BFMI were lower by 1.88 (0.72 SDS), 1.00 (0.60 SDS) and 0.71 (1.01 SDS) kg/m², respectively, than those of the girls in the control group.

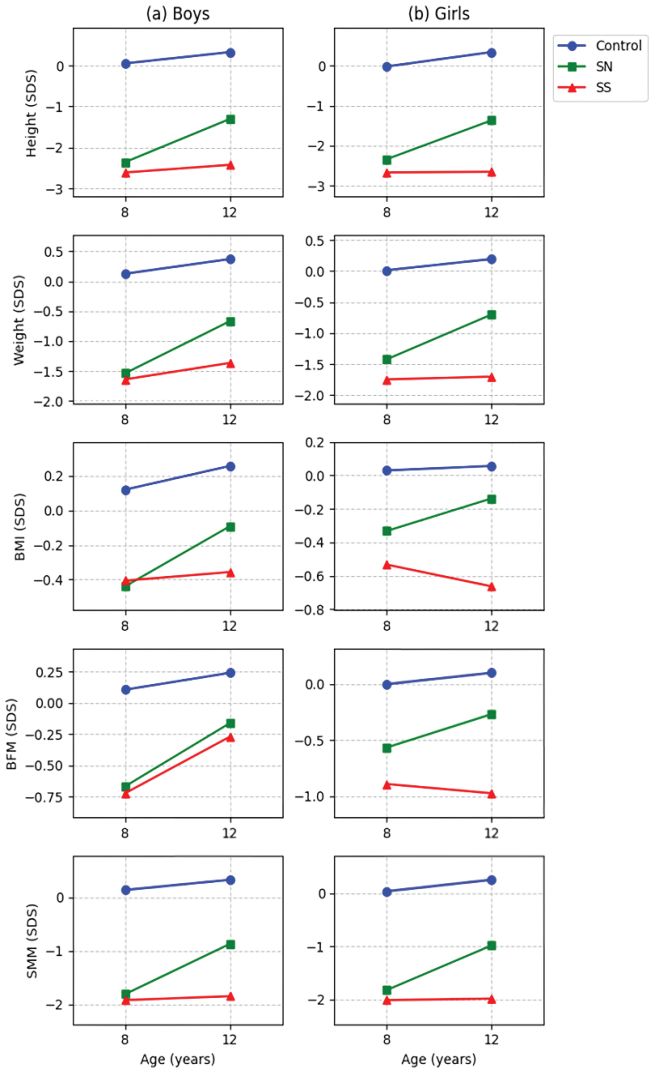

Figure 1. Changes of mean height, weight, and body composition at ages 8 and 12 across short-to-short statured, short-to-normal statured, and control groups

SN: short-to-normal statured group, SS: short-to-short statured group, BMI: body mass index, BFM: body fat mass, SMM: skeletal muscle mass, SDS: standard deviation score

When comparing the parameters between the girls in the SN and SS groups, it was observed that, unlike the boys, the girls in the SN group were already taller (1.21 cm & 0.33 SDS) and heavier (0.96 kg & 0.32 SDS) and had greater BFM (0.77 kg & 0.32 SDS) and SMM (0.15 kg & 0.19 SDS) by the age of 8 than the girls in the SS group. Moreover, their BMI (0.39 kg/m² & 0.20 SDS) and BFMI (0.47 kg/m² & 0.30 SDS) were also significantly higher. These discrepancies became more pronounced by 12 years of age. The girls in the SS group were shorter (7.17 cm & 1.28 SDS) and lighter (6.50 kg & 1.00 SDS), and their BFM and SMM were lower by 2.69 (0.70 SDS) and 2.24 (1.00 SDS) kg, respectively. Furthermore, their BMI and BFMI were lower by 1.34 (0.52 SDS) and 0.87 (0.53 SDS) kg/m², respectively. Notably, compared to girls in the SN group, the difference in SMMI was not significant at 8 years of age (0.00 kg/m² & 0.03 SDS), but it became significant by 12 years of age (0.38 kg/m² & 0.53 SDS).

Differences in Longitudinal Growth Trajectories of Height, Weight, and Body Composition Among SS, SN, and the Control Group from Pre-pubertal to Early Pubertal Stages

To assess the longitudinal differences in the height, weight and body composition growth across the SS, SN and control groups, we used the DID estimator (Table 3, Figure 2 and Appendix Table A3). This estimator computes these variances by assessing the changes in SDS between 8 and 12 years of age within each group. When comparing the data between the boys in the SS and control groups, the SDS changes in most parameters were not significant, except for the SMMI SDS change of 0.46 SDS. Conversely, the boys in the SN group demonstrated significantly greater increases in height (0.78 SDS), weight (0.62 SDS), BFM (0.37 SDS) and SMM (0.75 SDS) compared to the control group. Furthermore, when compared to the SS group, the boys in the SN group showed significantly greater increases in height (0.87 SDS), weight (0.59 SDS), SMM (0.86 SDS) and SMMI (0.75 SDS).

Similar trends were observed among the girls. When comparing the values between the girls in the SS and control groups, no significant differences were found in the SDS changes of any parameter. Conversely, the girls in the SN group displayed notable growth discrepancies with the control group. The SN group showed significantly greater increases in height (0.61 SDS), weight (0.54 SDS), SMM (0.62 SDS) and SMMI (0.39 SDS) than the control group. When compared to the SS group, the SN group exhibited significantly greater increases in height (0.95 SDS), weight (0.68 SDS), SMM (0.81 SDS) and SMMI (0.50 SDS).

Table 3. Comparison of height, weight, and body composition SDS changes between ages 8 and 12 across short-to-short statured, short-to-normal statured, and control groups

	Difference			Difference-in-difference		
	Control	SN	SS	Control-SN	Control-SS	SN-SS
Boys						
Height SDS (CI)	**0.28 (0.27-0.28)**	**1.05 (1.03-1.08)**	**0.19 (0.15-0.22)**	**-0.78† (-1.03- -0.53)**	0.09 (-0.26-0.44)	**0.87† (0.67-1.07)**
Weight SDS (CI)	**0.25 (0.23-0.26)**	**0.87 (0.81-0.93)**	**0.27 (0.20-0.35)**	**-0.62† (-0.93- -0.32)**	-0.03 (-0.45-0.40)	**0.59† (0.18-1.01)**
BFM SDS (CI)	**0.13 (0.12-0.15)**	**0.51 (0.44-0.57)**	**0.45 (0.36-0.54)**	**-0.37* (-0.69- -0.06)**	-0.32 (-0.76-0.12)	0.05 (-0.42-0.53)
SMM SDS (CI)	**0.19 (0.18-0.20)**	**0.94 (0.90-0.98)**	**0.07 (0.02-0.13)**	**-0.75† (-1.02- -0.47)**	0.12 (-0.27-0.50)	**0.86† (0.56-1.17)**
BMI SDS (CI)	**0.14 (0.13-0.15)**	**0.35 (0.28-0.42)**	**0.05 (-0.04-0.14)**	-0.21 (-0.52-0.10)	0.09 (-0.35-0.53)	0.30 (-0.19-0.79)
BFMI SDS (CI)	**0.08 (0.07-0.09)**	**0.39 (0.32-0.46)**	**0.47 (0.38-0.57)**	-0.31 (-0.63-0.00)	-0.40 (-0.84-0.05)	-0.08 (-0.59-0.42)
SMMI SDS (CI)	**0.09 (0.08-0.10)**	**0.37 (0.32-0.43)**	**-0.37 (-0.46- -0.29)**	-0.28 (-0.58-0.02)	**0.46* (0.05-0.88)**	**0.75† (0.33-1.16)**
Girls						
Height SDS (CI)	**0.36 (0.35-0.37)**	**0.97 (0.94-0.99)**	**0.02 (-0.03-0.07)**	**-0.61† (-0.87- -0.35)**	0.34 (-0.02-0.70)	**0.95† (0.74-1.16)**
Weight SDS (CI)	**0.18 (0.17-0.19)**	**0.72 (0.67-0.78)**	**0.04 (-0.04-0.13)**	**-0.54† (-0.83- -0.25)**	0.14 (-0.27-0.54)	**0.68† (0.27-1.08)**
BFM SDS (CI)	**0.10 (0.09-0.11)**	**0.30 (0.24-0.36)**	**-0.08 (-0.18-0.01)**	-0.20 (-0.50-0.11)	0.18 (-0.24-0.60)	0.38 (-0.09-0.85)
SMM SDS (CI)	**0.22 (0.21-0.23)**	**0.84 (0.80-0.88)**	**0.03 (-0.04-0.10)**	**-0.62† (-0.90- -0.34)**	0.19 (-0.20-0.58)	**0.81† (0.48-1.13)**
BMI SDS (CI)	**0.03 (0.02-0.04)**	**0.19 (0.13-0.26)**	**-0.13 (-0.22- -0.04)**	-0.17 (-0.47-0.14)	0.16 (-0.26-0.58)	0.32 (-0.15-0.80)
BFMI SDS (CI)	**0.04 (0.03-0.05)**	**0.17 (0.11-0.24)**	**-0.06 (-0.16-0.04)**	-0.14 (-0.44-0.17)	0.09 (-0.33-0.52)	0.23 (-0.26-0.73)
SMMI SDS (CI)	**0.03 (0.01-0.04)**	**0.42 (0.36-0.48)**	**-0.08 (-0.18-0.02)**	**-0.39* (-0.69- -0.09)**	0.10 (-0.31-0.52)	**0.50* (0.03-0.96)**

†p value < 0.01, *p value < 0.05.
SDS: standard deviation score, SN: short-to-normal statured group, SS: short-to-short statured group, BFM: body fat mass, SMM: skeletal muscle mass, BMI: body mass index, BFMI: body fat mass index, SMMI: skeletal muscle mass index, CI: 95% confidence interval

Discussion

The present study is the first to analyze and compare the longitudinal body composition changes between Korean children with a pre-pubertal short stature who maintained their short stature and those who attained a normal stature by early puberty. The cross-sectional analysis indicated that children in the SS group had significantly lower values for weight, BFM, SMM, BMI, BFMI, and SMMI compared to the control group at both assessed ages. In a longitudinal perspective, the SN group showed significantly larger increases in height (0.87 SDS for boys and 0.95 SDS for girls), weight (0.59 SDS for boys and 0.68 SDS for girls), and SMMI (0.75 SDS for boys and 0.50 SDS for girls) than the SS group, while there was no significant difference in BFMI between the groups.

To facilitate early intervention by clinicians, the present study focused on data collected before the period of late puberty, establishing the ages of 8 and 12 years as benchmarks for pre-pubertal and early pubertal stages, respectively. The rationale for selecting these age benchmarks is twofold. First, a child with a short stature who did not achieve a normal height by early puberty may have a persistent short stature or reduced final adult height. Even among children with CDGP, which are typically known to be able to naturally overcome their short stature, some of them may not reach their predicted adult height, particularly if the puberty onset is delayed (10). This suggests that, regardless of whether the short stature is due to an underlying organic cause or related to CDGP, the children who do not exhibit a normal growth pattern before the onset of puberty may experience a reduction in final adult height. Therefore, analyzing the growth patterns up to the early pubertal stage will facilitate timely interventions. Second, our prior research on the pubertal growth spurt within the GP cohort dataset used in this study, utilized the age of onset of the growth spurt (AGOS) as an indirect indicator of puberty onset. The findings revealed that the AGOS, within one SD of the normal distribution, was 10.17 ± 0.61 and 8.57 ± 0.68 years for boys and girls, respectively. Consequently, these age ranges were considered indicative of puberty onset, leading to the selection of the ages 8 and 12 years as the respective age thresholds for this study (9).

In this context, the children were categorized into three groups based on their stature at 8 and 12 years of age. Our findings showed that both boys and girls in the SS group were significantly shorter and lighter and had significantly lower BFM, SMM, BMI, BFMI, and SMMI at 8 and 12 years of age than the control group. However, the children with pre-pubertal short stature exhibited distinct growth patterns, with the differences between those who remained short-statured and those who achieved a normal stature becoming more pronounced over time. When assessing the growth differences across groups, the SN group demonstrated

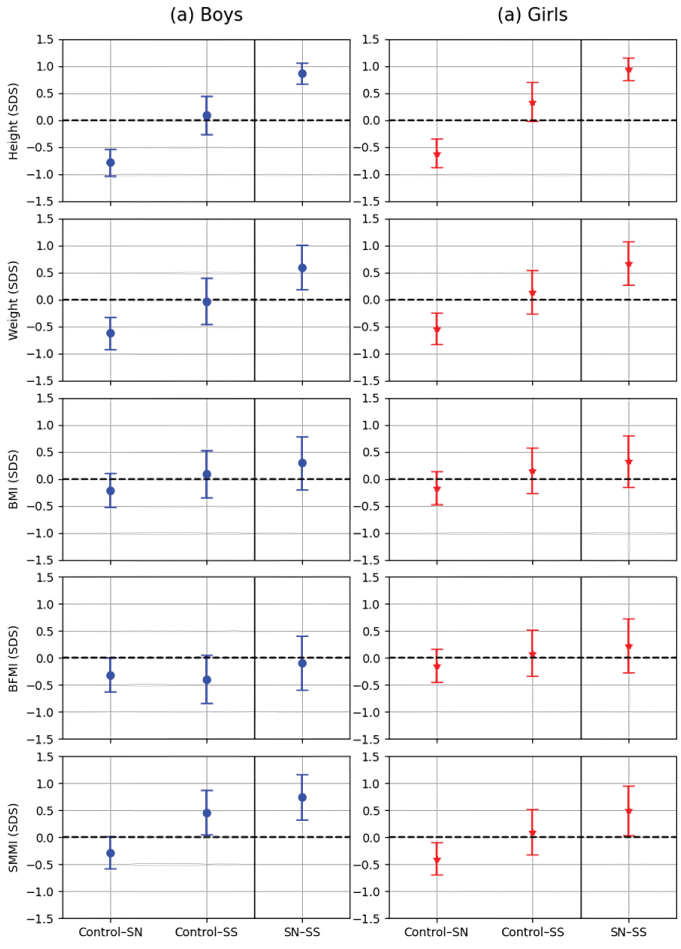

Figure 2. Comparison of height, weight, BMI, BFMI, and SMMI changes between ages 8 and 12 across short-to-short statured, short-to-normal statured, and control groups

SN: short-to-normal statured group, SS: short-to-short statured group, BMI: body mass index, BFMI: body fat mass index, SMMI: skeletal muscle mass index

significantly greater increases in height, weight, BFM and SMM than the control group. Additionally, compared to the SS group, the SN group exhibited greater increases in height, weight, SMM and SMMI. A significant difference in SMMI was observed between the boys in the SS and control groups, whilst no significant differences were found between girls in the SS and control groups. Overall, the SN group exhibited significantly greater increases in height, weight and SMM than the SS and control groups, with consistent trends observed in both sexes.

In the present study there was a significant difference in SMMI between the SN and SS groups, which is consistent with the results of a previous case-control study analyzing the body composition of preschool children with short stature (11). Short stature results from diverse etiologies, and numerous factors associated with lower SMMI have been identified among them. From the perspective of GH action, low SMMI in children with short stature can often be attributed to impaired skeletal muscle cell proliferation and myocyte differentiation resulting from reduced GH/IGF-1 axis activity, particularly in cases of GHD. This finding aligns with the results of a previous study conducted in China involving a similar age group (mean age of 10.00 ± 3.42 years). In that study, SMMI, measured using chest computed tomography (CT), was positively associated with serum GH peak and IGF-1 levels. Low peak GH and IGF-1 levels were identified as independent predictors of reduced SMMI in children with short stature (12,13). Consistent with these observations, studies investigating ISS also highlight reduced lean body mass in affected children. A case-control study involving preschool-age children with unexplained short stature reported significantly lower fat-free mass (FFM) and SMM compared to height-matched normal controls (11). Notably, SMMI was lower in children with short stature despite similar BMI values, suggesting a relative deficit in muscle tissue potentially linked to early-life growth impairment. In addition, the other factors contributing to a short stature may include a low lean body mass, as observed in individuals with ISS, decreased SMM due to malnutrition, including inadequate protein intake, and muscle wasting associated with chronic illnesses, including chronic kidney disease and cystic fibrosis (14,15,16). Importantly, however, there is a lack of direct statistical data linking endocrine abnormalities or chronic illnesses causally to short stature and reduced SMMI gain and so caution should be exercised when interpreting these associations. Furthermore, another plausible and often overlooked explanation is that many of the children with short stature might have been born SGA, either with low birthweight or low birth length, predisposing them to persistent short stature and reduced muscle mass later in life. Emerging research indicates that children with short stature who were born SGA may have reduced SMM compared to their peers. Persistent short stature in children born SGA is frequently associated with significant deficits in muscle mass. Schweizer et al. (17) studied 34 short prepubertal children born SGA (mean age approximately 7.3 years; height SDS approximately -3.3) and reported that these children exhibited significantly reduced muscle mass and impaired muscle function. Similarly, Rojo-Trejo et al. (18) compared 44 term-born SGA children aged 6-11 years to 57 appropriate-for-gestational-age peers. The SGA group demonstrated consistently lower measures of muscle and bone mass, including significantly lower appendicular skeletal muscle mass index and total body bone mineral content and density ($p \leq 0.005$).

Although these factors may all contribute to persistently low SMMI in children with short stature, it is important to recognize that many cases of short stature remain unexplained and are likely influenced by environmental factors. Indeed, more than half of short-stature cases are not associated with systemic diseases, endocrine disorders, or chromosomal abnormalities (19). Environmental factors, including socio-economic status, malnutrition, and lack of physical activity, have been widely studied and are commonly recognized as contributing factors (20,21).

Therefore, regardless of whether the cause of short stature is clearly identified, we believe it is essential to analyze a child's body composition to monitor children with persistently low SMMI. The individuals who consistently exhibit a low SMMI and short stature should receive increased attention and care, as they may be at risk for growth problems. This comprehensive approach ensures that both pathological causes and environmental influences are thoroughly evaluated, allowing for a better understanding of the underlying aetiology and potential presence of concurrent metabolic disorders associated with low SMMI (22,23).

The present study has a few limitations. The first limitation is that, although we adhered to the standard guidelines provided by InBody Co., Ltd. for BIA measurements, certain factors, such as the inability to uniformly control the hydration status or electrolyte balance across all individuals and the absence of temperature measurements, present challenges (24). Despite these challenges, BIA offers several advantages as a method for assessing body composition. Although alternative methodologies, including magnetic resonance imaging, CT and DXA are available, BIA stands out due to its simplicity, non-invasiveness and cost-effectiveness, making it particularly suitable for large-scale studies (25,26). Recent studies on multi-frequency BIA devices indicate reduced susceptibility to errors and the excellent reproducibility of these devices, supporting their reliability for use in longitudinal observations across children and adolescent populations (27,28). Another limitation of our study is that we longitudinally analyzed the body composition characteristics in children with pre-pubertal short stature persisting into the early pubertal stage, which did not encompass the entire age spectrum of children and adolescents, including the age the final adult height was achieved. Furthermore, since our cohort study was conducted in Gwangmyeong City, Gyeonggi Province, it may not fully represent the characteristics of the entire Korean population, potentially limiting the generalizability of our findings. Finally, in this study, the diminished gain in SMMI observed in the SS group, which failed to achieve normal height by early puberty, was initially interpreted as suggestive of growth failure. However, although our definitions of prepuberty and early puberty were based on AGOS obtained from previous research involving the same cohort (7,9), the absence of key parameters, including measured parental height, Tanner stage, bone age estimation, birth history (including gestational age, birth weight, and birth length), and height velocity, limits our ability to conclusively attribute these findings to true growth failure (2,10). Notably, our prior research on pubertal changes in body composition within the same cohort demonstrated that boys typically exhibit an earlier age at peak FFM velocity and a higher velocity compared to girls (7). This suggests a potentially greater variability in SMMI depend on pubertal staging in boys, particularly among those with CDGP. Consequently, without these additional parameters, distinguishing true pathological short stature from normal variants such as CDGP or familial short stature remains challenging. Therefore, future studies should incorporate these critical factors to enable a more precise and objective classification. Additionally, we plan to follow this cohort into late adolescence and adulthood to determine whether early pubertal SMMI trajectories are predictive of final adult height, thereby clarifying whether the observed differences reflect transient variations or enduring growth outcomes.

However, the greatest strength of our study lies in its being, to the best of our knowledge, the first longitudinal population-based study to demonstrate significant differences in SMMI among children with a pre-pubertal short stature that persists into early puberty, children with a pre-pubertal short stature who achieved a normal height, and children with a normal height. We are continuously collecting new participants' height, weight, and body composition data each year while expanding the geographical range of our subjects. We are also incorporating additional clinically relevant parameters, such as parental height, Tanner staging, bone age estimation, birth history (including gestational age, birth weight, and birth length), and height velocity into our data collection. In future study, by conducting longitudinal analyses on subjects who have reached their final adult height, we aim to evaluate the broader scope of data and understand how changes in body composition during different stages of pubertal development influence height growth. This comprehensive approach will enable a more detailed analysis of the impact of body composition on final adult stature.

In conclusion, our study could serve as a foundation for using longitudinal body composition assessment to identify high-risk children with short stature. The most significant increase in SMMI was observed in children who improved to normal height from pre-pubertal short stature. Children with

lower increases in SMMI may require further assessment for continued short stature.

Conclusion

This study analyzed anthropometric and body composition changes in children with pre-pubertal short stature who either achieved normal height or remained short by early puberty. Children who achieved normal height demonstrated greater increases in SMMI, height, and weight, with SMMI being the most significant factor in body composition trajectory than those who remained short. Lower increases in SMMI may indicate a need for further evaluation and potential intervention for persistent short stature.

Ethics

Ethics Committee Approval: The present study was approved by the Institutional Review Board of Yonsei University Health System, Severance Hospital (approval no: 4-2023-1470, date: 28.12.2023).

Informed Consent: Written informed consent was obtained from both the legal guardians and the students themselves prior to participation.

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Footnotes

Authorship Contributions

Concept: Junghwan Suh, Jihun Kim, Design: Junghwan Suh, Jihun Kim, Data Collection or Processing: Dohyun Chun, Analysis or Interpretation: Dohyun Chun, Literature Search: Seo Jung Kim, Writing: Dohyun Chun, Seo Jung Kim, Junghwan Suh, Jihun Kim.

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Availability of Data and Materials: The data that support the findings of this study are available from GP Co., Ltd. but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of GP Co., Ltd.

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Click the link to access Appendix Tables A1-A3: https://d2v96fxpocvxx.cloudfront.net/688d2d00-d207-464d-89b6-73f393f4f50c/content-images/8b478ad0-f7d9-4955-a011-a1be32b5a960.pdf

ORIGINAL ARTICLE

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Genotype, Phenotype, and Clinical Characteristics of Maturity-Onset Diabetes of the Young (MODY): Predominance of *GCK*-MODY

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What is already known on this topic?

Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes mellitus. To date, 14 different genes associated with MODY have been reported: hepatocyte nuclear factor-4-alpha; glucokinase; hepatocyte nuclear factor-1-alpha; pancreas-duodenum homeobox protein-1; hepatocyte nuclear factor-1 beta; neuronal differentiation-1; Kruppel-like factor 11; carboxyl ester lipase; paired box-4; insulin (*INS*); B lymphocyte kinase; ATP-binding cassette subfamily C member 8; potassium channel, inwardly rectifying, subfamily J member 11; and adaptor protein, phosphotyrosine interaction, pH domain, and leucine zipper containing 1. The diagnosis of MODY includes dominant inheritance with at least two (preferably three) consecutive affected generations; onset of diabetes is typically before the age of 25-30 years, there is evidence of significant but impaired residual insulin secretion reflected in c-peptide levels, and tests for autoantibodies associated with type 1 diabetes mellitus are negative in most cases (very rare exceptions have been reported). Stable, mild, non-progressive hyperglycemia is suggestive of glucokinase (*GCK*)-MODY in asymptomatic individuals.

What this study adds?

As in various studies conducted in children from Türkiye, the most frequently detected MODY type in our cohort was *GCK*-MODY. Although MODY is generally known as an autoantibody-negative type of diabetes, with islet cell antibody being particularly unusual, autoantibody positivity was detected in approximately one-quarter of the cases in our study and more than half of these were anti-islet cell antibodies.

Abstract

Objective: Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes characterised by early-onset diabetes and inherited in an autosomal dominant manner. MODY results from heterozygous mutations in genes important for pancreatic β-cell development or function. The objective was to identify the most common and rarest types of MODY amongst our cases with genetically confirmed MODY diagnosis, to evaluate clinical and laboratory features and treatment regimens.

Methods: The epidemiological, auxological, and laboratory data, genetic analysis results and treatment regimens of patients diagnosed with MODY were retrospectively evaluated.

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Results: Of the 44 cases included, 27 (61.4%) were male and the median age at diagnosis was 10.07 (1-16.8) years. There was a family history of diabetes in 42 (95.5%) cases. The distribution of gene variants was: 25 (55.8%) glucokinase (*GCK*), 4 (9.1%) hepatocyte nuclear factor-4-alpha, 4 (9.1%) carboxyl ester lipase, 2 (4.5%) B lymphocyte kinase, 4 (9.1%) ATP-binding cassette subfamily C member 8, 2 (4.5%) Kruppel-like factor 11, 1 (2.3%) insulin (*INS*), 1 (2.3%) potassium channel, inwardly rectifying, subfamily J member 11, and 1 (2.3%) adaptor protein, phosphotyrosine interaction, pH domain, and leucine zipper containing 1. At presentation, 23 (52.3%) of the cases had incidental hyperglycemia while 14 (31.8%) had polyuria and polydipsia. Diabetic ketoacidosis was detected in 4 (9.1%) and ketonemia in 3 (6.9%). At least one of the diabetes autoantibodies (anti-glutamate acid decarboxylase, anti-islet cell antibodies, anti-insulin autoantibodies) was detected in 11 (25%) cases, of which 7/11 were islet antibodies, and 5 patients (11%) had two autoantibodies positive simultaneously. In terms of treatment, 26 (59%) received diet and lifestyle changes only, 18 (41%) received oral antidiabetic agents and/or insulin, and 6 (13.6%) received both oral antidiabetic agents and insulin.
Conclusion: The most common type of MODY in our cohort was *GCK*-MODY. Although MODY is generally known as an autoantibody-negative type of diabetes, autoantibody positivity was detected in 11 of 44 cases (25%) in the present study.
Keywords: MODY, diabetes autoantibodies, childhood

Introduction

Maturity-onset diabetes of the young (MODY) represents the most prevalent form of monogenic diabetes, resulting from defects in a single gene or chromosomal locus. All currently identified MODY subtypes are attributed to dominant heterozygous mutations in genes that are pivotal for the development or function of pancreatic β-cells (1).

A total of 14 different genes have been identified as being associated with mutations that are linked to MODY. Of these, six encode key factors. The genes in question are: hepatocyte nuclear factor-4-alpha (*HNF4α*); glucokinase (*GCK*); hepatocyte nuclear factor-1-alpha (*HNF1α*); pancreas-duodenum homeobox protein-1 (*PDX1*); hepatocyte nuclear factor-1 beta (*HNF1β*); and neuronal differentiation-1 (*NEUROD1*). The following genes have been identified as being associated with MODY: Kruppel-like factor 11 (*KLF11*); carboxyl ester lipase (*CEL*); paired box-4 (*PAX4*); insulin (*INS*); B lymphocyte kinase (*BLK*); adenosine triphosphate (ATP)-binding cassette subfamily C member 8 (*ABCC8*); potassium channel, inwardly rectifying, subfamily J member 11 (*KCNJ11*); and adaptor protein, phosphotyrosine interaction, pH domain, and leucine zipper containing 1 (*APPL1*) (2).

The classic MODY phenotype is characterized by the absence of ketosis and the absence of insulin dependence, with a diagnosis of diabetes occurring before the age of 25 years. In addition, there must be a family history of at least one affected individual. These criteria are employed to define the MODY phenotype and to identify patients who may be suitable candidates for genetic testing (3,4).

The objective of this study was to describe the most common and rarer types of MODY in cases with genetically confirmed diagnoses in a single center cohort, and to evaluate the clinical diagnostic characteristics, genetic analysis results, follow-up, and treatment features of these patients.

Methods

Cases

The study was conducted retrospectively, analyzing the epidemiological, auxological, laboratory, genetic, and treatment data of 44 patients diagnosed with MODY and followed in two pediatric endocrinology clinics in Malatya between January 2013 and December 2020. The epidemiological data included age, gender, parental consanguinity, and family history of diabetes. Auxological data consisted of height (cm), weight (kg), and body mass index (BMI; kg/m²). Laboratory data included glucose, insulin, C-peptide, hemoglobin A1c (HbA1c), lipid profile (total cholesterol, total triglycerides, high-density lipoprotein, low-density lipoprotein, urine ketones, and diabetes autoantibodies. Genetic analysis results and treatment regimens were also retrospectively evaluated from patient follow-up records.

The auxological evaluations of the patients, conducted using standard measurement tools with a precision of 0.1 kg for weight and 0.1 cm for height, were performed using the auxology section of the ÇEDD-NET calculation system. This system was developed by the Turkish Society of Pediatric Endocrinology and Diabetes for use by pediatricians and pediatric endocrinology physicians (5).

For a classic MODY diagnosis, the following criteria were used: dominant inheritance with at least two (preferably three) consecutively affected generations (though *de novo* mutations have been reported); onset of diabetes typically before the age of 25 to 30 years; evidence of significant but impaired residual insulin secretion, reflected in C-peptide levels, regardless of whether the patient is treated with insulin; negative tests for antibodies associated with type 1 diabetes mellitus (T1DM), although again, very rare exceptions have been reported; and stable, mild, non-progressive hyperglycemia in asymptomatic individuals, suggesting *GCK*-MODY (3,4).

Genetic Analysis

At least three generation pedigrees of the cases were formed. Genomic DNA was extracted from peripheral blood with QiAamp DNA Blood Mini Kit (cat. no. 51106, Qiagen, Hilden, Germany). Next generation sequencing was performed by capture of the all exons and 10 bp exon-intron junctions of the 14 target MODY genes (*ABCC8, APPL1, BLK, CEL, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, KLF11, NEUROD1, PAX4,* and *PDX1*). Prior to library preparation, each sample was diluted to a fixed concentration of 20 ng using nuclease-free water, as required by the kit. Sequencing libraries were prepared according to the manufacturer's instructions. After library enrichment and quality control, the samples were sequenced using the Illumina MiSeq platform (Illumina, San Diego, CA, USA) with 100 bp paired-end reads at an average sequencing depth of 100x. Demultiplexed FASTQ files were processed individually using Qiagen Bioinformatics solutions. The sequencing reads were aligned to the human genome reference, GRCh37 (Genome Reference Consortium human build 37). Annotation of detected variants was performed using InterVar, Franklin, VarSome, ClinVar, OMIM, and Pubmed. Variants with a frequency higher than 0.5% were filtered out. dbNSFP (contains SIFT, PolyPhen-2, LRT, and Mutation Taster) was used to predict the pathogenicity of variants. Rare variants were classified according to the American College of Medical Genetics and Genomics/the Association for Molecular Pathology variant interpretation framework (6). Segregation analyzes were performed on family members who consented to be included in this study.

Statistical Analysis

Statistical calculations were performed using the Statistical Package for Social Sciences, version 29.0 (IBM Corp., Armonk, NY, USA). Quantitative variables that followed a normal distribution are expressed as mean and standard deviation (SD), while those that did not confirm to normal distribution were reported as median (minimum-maximum). Qualitative variables were expressed as frequency and percentage.

Results

In the 44 patients included in the study, the male-to-female ratio was 1.58:1. The mean birth weight (n = 40) was 3078 ± 514.8 g. Ten patients (22.7%) had additional (extrapancreatic) diseases/findings. The extrapancreatic findings included attention deficit hyperactivity disorder (two patients), epilepsy (two patients), intellectual disability (one patient), hepatosteatosis (one patient), asthma (one patient), ectopic kidney (one patient), increased echogenicity of the renal parenchyma (one patient), hypertension (one patient), juvenile idiopathic arthritis (one patient), primary ovarian insufficiency (one patient), arhythmia (one patient), and precocious puberty (one patient). Imaging studies (abdominal ultrasound/magnetic resonance imaging) were performed in 31 (70.4%) patients, with no pathological findings reported. The other clinical and laboratory findings of the patients are presented in Table 1.

As a presenting complaint, incidental hyperglycemia was significantly more common in patients diagnosed with *GCK*-MODY, while polyuria and polydipsia were more prevalent in other MODY types ($p < 0.05$). Diabetic ketoacidosis was detected only in MODY cases other than *GCK*-MODY ($p < 0.05$). The HbA1c levels were significantly higher in non-*GCK*-MODY cases ($p < 0.05$). While the majority of *GCK*-MODY cases were treated with lifestyle changes alone, the use of pharmacotherapy in addition to lifestyle modifications was significantly more common in non-*GCK*-MODY ($p < 0.05$). The simultaneous positivity of two tested diabetes autoantibodies was observed only in non-*GCK*-MODY. The genes and mutations identified in the cases are shown in Table 2.

Characteristics of *GCK*-MODY Patients

In the 25 patients diagnosed with *GCK*-MODY, the male-to-female ratio was 1.5. Four patients (16%) had additional (extrapancreatic) diseases/findings. The additional findings included one patient with a combination of intellectual disability, primary ovarian insufficiency, and arrhythmia, while the other three patients presented with precocious puberty, epilepsy, and juvenile idiopathic arthritis, respectively. Ketonemia was detected in one patient diagnosed with *GCK*-MODY (Patient 3 in Table 3). This patient's fasting blood glucose at presentation was 950 mg/dL, with a C-peptide level of 0.43 ng/mL, fasting insulin of 1.99 µU/mL, and an HbA1c of 11.6%. Anti-GAD positivity was also identified in this patient, who was subsequently treated with insulin. During follow-up, the HbA1c value decreased to 7.4%. All patients were provided with an appropriate dietary program. Only two patients received metformin therapy. These patients had a BMI greater than the 95th percentile, with one showing impaired glucose tolerance (IGT) on oral glucose tolerance test (OGTT), while the other had a postprandial glucose level in the diabetic range. Except for the patient who started insulin therapy, all other patients maintained an HbA1c level below 7% during their initial assessment and follow-up. The mutations detected in the *GCK* gene and the clinical characteristics of the patients are shown in Table 3.

Characteristics of non-*GCK*-MODY Cases

Among the four patients diagnosed with *HNF1A*-MODY, three were related. The average age at presentation was 11.2 years. All patients had BMI SD score values within the normal range. Three diabetes autoantibodies [anti-glutamic acid decarboxylase (anti-GAD), islet cell antibodies (ICA), insulin autoantibodies (IAA)] were assessed in these cases. Only one patient (Patient 2 in Table 4) tested positive for two diabetes autoantibodies (anti-GAD and ICA). This patient presented with fasting hyperglycemia and an HbA1c level in the prediabetic range, with a normal OGTT result. The patient treated with diet alone maintained an HbA1c level within the normal range. One of the other three patients (Patient 4 in Table 4) had normal fasting glucose and HbA1c levels at presentation and continued to remain within the normal range with dietary management. The remaining two patients had fasting glucose and HbA1c values at diabetic levels. Ketonemia was detected in one of these patients at

Table 1. Clinical and laboratory features of patients diagnosed with MODY

	MODYs (n = 44)	*GCK*-MODY (n = 25)	Non-*GCK* MODYs (n = 19)
Male/female	1.58	1.5	1.71
Age at diagnosis, (years)	10 (± 4.19)	9.85 (± 4.19)	10.36 (± 4.29)
Positive family history, n (%)	42 (95.45)	24 (96)	18 (94.73)
Consanguineous marriage, n (%)	10 (22.72)	7 (28)	3 (15.78)
Mean BMI-SDS	-0.45 (± 1.45)	-0.28 (± 1.26)	-0.68 (± 1.66)
BMI > 95th p, n (%)	4 (9.1)	3 (12)	1 (5.26)
BMI < 5th p, n (%)	10 (22.72)	3 (12)	7 (36.84)
Incidental hyperglycemia, n (%)	23 (52.27)	19 (76)	4 (21)
Polyuria-polydipsia, n (%)	14 (31.81)	2 (8)	12 (63.15)
DKA, n (%)	4 (9.1)	0	4 (21.05)
Diabetic ketonemia, n (%)	3 (6.8)	1 (4)	2 (10.52)
Triglyceride, (mg/dL)	91.05 (± 46.79)	85.33 (± 45.63)	99 (± 48.80)
Total cholesterol, (mg/dL)	158.88 (± 34.54)	152.90 (± 26.22)	167.26 (± 43.25)
HDL-cholesterol, (mg/dL)	49.41 (± 15.11)	49.77 (± 13.13)	48.92 (± 18)
LDL-cholesterol, (mg/dL)	90.83 (± 28.51)	86 (± 23.29)	97.58 (± 34.25)
HbA1c, (%)	7.78 (± 2.98)	6.49 (± 1.17)	9.48 (± 3.75)
Fasting insulin (IU/L)	6.68 (± 7.06)	6.24 (± 4.57)	7.29 (± 9.64)
C-peptide, (ng/mL)	1.24 (± 0.95)	1.21 (± 0.62)	1.27 (± 1.29)
Fasting glucose, (mg/dL)	210.5 (± 202.7)	159.3 (± 169.4)	277.9 (± 226.9)
Anti-GAD (+), n (%)	7 (15.9)	3 (12)	4 (21)
Anti-ICA (+), n (%)	7 (15.9)	2 (8)	5 (26.3)
Anti-IAA (+), n (%)	2 (4.5)	1 (4)	1 (5.2)
Anti-GAD + anti-ICA (+), n (%)	4 (9)	0	4 (21)
Anti-ICA + anti-IAA (+), n (%)	1 (2.3)	0	1 (5.2)
Only diet and lifestyle changes, n (%)	26 (59)	22 (88)	4 (21)
Diet and lifestyle changes + oral antidiabetic drugs and/or insulin, n (%)	18 (41)	3 (12)	15 (78.9)
Diet and lifestyle changes and oral antidiabetic drugs and insulin n (%)	6 (13.6)	0	6 (31.5)

BMI: body mass index, DKA: diabetic ketoasidosis, HDL: high density lipoprotein, LDL: low density lipoprotein GAD: glutamic acid decarboxylase, ICA: islet cell antibodies, IAA: insulin autoantibodies, MODY: maturity-onset diabetes of the young, GCK: glucokinase, SDS: standard deviation score, HbA1c: hemoglobin A1c

Table 2. Genes with variation detected in MODY cases and patient numbers

Gene	*GCK*	*HNF1a*	*CEL*	*BLK*	*ABCC8*	*KLF11*	*INS*	*KCNJ11*	*APPL1*
n = 44	25	4	4	2	4	2	1	1	1
%	56.8	9.1	9.1	4.5	9.1	4.5	2.3	2.3	2.3

GCK: glucokinase, *HNF1a*: hepatocyte nuclear factor-1-alpha, *CEL*: carboxyl ester lipase, *BLK*: B lymphocyte kinase, *ABCC8*: ATP-binding cassette subfamily C member 8, *KLF11*: Kruppel-like factor 11, *INS*: insulin, *KCNJ11*: potassium channel, inwardly rectifying, subfamily J member 11, *APPL1*: adaptor protein, phosphotyrosine interaction, pH domain, and leucine zipper containing 1

Table 3. Clinical and laboratory features of *GCK*-MODY cases

Patient	Gender	Age (Year)	Presentation	Positive family history	BMI (%)	Transcript number/variant	Protein	Zygosity	ACMG classification	Diabetes autoantibody positivity	Treatment
1	M	7.2	Polyuria- polydipsia	3 generations	25-50	NM_00134800.1: c.904 G > C	p.Val302Met	Heterozygous	Likely pathogenic	GAD	Only diet
2	M	13.2	Incidental hyperglycemia	No[ǂ]	5-15	NM_00134800.1: c.565 A > G	p.I189V	Homozygous	Likely pathogenic	-	Only diet
3	M	5.4	Polyuria- polydipsia	3 generations	25-50	NM_000162.5: c.565A > G	p.I189V	Heterozygous	Likely pathogenic	GAD*	Insulin
4	F	16.6	Incidental hyperglycemia	3 generations	> 95	NM_00134800.1: c.667 G > A	p.Gly223Ser	Heterozygous	Pathogenic	GAD	Metformin
5	M	11.6	Incidental hyperglycemia	3 generations	25-50	NM_00134800.1: c.239 G > C	p.Gly80Ala	Heterozygous	Pathogenic	-	Only diet
6	M	7.5	Incidental hyperglycemia	3 generations	25-50	NM_00134800.1: c.1195 G > T	p.Glu399*	Heterozygous	Pathogenic	-	Only diet
7	M	2.6	Incidental hyperglycemia	F + 3 generations	85-95	NM_000162.5: c.736G > C	p.G246R	Heterozygous	Pathogenic	-	Only diet
8	F	16.8	Incidental hyperglycemia	M + F + 3 generations[ǂ]	< 5	NM_00134800.1: c.1178T > C	p.M393T	Heterozygous	Pathogenic	-	Only diet
9	F	2.4	Incidental hyperglycemia	F + B/S + 3 generations	5-15	NM_00134800.1: c.565 A > G	p.I189V	Homozygous	Likely pathogenic	-	Only diet
10	F	14	Absence of menarche	3 generations[ǂ]	50-75	NM_033507.3: c.-16_-2delTTAGCCCCTCGGAGA	-	Heterozygous	VUS	-	Only diet
11	F	10.5	Incidental hyperglycemia	M(GDM) + 3 generations	> 95	NM_00134800.1: c.667 G > A	p.Gly223Ser	Heterozygous	Pathogenic	-	Only diet
12	F	11.1	Incidental hyperglycemia	F + 3 generations	15-25	NM_00134800.1: c.704 T > C	p.Met235Thr	Heterozygous	Pathogenic	-	Only diet
13	M	2.9	Family history of diabetes	F + B/S + 3 generations	15-25	NM_000162.5: c.1178T > C	p.M393T	Heterozygous	Pathogenic	-	Only diet
14	M	8.1	Family history of diabetes	F + B/S + 3 generations	5-15	NM_00134800.1: c.565 A > G	p.I189V	Heterozygous	Likely pathogenic	-	Only diet
15	M	13.1	Family history of diabetes	M(GDM) + B/S[ǂ]	50-75	NM_00134800.1: c.565 A > G,	p.I189V	Homozygous	Likely pathogenic	-	Only diet
16	F	11	Incidental hyperglycemia	M + 3 generations	5-15	NM_00134800.1: c.565 A > G	p.I189V	Heterozygous	Likely pathogenic	-	Only diet
17	M	6.4	Incidental hyperglycemia	F + B/S + 3 generations	75-85	NM_000162.5: c.1178T > C	p.M393T	Heterozygous	Pathogenic	IAA	Only diet
18	M	12.1	Incidental hyperglycemia	M + 3 generations	5-15	NM_00134800.1: c.1178T > C	p.M393T	Heterozygous	Pathogenic	-	Only diet
19	M	12.8	Incidental hyperglycemia	M(GDM) + F + 3 generations	< 5	NM_00134800.1: c.1009 C > T	p.Gln337X	Heterozygous	Pathogenic	-	Only diet
20	F	11.5	Incidental hyperglycemia	No	50-75	NM_000162.5: c.565A > G	p.I189V	Heterozygous	Likely pathogenic	-	Only diet
21	M	16.4	Incidental hyperglycemia	M + 3 generation	15-25	NM_00134800.1: c.667 G > A	p.Gly223Ser	Heterozygous	Pathogenic	ICA	Only diet
22	M	7.5	Incidental hyperglycemia	M(GDM) + B/S[ǂ]	75-85	NM_00134800.1: c.565 A > G	p.I189V	Homozygous	Likely pathogenic	-	Only diet
23	F	6.6	Incidental hyperglycemia	M + 3 generations	15-25	NM_00134800.1: c.565 A > G	p.I189V	Heterozygous	Likely pathogenic	-	Only diet
24	M	8.6	Incidental hyperglycemia	M + 3 generations[ǂ]	> 95	NM_000162.5: c.1178T > C	p.M393T	Heterozygous	Pathogenic	-	Metformin
25	F	9.5	Incidental hyperglycemia	3 generations	< 5	NM_000162.5: c.565 A > G	p.I189V	Heterozygous	Likely pathogenic	ICA	Only diet

Patients 15 and 22 are cousins; Patients 13 and 17 are brothers; Patients 9 and 14 are brothers.

ǂ: consanguineous marriage; *: presented with ketonemia.

M: mother, F: father, B/S: brother/sister, GDM: gestational diabetes mellitus, VUS: variant of uncertain significance, GAD: glutamic acid decarboxylase, ICA: islet cell antibodies, IAA: insulin autoantibodies, BMI: body mass index, ACMG: American College of Medical Genetics and Genomics, GCK: glucokinase

Table 4. Clinical and laboratory features of non-*GCK*-MODY cases

Patient	Gender	Age (Year)	Presentation	Positive family history	BMI (%)	Gene	Transcript number/ variation	Protein	Zigosity	ACMG classification	Diabetes autoantibody positivity	Treatment
1	F	13.1	Incidental hyperglycemia	M + F + B/S + 3 generations	50-75	*HNF1A*	NM_000545.8: c.526 + 1 G > C	-	Heterozygous	Pathogenic	-	Metformin
2	M	9.1	Incidental hyperglycemia	M + F + B/S + 3 generations‡	75-85	*HNF1A*	NM_000545.8: c.526 + 1 G > C	-	Heterozygous	Pathogenic	GAD, ICA	Only diet
3	F	14.8	Polyuria-polydipsia	M + F + B/S + 3 generations‡	50-75	*HNF1A*	NM_000545.8: c.526 + 1 G > C	-	Heterozygous	Pathogenic	-	Met + Ins[2]
4	M	7.8	Polyuria-polydipsia	M + 4th degree relative	15-25	*HNF1A*	NM_000545.8: c.716 C > T	p.Ala239Val	Heterozygous	Likely pathogenic	-	Only diet
5	M	15.7	Polyuria-polydipsia	B/S + 2nd degree relative	< 5	*CEL*	NM_001807.6: c.1454T > C	p.Ile485Thr	Heterozygous	VUS	GAD, ICA	Met + Ins
6	F	12	Not gaining weight	3 generations	< 5	*CEL*	NM_001807.6: c.460G > A	p.G154 > R	Heterozygous	VUS	-	Only diet
7	M	11	Polyuria-polydipsia	3rd degree relative	15-25	*CEL*	NM_001807.5: c.1454T > C	p.Ile485Thr	Heterozygous	VUS	-	Met + Ins
8	F	1	Polyuria-polydipsia	3 generations	5-15	*CEL*	NM_001807.5: c.1974delC	p.V659fs*45	Heterozygous	Likely pathogenic	GAD, ICA	Insulin[1]
9	M	3.3	Low C-peptide	3 generations	15-25	*BLK*	NM_001715.3: c.391C > T	p.R131W	Heterozygous	VUS	-	Only diet
10	M	13.7	Overweight	3 generations	85-95	*BLK*	NM_001715.3: c.773-5C > G	-	Heterozygous	VUS	-	Metformin
11	M	5	Polyuria-polydipsia	M	< 5	*ABCC8*	NM_000352.6: c.1261G > A	p.V421I	Heterozygous	Likely pathogenic	-	Insulin[1]
12	F	10.8	Polyuria- polydipsia	No	< 5	*ABCC8*	NM_000352.6: c.1261G > A	p.V421I	Heterozygous	Likely pathogenic	-	Insulin[2]
13	M	15.2	Incidental hyperglycemia	3 generations	> 95	*ABCC8*	NM_000352.6: c.1252T > C	p.C418R	Heterozygous	VUS	-	Met + ins
14	M	12.4	Polyuria-polydipsia	M + 2nd degree relative‡	85-95	*ABCC8*	NM_000352.6: c.2617C > T	p.L873F	Heterozygous	VUS	-	Metformin
15	M	6.7	Polyuria-polydipsia	2nd degree relative	85-95	*KLF11*	NM_003597.5: c.308C > T	p.T103I	Heterozygous	VUS	-	Insulin[1]
16	F	9.7	Polyuria-polydipsia	3 generations	< 5	*KLF11*	NM_003597.5: c.145G > A	p.Glu49Lys	Heterozygous	VUS	IAA, ICA	Met + Ins
17	F	6.7	Polyuria-polydipsia	3 generations	5-15	*KCNJ11*	NM_000525.4: c.595_596delATinsGG	p.M199G	Heterozygous	Likely pathogenic	GAD, ICA	Insulin
18	M	13	Polyuria-polydipsia	3 generations + 2nd degree relative	< 5	*INS*	NM_000207.3: c.71C > T	p.A24V	Heterozygous	Pathogenic	-	Insulin[1]
19	M	15.3	Incidental hyperglycemia	3 generations	< 5	*APPL1*	NM_012096.3: c.2018C > G	p.S673C	Heterozygous	VUS	-	Met + Ins

‡: consanguineous marriage; [1]: presented with ketoacidosis; [2]: presented with ketonemia.
M: mother, F: father, B/S: brother/sister, GDM: gestational diabetes mellitus, VUS: variant of uncertain significance, GAD: glutamic acid decarboxylase, ICA: islet cell antibodies, IAA: insulin autoantibodies.
HNF1A: hepatocyte nuclear factor-1-alpha, CEL: carboxyl ester lipase, BLK: B lymphocyte kinase, ABCC8: ATP-binding cassette subfamily C member 8, KLF11: Kruppel-like factor 11, INS: insulin, KCNJ11: potassium channel, inwardly rectifying, subfamily J member 11, APPL1: adaptor protein, phosphotyrosine interaction, pH domain, and leucine zipper containing 1

presentation, who was treated with insulin, while the other patient was managed with oral antidiabetic agents.

Among the four patients diagnosed with *CEL*-MODY, one presented with an increase in renal parenchyma echogenicity as an additional condition, while another had an ectopic kidney. Renal function was found to be normal in both cases. One patient (Patient 7 in Table 4) presented with intermittent abdominal pain related to meals, and the fecal elastase value was measured at 117 µg/mL (normal: > 200 µg/mL; mild exocrine pancreatic insufficiency: 100-200 µg/mL; exocrine pancreatic insufficiency: < 100 µg/mL), indicating mild exocrine pancreatic insufficiency, and was referred to the pediatric gastroenterology department for dietary management. Although the c.1454T > C variant detected in this patient was classified as benign by some databases, the detection of exocrine pancreatic insufficiency seen in *CEL*-MODY led us to classify this variant as a variant of uncertain clinical significance (VUS). Fecal elastase levels could not be evaluated in other cases. At presentation, all patients had normal c-peptide levels. Two patients (Patients 5 and 8 in Table 4) tested positive for two diabetes autoantibodies (anti-GAD and ICA) simultaneously. One (Patient 6 in Table 4) presented with failure to gain weight and was normoglycemic but had an HbA1c value in the prediabetic range. This patient's OGTT was normal, and during follow-up, the HbA1c value normalized with dietary management. The other three patients had HbA1c values at diabetic levels and were treated with insulin.

Of the two patients diagnosed with *BLK*-MODY, one was overweight while the other had a normal BMI. At presentation, the overweight patient had fasting hyperglycemia and prediabetic HbA1c, while the other patient (Patient 9 in Table 4) had fasting hyperglycemia, low C-peptide and normal HbA1c. The overweight patient was treated with metformin, while the other patient was monitored with diet modification alone. During follow-up, their HbA1c levels remained below 6%.

Of the four patients diagnosed with *ABCC8*-MODY, one was obese, one was overweight, and two were malnourished, based on their BMIs. Three patients had diabetic fasting glucose and HbA1c levels, while one patient had only prediabetic HbA1c levels (6.2%) (Patient 14 in Table 4). One of the patients with malnutrition had ketoacidosis (Patient 11 in Table 4), and the other had ketosis (Patient 12 in Table 4). All three diabetes autoantibodies (anti-GAD, ICA, IAA) were found to be negative. Two patients with ketosis and ketoacidosis were treated with insulin, while the patient with obesity was treated with insulin after a short period of metformin use. The patient who was overweight and had a prediabetic HbA1c level was followed up with oral antidiabetics. The patient, whose treatment compliance was poor, had a final HbA1c level of 7%.

Two patients were diagnosed with *KLF11*-MODY; one was overweight and had diabetic levels of glucose and HbA1c and was treated with insulin. The other patient had malnutrition, presenting with fasting hyperglycemia and a diabetic HbA1c level of 6.8%. This patient showed IGT on the OGTT, and two diabetes autoantibodies (ICA and IAA) were positive. Initially treated with metformin, this patient's treatment was later supplemented with insulin. This patient also had attention deficit hyperactivity disorder as an additional condition.

The genetic and clinical characteristics of non-*GCK*-MODY cases are summarized in Table 4.

Discussion

Approximately 80% of MODY cases are misdiagnosed as type 1 or type 2 diabetes, which complicates prevalence and incidence estimates (7). MODY is considered the most common form of monogenic diabetes, accounting for approximately 1-6.3% of diabetes cases reported in the literature (2,8,9,10,11,12).

Genes causing MODY affect insulin secretion by disrupting insulin release, glucose metabolism in pancreatic beta cells, or activating ATP-dependent potassium channels. Patients typically have heterozygous mutations. Penetrance and expressivity can vary significantly among family members (13). In our cohort, most patients (90.9%) had heterozygous mutations, while only four patients had homozygous mutations. Among the homozygous patients, three had a history of parental consanguinity.

GCK-MODY is one of the most common types of MODY among European Caucasians (14). In Türkiye, various studies conducted in children have also identified *GCK*-MODY as the most frequently detected type of MODY (15,16,17,18,19). One study found that approximately one in four children diagnosed with MODY had *GCK*-MODY (19). In the present study, *GCK*-MODY was the most prevalent type, accounting for well over half (56.8%) of cases. The mutations most frequently identified in the *GCK* gene, p.M393T and p.I189V, which are classified as potentially pathogenic, have also been detected in two previous studies conducted in Türkiye (20,21).

Although *GCK*-MODY is known as an untreated form of MODY characterized by mild, non-progressive fasting hyperglycemia in childhood, and no complications (1), one of our *GCK*-MODY patients (Patient 3 in Table 3) received insulin therapy. As in this patient, a case report from Italy

presented cases of siblings who were both positivefor diabetes autoantibody (1 or 2 of them) and had the same *GCK* gene variant, and treated with intermittent insulin and continuous insulin (22). Although a single diabetes autoantibody positivity has a poor predictive value for the diagnosis of T1DM, considering that only three diabetes autoantibodies were measured in our patient. It is possible that this patient may have been positive for other diabetes antibodies that were not evaluated. Thus, we believe this case may be a rare case of *GCK*-MODY and type 1 diabetes coexisting.

Mutations in the *HNF1A* and *GCK* genes have been identified as the most common causes of MODY in many studies conducted in Europe, North America, and some Asian countries (2,23). In the present study, *HNF1A*-MODY was detected in less than 10% of the cohort, which was the same rate as for *CEL*-MODY and *ABCC8*-MODY (all n = 4). This finding is unusual and suggests that the observed rate of *CEL*-MODY in our cohort was higher than that reported in many studies conducted both in our country and in the world. However, as the cohort size was modest, then this may simply be an effect of the smaller numbers.

Diabetes autoantibody positivity (anti-GAD, anti-ICA, anti-IAA) was detected in a quarter of the patients. This rate is higher than the diabetes autoantibody positivity rate of 11.2% found in the largest multicenter study conducted in our country, which presented 224 patients with MODY (19). Among these, five patients exhibited positivity for two autoantibodies simultaneously. Anti-ICA positivity was present in a total of 7/11 cases, and in addition to this antibody, four patients were positive for anti-GAD (*CEL, HNF1A, KCNJ11, KLF11*), while one case demonstrated positivity for anti-IAA (*KLF11*). Variants detected with diabetes autoantibody positivity are shown in Table 3 and Table 4 and five of these variants are classified as likely pathogenic, four as pathogenic, and two as VUS.

Twenty-six (59%) of the cases were treated with lifestyle changes and diet alone and of these 22 were *GCK*-MODY, which was also 88% of all *GCK*-MODY cases. Eighteen (41%) of the cases were treated with oral antidiabetics and/or insulin. Six cases used both oral antidiabetics and insulin during the treatment process. These cases are shown in Table 4.

Study Limitations

The retrospective nature of the study, the small number of cases, the detection of many variants of unknown clinical significance in genes associated with MODY, especially in the *CEL* gene, as a result of genetic analysis, and the inability to perform segregation analysis and functional studies in these cases are the factors limiting this study. Another limitation of the study was that the diabetes autoantibodies (anti-GAD, ICA, IAA) tests were performed in external laboratories, so detailed information about the method used (ELISA or immunofluorescence) was not available. Furthermore, since quantitative values were not available for all cases, these data are presented only as 'positive' and 'negative'.

Conclusion

To date, many different genes have been identified as causes of MODY, each with distinct clinical characteristics and most requiring different treatments. Therefore, the impact of accurate biomolecular genetic diagnosis is significant for many patients, as it can lead to the cessation of inappropriate treatment, for example, insulin injections, after several years of therapy. However, many patients remain undiagnosed or experience long delays between the initial diabetes diagnosis and the correct genetic diagnosis. Thus, in cases where the type of diabetes is uncertain, biomarkers used in differential diagnosis (clinical, metabolic, immune, genetic) should be carefully evaluated and, if necessary, reassessed during follow-up.

In addition, clarifying the genetic etiology is important for identifying individuals at risk. Genetic studies, functional studies, and larger case series are needed to identify new MODY-related loci and to elucidate genotype-phenotype correlations. In coming years, the introduction of gene-targeted therapies will likely contribute to the management of these cases.

Ethics

Ethics Committee Approval: The study received approval from the Clinicial Research Ethics Committee of Malatya Training and Research Hospital (approval number: 23536505-604.02, date: 17.08.2020).

Informed Consent: Segregation analyzes were performed on family members who consented to be included in this study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Leman Kayaş, Ayşehan Akıncı, İsmail Dündar, Nurdan Çiftçi, Zeynep Esener, İbrahim Tekedereli, Mustafa Doğan, Concept: Leman Kayaş, Ayşehan Akıncı, Emine Çamtosun, İsmail Dündar, Mustafa

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ORIGINAL ARTICLE

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A Comprehensive Child Psychiatry Approach for Managing Patients with Differences of Sexual Development in a Multidisciplinary Setting: An Alternative Follow-up Model

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What is already known on this topic?

Differences of sexual development (DSD) is a complex spectrum of conditions that requires a multidisciplinary approach, including psychiatric support. These patients are at a higher risk for psychiatric disorders, particularly depression and anxiety. However, long-term psychiatric follow-up is often inadequate within existing healthcare systems, leading to significant gaps in psychosocial adaptation. Current guidelines emphasize the importance of structured psychiatric care for patients with DSD, yet no standardized follow-up model has been established. Moreover, research investigating the impact of psychiatric support on patient outcomes and the effectiveness of clinical training models in DSD management remain limited.

What this study adds?

This study introduces a structured psychiatric follow-up model for patients with DSD, integrating psychiatry residents into multidisciplinary care. Findings suggest that this model maintains patient care quality while enhancing psychiatric training, improving residents' skills in DSD management. Unlike previous research focusing on medical aspects, this study highlights the importance of long-term psychiatric follow-up and offers a practical framework for integrating psychiatric care into DSD management.

Abstract

Objective: To examine the implementation of a new psychiatric follow-up model for patients with differences of sexual development (DSD), a group of conditions affecting gender determination and differentiation, focusing on the model's impact on patient care and residents' training.

Methods: Data from patients monitored between March 2000 and November 2023 and 28 child and adolescent psychiatry residents in a tertiary-care center were analyzed. Data was collected before and after implementing the new model using psychiatric assessment and the Clinical Global Impression (CGI) and Global Assessment Scale (GAS).

Results: The patient cohort consisted of 129 patients with DSD, of whom 10 (7.75%) were lost to follow up. Of the remaining 119 patients, 89 (74.8%) were monitored by two expert specialists prior to the model's implementation, while 30 (25.2%) were cared for by junior child and adolescent psychiatry residents under supervision following the implementation of the new model. The mean age of the patients was 10.86 ± 6.32 years. No significant differences in the prevalence of psychiatric disorders or in CGI or GAS scores before and after implementing the new education model were found ($p > 0.05$). The most common psychiatric diagnosis in our sample was attention-deficit/hyperactivity disorder (19.4%), followed by intellectual disability and major depressive disorder, each accounting for 14.0%. Residents reported enhanced competence in managing patients with DSD (14.3%), improved communication skills, and better

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identification of subthreshold psychiatric symptoms (25%), as well as a greater understanding of the multidisciplinary approach (14.3%).
Conclusion: This study highlighted the importance of structured psychiatric support in the management of DSD. Furthermore, the education of future psychiatrists was subjectively improved.
Keywords: Child and adolescent psychiatry, consultation-liaison psychiatry, differences of sexual development, education model, psychiatric follow-up, residency training

Introduction

Differences of sexual development (DSD) are a group of conditions involving developmental challenges in the processes of gender determination and differentiation, occurring in approximately 1 in 4,500 to 5,500 births (1,2). International consensus guidelines recommend a personalized treatment approach managed by a multidisciplinary team to support individuals with DSD. Child and adolescent psychiatry (CAP) is one of the essential specialties within this multidisciplinary team (2,3).

CAP plays an important role in the comprehensive assessment of an individual with DSD, as they are reported to be at higher risk for certain psychiatric conditions. Lifetime prevalence rates for depression and anxiety disorders in this population are approximately 7.1% and 19.2%, respectively. Moreover, these patients may encounter challenges related to gender identity development, body image, and self-esteem (4,5,6). Therefore, providing psychiatric support to both the patients and their families from the moment they receive the DSD diagnosis is part of optimal management of DSD (7).

DSD may impact psychosexual development, a process that continues to evolve, particularly throughout adolescence and well into adulthood (8). Studies suggest that while patients often have access to psychiatric support at the time of diagnosis, some may face difficulties accessing the full range of multidisciplinary care during follow-up (2). One study exploring patient experiences with care revealed that while medical services were accessible, there were gaps in psychosocial support. Patients expressed a desire for continuous access to psychosocial support throughout their lives (9). A multicenter study conducted across six countries found that psychiatric issues persist for these patients into adulthood, highlighting the need for ongoing psychiatric follow-up into adulthood. Therefore, transitioning from adolescent to adult psychiatric care, while ensuring ongoing monitoring for residual issues and maintaining the sustainability and effectiveness of psychiatric services, will be important (5). Effective long-term follow-up requires specialist centers with an experienced multidisciplinary team, as emphasized in consensus reports (2).

The literature defines detailed approaches and management strategies for gender assignment including multidisciplinary teamwork; however, there is a relative scarcity of studies that thoroughly explore the psychiatric care provided to these patients (10).

DSD Council Structure and Function

For over twenty years, the multidisciplinary DSD council at Ege University has collaborated across various specialties, including pediatric endocrinology, pediatric surgery, pediatric urology, pediatric genetics, medical genetics, and child psychiatry, monitoring a substantial number of patients. The council convenes monthly and each meeting is dedicated to discussing new and follow-up cases, with the goal of developing individualized, holistic care plans for each patient and their family.

Endocrinologists contribute insights into hormonal status and prognosis, surgeons and urologists assess potential surgical interventions in consultation with psychiatry to ensure psychosocial readiness, and geneticists provide diagnostic clarity and guidance on family history. The CAP team evaluates psychological well-being, emotional resilience, and family dynamics to inform the timing and scope of medical decisions. Within this framework, our clinic plays a key role by offering psychosocial support and psychiatric follow-up for the team (11). The psychiatric follow-up results from the Ege multidisciplinary DSD council have been presented in several studies (11,12,13).

The Department of Child and Adolescent Psychiatry at Ege University provides care for children and adolescents aged 0-18 years, with follow-ups organized in various subunits based on the patients' age and diagnoses. Psychiatry residents in specialty training rotate through all clinical subunits and receive supervision from relevant faculty members. Children and adolescents with physical illnesses like DSD are monitored in the consultation-liaison (CL) outpatient subunit. All DSD cases are managed within this unit under the supervision of a faculty member (NBÖ), who specializes in gender development and CL psychiatry. Patients also receive ongoing follow-up from relevant pediatric specialties, ensuring a full multidisciplinary approach.

As part of this multidisciplinary follow-up process, all children diagnosed with DSD by the pediatric endocrinology department who are deemed at risk for psychiatric disorders, or who present with significant psychiatric symptoms,

are referred to the CAP CL outpatient subunit. Previously, DSD patients were managed by two experienced faculty members in child psychiatry. To address increasing clinical demands and simultaneously enhance residency training, a new psychiatry follow-up model was introduced, allowing residents in the CL subunit to conduct patient evaluations and coordinate treatments under supervision of faculty members.

Structure of the Psychiatric Follow-up Model

In the previous model used at our center, psychiatric care for DSD patients was provided solely by two experienced faculty members. The revised model incorporated psychiatry residents into the care process under close supervision, aiming to both sustain high-quality follow-up and enhance residency education.

In the new training and DSD patient follow-up model, the CAP resident in the CL subunit conducts a comprehensive assessment of the patient and their family, based around the patient's unique psychiatric needs, under the supervision of a faculty member, and coordinates necessary treatment, ensuring that a psychiatric follow-up plan is individually tailored for each case. Individuals with gender dysphoria or gender confusion, those experiencing uncertainty, and those presenting symptoms related to depression and anxiety are closely monitored at least once every two weeks. Patients experiencing mood disorders, such as depression, and those with severe anxiety symptoms were provided with psychopharmacological treatment when necessary, including antidepressants and anxiolytics, and were predominantly followed up with supportive psychotherapy and cognitive-behavioral approaches.

Individuals without gender-related uncertainties or difficulties, and with a stable psychiatric profile, were evaluated every three to six months. Psychiatric supervision is conducted weekly for half a day by the psychiatric team coordinator. The members of the psychiatric team in this model include a specialist supervisor in CAP, a resident physician, a psychologist from the CAP psychiatry CL subunit team, and a social worker. The resident physician may refer patients to the psychologist for testing or additional psychological and/or psychosocial interventions when deemed necessary. Parental evaluation and consultations are conducted by either the assigned social worker or the psychologist, tailored to individual needs. All procedures are carried out under the supervision of the team coordinator, who specializes in CAP, CL psychiatry and gender development (13).

To ensure continuity of patient care and follow-up, the same child psychiatry resident follows each DSD patient throughout their entire residency, regardless of rotation schedules, including rotations in adult psychiatry and pediatric neurology. This approach is intended to strengthen the child physician residents' skills in providing long-term, cross-disciplinary care, while fostering consistent management and a sustained, trusting relationship between physician and patient-particularly in sensitive domains such as gender development and identity. This model enables child psychiatry residents to maintain continuity in monitoring their patients, even as they rotate through different outpatient clinics, allowing for close observation of developmental progress and adjusting treatment as necessary. The model is based on the premise that continuity with a single clinician is a priority for DSD cases, where careful monitoring of growth and psychosocial changes is particularly important. This approach aims to strengthen the therapeutic relationship and ensure continuity for both patients and residents while also enhancing the education of the residents in the field of pediatric CL psychiatry (Figure 1).

The aim of the present study was to describe the implementation of this revised training and DSD patient follow-up model, which was initiated in 2022. While existing literature emphasizes the role of multidisciplinary teams in the holistic care of DSD (10,14), fewer studies have examined the educational impact of these systems within child psychiatry training. Collaboration within the team in managing such rare cases, along with supervision of individual follow-ups, is very important in child psychiatry training (15). Our focus is therefore twofold: firstly, to assess the model's effectiveness in providing psychiatric care to patients with DSD, and secondly to evaluate the contribution of this model to resident training in pediatric CL psychiatry.

Methods

Measures: DSD Patients

Sociodemographic Data Form: the form collected data on patients' and family members' mental and physical health status, including age at diagnosis, initial clinic visit age, psychiatric follow-up frequency, pediatric treatment plans, scheduled surgeries, hospitalizations, and psychiatric medication use.

Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL): Psychiatric diagnoses were established using the K-SADS, a validated, semi-structured diagnostic interview aligned with DSM-IV and DSM-5 criteria (16). This tool is widely used in CAP, with established validity and reliability in the Turkish population (17).

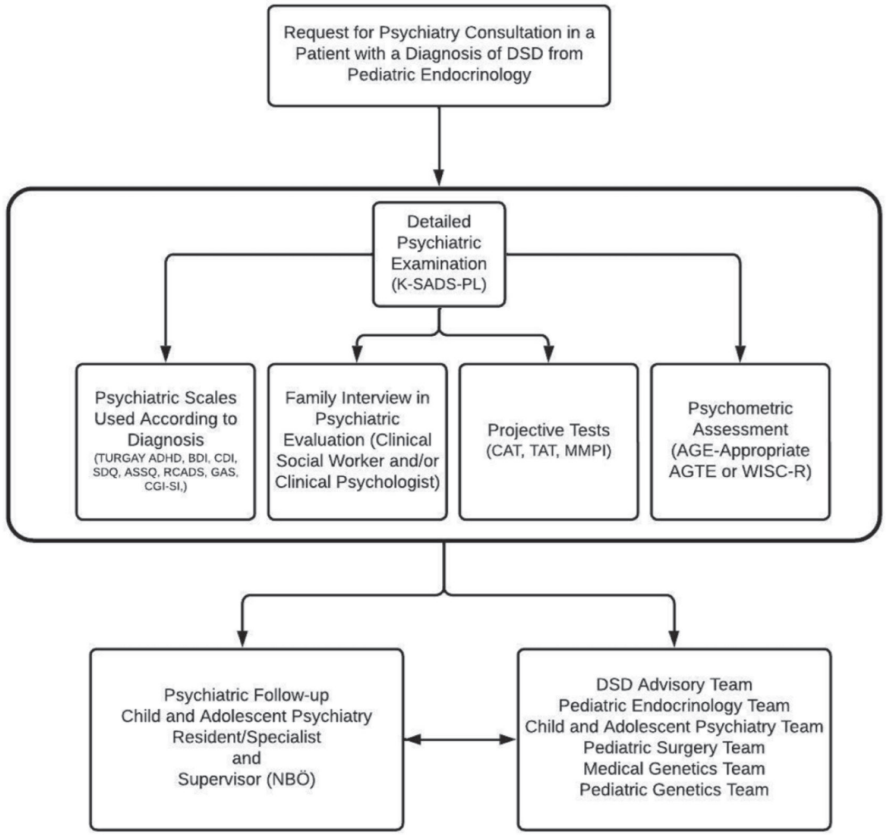

Figure 1. Psychiatric assessment flowchart for a patient referred to the pediatric CL outpatient clinic

DSD: differences of sexual development, K-SADS-PL: kiddie schedule for affective disorders and schizophrenia, ADHD: attention deficit and hyperactivity disorder, CGI: clinical global impression, GAS: global assessment scale, CL: consultation-liaison

Global Assessment Scale (GAS): A 0-100 scale assessing overall well-being and functionality, incorporating symptom severity, social competence, and problem-solving ability (18). The GAS, later adapted as the Global Assessment of Functioning, is a single-item clinician rating of overall psychosocial functioning on a 0-100 scale. Similar to the Clinical Global Impression (CGI), it is grounded in clinical judgment and has strong face validity, which has supported its adoption in many countries without the need for extensive validation studies. Its simplicity and global nature have made it a standard outcome measure in psychiatric research and practice.

CGI: A standardized three-item tool evaluating illness severity, treatment response, and side effects, frequently used in clinical research (19). The CGI scale is a clinician-rated measure of overall illness severity and treatment response. It is intentionally simple and based on clinical observation, providing a face-valid global index rather than a detailed psychometric instrument. Due to its practicality and high face validity, the CGI has been widely used internationally without formal validation studies in many languages or cultural contexts.

Measures: CAP Residents

Visual Analogue Scale (VAS): A 0-10 scale used to quantify subjective experiences. In this study, VAS assessed CAP residents' perceived competence in managing DSD patients and the model's impact on complex psychiatric conditions, including gender dysphoria (20).

Study Sample

This study presents the follow-up data of 129 patients who were monitored under the "Ege DSD Model" for DSD at our clinic between March 2000 and November 2023. The inclusion criteria were: 1) being followed-up by our hospital's DSD Council; and 2) to have undergone at least one psychiatric evaluation. Patients who were followed by the DSD council but had not been referred to psychiatric services were excluded, as they were deemed outside the scope of this study. Informed consent and verbal assent were sought and obtained from all patients and their families.

Furthermore, the psychiatric training benefits, perceived management competencies, and contributions to consultation skills of 28 participating CAP residents who

had completed their training under this model were also evaluated.

The study received approval from the Ege University Medical Research Ethics Committee (approval number: 24-5.1T/46, date: 23.05.2024).

Statistical Analysis

Statistical analyses were performed using SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Sociodemographic variables and psychiatric diagnoses of DSD patients are reported as percentages. Differences in psychiatric disorders before and after the model implementation were assessed using the chi-square test, as the two groups were independent. Changes in CGI and GAS scores for individual patients at two time points (T1—start of follow-up and T2—last psychiatric interview) were analyzed with the Wilcoxon Signed Ranks test, due to the non-normal distribution of scores across groups and time points. To compare CGI and GAS scores between the pre- and post-model groups, the Mann-Whitney U test was employed separately for T1 and T2.

Results

The potential patient cohort consisted of 129 patients with DSD and the resident cohort included 28 doctors associated with the DSD follow-up model. The mean ± standard deviation age of the patients was 10.86 ± 6.32 years. Out of the 129 patients, 10 (77.5%) were lost to follow-up, leaving 119 patients for the analysis. Among these, 89 (74.8%) were monitored by two expert faculty members, while 30 (25.2%) patients were cared for by junior doctors under close supervision following the implementation of the new model. Supervision meetings regarding DSD patients were held at least once a week, and participation of the residents in the monthly DSD multidisciplinary council was mandatory.

The most frequently diagnosed psychiatric disorder in our sample was attention deficit hyperactivity disorder (19.4%), followed by intellectual disability and major depressive disorder, each at 14.0%. There were no significant differences in the rates of psychiatric disorders before and after the model's implementation, indicating that the prevalence of these disorders was consistent whether patients were followed by a single faculty member or by residents, under supervision. Psychiatric diagnoses observed in DSD patients before and after model implementation are summarized in Table 1. In addition, there were no significant differences in either GAS or CGI scores before and after model implementation (Table 2). Supplementary Table 1 provides a detailed overview of the various differences in sex development including karyotype and the psychiatric disorders associated with them.

Among the 28 doctors participating in our study, 16 were current residents at our institution, while 12 had completed their training and were CAP specialists at the time of assessment. Table 3 summarizes the participants' expertise in CL psychiatry and DSD, as well as their perceptions of the model.

Both former and current residents reported following up the DSD patients under their care every 1-3 months. The median duration of CL outpatient subunit rotations was similar for residents and specialists, at 3 months. However, residents had a median inpatient rotation duration of zero months, compared to 3 months for specialists. All doctors, regardless of their training level, had followed up with at least one DSD patient, and all specialists had attended the DSD council at least once. The model was positively perceived by the doctors in terms of enhancing psychiatry education, general psychiatric competence, and the management of gender dysphoria.

When asked about the model's impact on psychiatric competence, 4 (14.3%) participants noted an improved understanding of gender, gender dysphoria, and DSD, describing a shift in their perspective towards gender and a deeper appreciation for non-binary thinking. Moreover, 7 (25%) reported enhanced skills in general communication and in identifying psychiatric disorders and subthreshold symptoms. Furthermore, 4 (14.3%) reported a better grasp of the multidisciplinary approach and the importance of coordinating follow-up with other specialties, such as pediatric endocrinology.

Regarding suggestions for improving the model, out of 20 respondents, 9 (45%) had no additional recommendations. Of the remaining participants, 5 (25%) suggested implementing a joint follow-up model or increasing contact with other specialties involved in DSD patients' care. Finally, 6 (30%) recommended more supervision and clearer instructions, preferably in written format, for those just starting follow-up.

Discussion

The present study investigated the psychiatric follow-up model employed in the care of patients with DSD, evaluating its impact on patient care and its contribution to the training of CAP residents. Drawing on data from 119 DSD patients and 28 psychiatry residents, the study highlighted both

Table 1. Psychiatric diagnoses of patients with differences of sex development before and after model implementation

	Before model implementation (n = 99)		After model implementation (n = 30)		Total sample		X^2	p
	n	%	n	%	n	%		
Psychiatric diagnoses, n (%)								
None	55	55.6	14	46.7	69	53.5	0.731	0.392[a]
ADHD*	18	18.2	7	23.3	25	19.4	0.391	0.532[a]
Learning disability	3	3	2	6.7	5	3.9	-	0.366[b]
Intellectual disability	14	14.1	4	13.3	18	14.0	-	0.1000[b]
Autism spectrum disorder	1	1	0	0	1	0.8	-	0.1000[b]
Anxiety disorder	4	4	3	10	7	5.4	-	0.352[b]
Major depressive disorder	13	13.1	5	16.7	18	14	-	0.764[b]
Conduct disorder	5	5	0	0	5	3.9	-	0.590[b]

*: Attention deficit and hyperactivity disorder, [a]: Pearson chi-square test, [b]: Fisher's exact test

Table 2. Changes in global assessment scale (GAS) and clinical global impressions (CGI) scores over time before and after the implementation of the model

	Before model implementation (n = 89)*			After model implementation (n = 30)			Between groups p	
	T1 (M ± SD) Median (min.-max.)	T2 (M ± SD) Median (min.-max.)	p	T1 (M ± SD) Median (min.-max.)	T2 (M ± SD) Median (min.-max.)	p	T1	T2
GAS	81.67 ± 16.35 85 (35-95)	84.89 ± 13.69 95 (35-95)	< 0.001	76.33 ± 17.76 85 (25-95)	83.5 ± 13.46 85 (35-95)	0.006	0.074	0.341
CGI**	3.35 ± 0.88 3 (2-5)	2.59 ± 0.91 2 (1-4)	0.002	3.64 ± 1.15 3.5 (2-6)	2.21 ± .80 2 (1-4)	0.002	0.442	0.211

*: Ten patients were lost to follow-up, **: CGI at T1 n = 31 CGI at T2 n = 14
SD: standard deviation, min.-max.: minimum-maximum

Table 3. Child and adolescent psychiatry residents and specialists' expertise in consultation-liaison psychiatry and patient follow-up

	Resident n = 16 mdn, (min.-max.)	Specialist n = 12 mdn, (min.-max.)
Residency duration	14 (12-54)	-
Consultation-Liaison psychiatry outpatient clinic rotation (months)	3 (0-3)	3 (2-5)
Consultation-Liaison psychiatry inpatient rotation (months)	0 (0-5)	4.5 (3-9)
DSD* patients followed up	1 (1-2)	2 (1-4)
DSD councils attended	1 (0-2)	2.5 (1-4)
DSD psychiatric competence at PGY-1** (1-10)	7 (3-9)	6 (1-8)
Model's perceived contribution for psychiatric competence for gender dysphoria (1-10)	4 (0-10)	8 (1-10)
Model's perceived contribution for psychiatric competence for gender dysphoria at PGY-1 (1-10)	8 (7-10)	10 (8-10)
Model's perceived contribution for psychiatry education (1-10)	8 (4-10)	10 (7-10)
Model's perceived contribution for general psychiatric competence (1-10)	9 (7-10)	10 (7-10)

*: Differences of sexual development
**: Post graduate year
DSD: differences of sexual development, PGY-1: post-graduate year 1, min.-max.: minimum-maximum

the challenges and the opportunities in managing these complex cases within a multidisciplinary framework, organized under two key themes: optimizing DSD patient care and advancing pediatric CL psychiatry education within the scope of general CAP residency training.

DSD Patient Care

The primary focus when implementing a new model is to ensure and, ideally, improve the quaity of care. In the management and follow-up of patients with DSD, the roles of various disciplines are relatively well-defined, with consensus guidelines detailing the responsibilities

of multidisciplinary council members, their working principles, appropriate terminology, and surgical decision-making processes. However, studies have emphasized the importance of integrating psychiatric services into these teams (2).

Our findings revealed no significant differences in psychiatric disorder rates before and after the implementation of our model, indicating that the prevalence of these disorders remained consistent whether patients were followed by a single faculty member or by residents under supervision. This consistency underscores the continuity of care provided throughout the diagnostic and follow-up processes, an essential factor in managing DSD. Despite recommendations for holistic, multidisciplinary care, patients often face challenges in accessing services and may disengage from follow-up over time (2). Given that DSD is typically diagnosed at a very young age, the needs of patients and their families evolve significantly as they progress through developmental stages. Issues, such as gender-related questions, challenges with sex development, and fertility concerns, may emerge, necessitating sustained psychiatric support to address growing anxieties and prevent feelings of alienation arising from the constantly changing physiological and neurodevelopmental landscape (21,22). Consistent follow-up by a single mental health professional may play a pivotal role in mitigating these challenges.

The absence of significant differences in GAS and CGI scores before and after the implementation of the new model indicated a good transition from care provided by a single faculty member to care delivered by a closely supervised resident. This transition not only reduced the workload but also ensured the effective sustainability of psychiatric care, as no significant changes were observed in patients' global functioning or clinical well-being. Although 30 patients previously managed by two senior physicians were redistributed to residents, the exact quantitative reduction in physician workload could not be measured due to the inherently variable nature of follow-up intensity and the multidisciplinary character of care. While supervisors retained overall responsibility, involving residents in the follow-up of high-frequency patients offered both a time advantage and educational benefits and exposure to a very rare clinical population. Beyond measurable outcomes, psychiatric follow-up plays a critical role in maintaining treatment adherence and the clinical course of physical illnesses. Comorbid psychiatric disorders can negatively affect both the progression of physical diseases and treatment compliance (23). Therefore, to ensure diagnostic accuracy and the effective coordination of multidisciplinary care, it is essential that follow-up is conducted by a psychiatrist (24). This approach is particularly valuable in maintaining therapeutic support and fostering trust in the medical team. Notably, while 95% of centers with multidisciplinary councils provide primary psychological support, only 40% maintain continuity of psychiatric services (10,25). Psychiatric professionals in this field often face challenges, including less organization compared to other medical disciplines and significant variability between centers in the scope of psychiatric care and the training of providers (22). In addition, limited data on psychosocial care delivery and training processes have hindered efforts to standardize psychiatric services (22).

These challenges are especially relevant in our context. Although comprehensive epidemiological data are lacking in our country, it is assumed that cases of DSD are more frequently observed due to factors such as the high prevalence of consanguineous marriages and thus the greater incidence of genetically inherited syndromic conditions (26). The elevated rate of intellectual disability identified in our study may also be associated with these genetic and epidemiological characteristics. This unique patient profile enhances both the clinical complexity addressed by our model and its educational value. In this context, the model we present is not merely a local initiative but a sustainable and instructive framework that can be implemented in other high-volume centers with similar characteristics. While it may not be feasible to develop a disorder-specific training curriculum for DSD, integrating this model into existing psychiatry training programs has potential for generalizability in terms of both psychiatric education and service delivery. Moreover, building trust with the treatment team is a central component of DSD psychotherapy. Anger toward the medical system is a well-documented challenge. Breaking through this anger and establishing trust with the treatment team are believed to be more effectively achieved through consistent and well-structured support systems (27). DSD patients also frequently experience concerns about being perceived as shameful or stigmatized (28). Studies have shown a positive correlation between satisfaction with healthcare communication and improved psychosocial outcomes in these patients (29). A follow-up study with DSD patients found that 80% of patients reported needing psychiatric support at some point in their lives, yet only 22.2% (n = 218) had received psychological support during childhood or adolescence. Most participants felt that psychological support should always be available (7). These findings from a large-scale, long-term study underline the necessity and continuity of psychiatric follow-up in DSD care. The comparable recovery (CGI) and functionality (GAS) outcomes between the two models further validate the continuity achieved with the new model. By maintaining

this continuity through a single senior mental health professional, the therapeutic alliance is strengthened, building trust in the medical system while ensuring the quality and consistency of psychiatric support. The model presented in this study offers a potential solution to these challenges, providing a structured framework that ensures continuity of care, reduces workload, and supports the evolving needs of patients and their families while fostering the development of future psychiatric professionals.

Pediatric CL in CAP Resident Training

The number of child psychiatry specialists in CL services is extremely limited. In recent years, the increasing number of child psychiatry residents has highlighted the growing importance of supervision meetings for managing rare cases in training and education, as the rising demand for skilled supervisors with extensive experience in the field has become harder to meet (15). Due to the challenges in accessing specialists with expertise in this area, systems such as e-consultation are currently being developed for DSD council collaborations. While these systems may improve patient access to specialists, there is no research addressing their sustainability or their ability to meet the increasing demand for resident training (30).

To meet the increasing demands in both education and clinical care, especially for complex conditions like DSD, our clinic implemented a resident training and follow-up model supported by a single faculty member wherein each DSD patient was assigned to a specific resident, who presents the case during supervision meetings. This model has significant potential to enhance child and adolescent psychiatrists' competence and awareness in managing DSD while meeting the increasing psychiatric needs of patients. Under this system, each resident in training was also responsible for presenting the patient's diagnosis, follow-up, and treatment progress during supervision meetings with the faculty member. This approach enriches residents' clinical experience and promotes peer support within the training process.

A review of the literature highlighted the importance of providing consistent supervision in CAP residency training, tailored to specific psychotherapeutic and interdisciplinary skill development needs (31). With the model currently in use, we believe we may contribute meaningfully to this area. While it may not be feasible to design disorder-specific training content for DSD within child psychiatry education, we believe that this model may be effectively integrated into residency programs at high-volume centers, complementing existing educational curricula.

Although no formal comparisons were conducted, the similar number of DSD patient follow-ups managed by residents (median: 1, range: 1-2) and those who had completed their specialty training (median: 2, range: 1-4) was promising, particularly when considered in light of the consistent CGI and GAS scores. The model's perceived impact on psychiatric education and overall psychiatric competence appeared comparable between current residents and specialists who had completed their training. This suggests that the competencies developed during residency were effectively established and translated into professional practice.

Feedback from residents indicated that most participants gained knowledge about gender dysphoria and DSD. However, perceived competence in managing gender dysphoria differed significantly between the two groups. Residents in training reported a median perceived competence of 4 (range: 0-10), compared to a median of 8 (range: 1-10) among specialists, indicating that expertise in this area requires additional time and experience to fully develop, regardless of DSD follow-up exposure during residency. It is known that biased approaches to gender could influence the diagnostic process among some residents (32). In DSD follow-up, the primary concerns of patients and their families often revolve around issues related to gender determination (21). Promoting a non-binary perspective on gender, instead of using terms such as "intersex", is known to improve compliance and collaboration during the information-sharing process (2). In this context, ensuring that young residents understand the contemporary and ethical approaches to DSD is considered crucial for the positive development of future psychiatric services. The increase in residents' knowledge as they transition to becoming specialists demonstrates the model's positive impact on psychiatric education, probably through shifts in residents' perspectives on gender, including a greater appreciation for non-binary thinking.

Residents also reported increased awareness of the importance of a multidisciplinary approach in DSD care and emphasized the need to strengthen coordination with other specialties. This underscores the importance of adopting a holistic approach in the management of DSD patients, as recommended by most consensus guidelines. Suggestions from participants for improving the model should be considered in creating a more effective follow-up process. Implementing a unified follow-up model and enhancing communication with other specialties are fundamental requirements for better monitoring of DSD patients (33). Moreover, providing more supervision and clear guidance for new residents, particularly in written form, may help strengthen the training process.

Study Limitations

This study presents several notable strengths and some important limitations that merit discussion. A major strength of this study was its focus on the psychiatric care of DSD patients, addressing a gap in research, as most studies on DSD have primarily concentrated on other medical fields with limited attention to psychiatric care (7,29,34), highlighting the importance of data collection in the field (35). The maintenance of data records related to the model is especially valuable given the scarcity of data in this area. Furthermore, the findings demonstrated that continuity of care can be effectively maintained through structured follow-up protocols, even with transitions in service providers, offering practical insights into integrating psychiatric services within multidisciplinary councils while emphasizing consistency and therapeutic support. Another strength is its unique focus on improving educational quality by incorporating resident feedback, addressing a gap in the literature predominantly centered on patient and parent perspectives (29,36).

However, the study is not without its limitations. The lack of formal measurements assessing resident training represents a significant shortcoming. In addition, the relatively small number of patients monitored may limit the generalizability of the findings. The study also provided limited exploration of broader systemic challenges, such as access disparities and variability in psychiatric care organization across centers, which require further investigation. No assessment of the workload saving for the senior psychiatrist was made although subjectively, a reduction in workload was reported. Lastly, the scarcity of psychiatric-focused research in DSD and residency training suggests the need for larger-scale studies to validate and expand upon these findings.

This study reflects the experience of a single institution within a specific healthcare and cultural context, which may again limit the generalizability of the findings to other regions or systems. Factors such as institutional structure, healthcare access, cultural perceptions of gender and identity, and training protocols vary widely across countries and may influence the applicability of this model elsewhere. However, we believe that sharing localized models of care, such as the integration of child psychiatry residents into DSD follow-up under structured supervision, can enhance international dialogue on psychiatric service design for rare and complex conditions. By exchanging knowledge across different healthcare settings and cultural frameworks, we may uncover shared challenges and develop more adaptable, collaborative approaches to care. In this context, we view our study as a contribution to a broader effort to optimize psychiatric support for individuals with DSD through mutual learning, reflection, and innovation.

Although this model was developed within a tertiary care university hospital, its core elements, such as structured supervision, resident continuity, and multidisciplinary collaboration, are not limited to such institutions. We believe these principles can be adapted across a range of healthcare and training environments, including secondary centers and community-based systems where both psychiatric care and medical education are delivered, beyond highly specialized settings.

Conclusion

This study highlighted the importance of continuity of care in the management of patients with DSD, particularly through the integration of psychiatric services within multidisciplinary care teams. The implementation of a revised follow-up model, shifting some responsibility from a single faculty member to supervised child psychiatry residents, resulted in no significant differences in psychiatric disorder rates or clinical outcome measures. These findings support the model's capacity to maintain high-quality, consistent psychiatric care.

Despite international recommendations for holistic, multidisciplinary care, access to continuous psychiatric services remains limited in many settings. Our results suggest that, with structured supervision and individualized follow-up protocols, continuity can be preserved even as care providers change. This model may serve as a valuable framework for other high-volume centers aiming to balance service provision with resident education.

Ethics

Ethics Committee Approval: The study received approval from the Ege University Medical Research Ethics Committee (approval number: 24-5.1T/46, date: 23.05.2024).

Informed Consent: Informed consent and verbal assent were sought and obtained from all patients and their families.

Footnotes

Authorship Contributions

Concept: N. Burcu Özbaran, Design: N. Burcu Özbaran, Hazal Yağmur Yılancıoğlu, Data Collection or Processing: İpek İnal Kaleli, Yağmur Beste Cankorur Haklı, Ceren İçöz, Deniz Özalp Kızılay, Samim Özen, Analysis or Interpretation: N. Burcu Özbaran, İpek İnal Kaleli, Literature Search: Hazal Yağmur Yılancıoğlu, Writing: Hazal Yağmur Yılancıoğlu.

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ORIGINAL ARTICLE

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The First-Year Outcomes of the Nationwide Neonatal CAH Screening in Türkiye: High Rate of False Positives for 21-Hydroxylase Deficiency and a Higher Detection Rate of Non-Classical Cases

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What is already known on this topic?

Salt-wasting 21-hydroxylase deficiency congenital adrenal hyperplasia (21-OHD CAH) is a recessive disorder that can lead to high mortality if treatment is not initiated early. Neonatal screening, particularly in males and in groups with limited access to healthcare, reduces mortality and morbidity associated with 21-OHD CAH. In Türkiye, neonatal CAH screening began with pilot studies in 2017 and gradually expanded to become nationwide in 2022.

What this study adds?

The prevalence of classical 21-OHD CAH in the nationwide CAH screening in Türkiye is 1:12,044. Implementing updated cutoffs will help reduce false positives, lower neonatal screening costs, and prevent the detection of non-classical CAH cases.

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Abstract

Objective: Neonatal screening for congenital adrenal hyperplasia (CAH) was implemented nationwide in Türkiye in 2022. The performance of this screening program in its first year was assessed.

Methods: This retrospective, descriptive study included neonates born in Türkiye between January 1 and December 31, 2022, with gestational age ≥32 weeks and birth weight ≥1500 grams. The screening protocol used a two-tier approach. In the first step, 17α-hydroxyprogesterone (17-OHP) levels were measured using fluoroimmunoassay (FIA) in dried blood spots (DBS) collected at 3-5 days of life. Infants with positive results underwent second-tier testing using liquid chromatography-tandem mass spectrometry to measure 17-OHP, 21-deoxycortisol (21-DF), cortisol (F), and 11-deoxycortisol (S) in DBS. Those with a steroid ratio (21-DF + 17-OHP)/F ≥1 were referred to pediatric endocrinology clinics for diagnostic evaluation.

Results: Of 1,096,069 neonates screened (including 149,652 refugees), second-tier tests were performed on 70,455 (6.88%) infants, and 3,429 (0.27%) were referred to clinics, resulting in 91 confirmed cases of classical 21-hydroxylase deficiency (21-OHD) CAH (77; salt-wasting, 14; simple virilizing). Twenty-two patients were diagnosed with non-classical 21-OHD CAH. The frequency of classical 21-OHD was 1 in 12,044. The first-tier FIA-17-OHP values were below 17.5 ng/mL in 99.8% of healthy neonates with ≥36 weeks gestation or ≥2500 grams and below 50 ng/mL in those with 32-36 weeks or 1500-2500 grams.

Conclusion: Neonatal CAH screening facilitates early diagnosis of 21-OHD and improved patient care. Using refined cut-offs may reduce referrals six-fold and eliminate second-tier testing for 95% of infants. Ongoing evaluation can enhance the efficiency and cost-effectiveness of the screening protocol.

Keywords: Neonatal screening, congenital adrenal hyperplasia, second-tier, steroid profiling, LC-MS/MS

Introduction

Neonatal screening (NS) for congenital adrenal hyperplasia (CAH) reduces mortality and morbidity associated with classical 21-hydroxylase deficiency (21-OHD). Therefore, it is included in the NS programs of many developed countries and is recommended by international guidelines (1).

Although novel, molecular-based CAH screening methods, such as long-read sequencing, show promise, hormone measurement-based screening methodologies, particularly those utilizing mass spectrometric steroid profiling, remain highly sensitive in the early diagnosis of the condition (2,3). Consequently, current practices favor two-tiered screening programs, with the second-tier employing liquid chromatography-tandem mass spectrometry (LC-MS/MS) (1).

In Türkiye, CAH has been included in the NS program since 2017. The second-tier of the program involves measuring 17α-hydroxyprogesterone (17-OHP), 21-deoxycortisol (21-DF), cortisol (F), and 11-deoxycortisol (S) in dried blood spots (DBS) using LC-MS/MS and Türkiye is one of the first countries in the world to adopt this approach. Of note, the inclusion of 21-DF and S in the second-tier testing not only reduces the false positivity of the screening but also facilitates the differentiation of rare CAH forms that may present with elevated 17-OHP levels (4). This feature is particularly important in countries like Türkiye, where consanguineous marriages are common, to effectively identify the targetted patient for screening. However, in contrast to many other countries that use the dissociation-enhanced lanthanide fluoroimmunoassay method to measure 17-OHP in the first step of screening, the fluoroimmunoassay (FIA) method was employed for economic reasons. FIA-17-OHP cut-off values of 10 ng/mL and 15 ng/mL were used in the first step of screening for newborns ≥36 weeks and/or ≥2500 g, and for those 32-36 weeks and/or 1500-2500 g, respectively. The cut-off values used in the screening were determined based on examples from previous screening programs (3,5). Audits of the pilot NS for CAH conducted in Türkiye between 2017 and 2022 were used to analyze false-positive (FP) rates and overall effectiveness (6,7). The aim of this study was to evaluate the outcomes of the first year of the nationwide neonatal CAH screening program, which was expanded to cover the whole country in 2022, and to develop strategies for improvement based on the identified pitfalls.

Methods

A retrospective, cross-sectional study was conducted based on reports generated from the screening program database, including all newborns screened under the authority of Turkish Directorate of Public Health (TDPH) from 1 January to December 31, 2022.

DBS samples were collected on filter paper ("Guthrie" cards) between the third and fifth days of life by heel prick, at public health units, general hospitals, and maternity hospitals. The CAH screening algorithm is presented in Figure 1.

Initial CAH screening was based on the measurement of 17-OHP in DBS on filter paper by FIA (Labsystems Diagnostics, Finland). If the 17-OHP level exceeded the cut-off in the first-tier immunoassay, the filter paper was analyzed using LC-MS/MS for a steroid profile of 17-OHP, 21-DF, F, and S (6,7). Normal values were: for neonates 32-36 weeks and/or 1500-2500 g, 17-OHP < 8 ng/mL, 21-DF < 1.5 ng/mL, F > 50 ng/mL, S < 1.8 ng/mL; for neonates ≥36 weeks

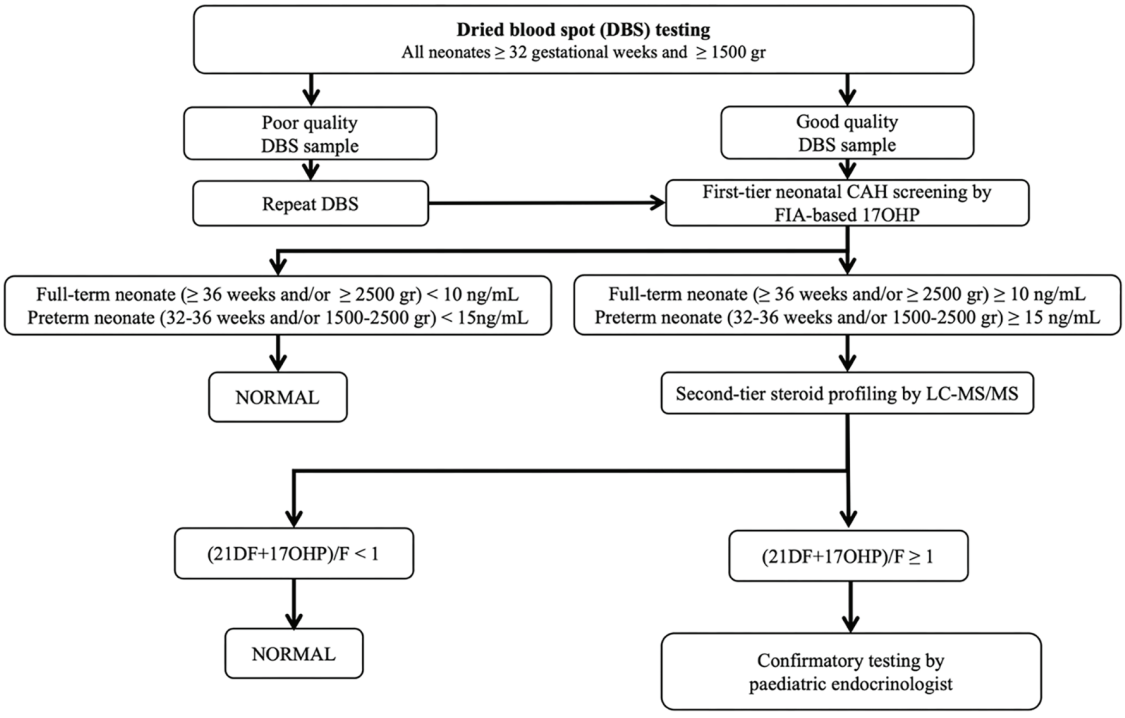


Figure 1. The flowchart of neonatal CAH screening, which became nationwide in Türkiye in 2022. Screening is carried out in Türkiye in all newborns above 32 weeks of gestation and 1500 g birth weight with a single sample two-tier testing strategy

CAH: congenital adrenal hyperplasia, FIA: fluoroimmunoassay, 17OHP: 17α-hydroxyprogesterone, LC-MS/MS: liquid chromatography-tandem mass spectrometry, 21DF: 21-deoxycortisol

and/or ≥2500 g, 17-OHP < 1.5 ng/mL, 21-DF < 1.5 ng/mL, F > 50 ng/mL, S < 1.8 ng/mL. A (21-DF + 17-OHP)/F ratio ≥1 and/or S > 10 ng/mL were the main criteria for referral for further clinical evaluation for 21-OHD and 11β-hydroxylase deficiency (11β-OHD) CAH, respectively.

Classical CAH was defined as an elevated 17-OHP level confirmed by retest and/or clinical evaluation, followed by genotyping. False positives were characterized by the absence of genital abnormalities and/or salt-wasting (SW), with normal 17-OHP levels on retest. The clinical, laboratory, and genetic investigation results of infants diagnosed with CAH were collected from the centers where they were followed after referral to clinics. We also collected information from the centers on which type of 21-OHD, SW, simple virilizing (SV) or non-classical (NC) the patients diagnosed with CAH had. SW CAH is the most severe form, caused by complete enzyme deficiency, leading to low cortisol and aldosterone, and high androgen levels, resulting in prenatal virilization of females. Without treatment, infants may die within weeks due to SW crisis. SV CAH, with mild residual 21-OH activity (1-5%), has sufficient aldosterone to prevent salt loss but still requires glucocorticoid treatment for cortisol deficiency and androgen excess. NC CAH, with 30–50% enzyme activity, maintains normal cortisol and aldosterone but has elevated androgens, typically diagnosed in childhood or young adulthood due to symptoms of androgen excess (8).

Final calculations of true-positive (TP), FP, true-negative (TN) and false-negative (FN) screening results were recorded. Efficiency of screening protocol was assessed with positive predictive value (PPV), sensitivity and specificity, calculated using the following formulae: PPV = TP/(TP + FP), sensitivity = TP/(TP + FN), specificity = TN/(TN + FP). Although it is not always possible to reach babies born in the country, especially refugee babies, data from the TDPH were compared with data from pediatric endocrine centers, and data from the TDPH were reviewed by a member of a NS scientific advisory committee (TG) to reduce FN and TN rate.

Ethics

The parents were informed about Turkish newborn screening. Heel-prick blood samples were collected from live-born babies after written consent from the parents was obtained. The study was carried out with the written permission of the Scientific Committee of the TDPH.

Statistical Analysis

Statistical evaluation was performed using GraphPad Prism® V9.0 software (GraphPad Software Inc., San Diego, California, USA). The results for each steroid are reported as mean, standard deviation or as median (interquartile range) in the text. We performed a t-test for the comparison of the means of two independent samples. Values were considered statistically significant when the p value was less than 0.05.

Results

The total number of newborns who underwent CAH screening was 1,096,069 (including 149,652 refugees). Of these babies, 1,015,200 (92.6%) were ≥36 gestational weeks and/or ≥2500 g birth weight. Of these infants, 70,455 (6.9%) underwent second-tier testing because their FIA-17-OHP levels were above the first-tier cut-off values.

For healthy infants without a final diagnosis of CAH, the 99.8th percentile values for first-tier FIA-17-OHP measurements were found to be below 50 ng/mL for those with a gestational age of 32-36 weeks and/or a birth weight of 1500-2500 g, and below 17.5 ng/mL for those with a gestational age of ≥36 weeks and/or a birth weight of ≥2500 g.

Neonates, who failed to pass second-tier testing (3,429 of 70,455; 4.8%); were referred to pediatric endocrinology clinics for further evaluation, which corresponds to an overall recall rate of 0.31%. The average number of days for referral of neonates to the clinic was 11.75 ± 6.05 days. Consequently, 113 neonates were diagnosed with CAH (55 females, 58 males). Seventy-seven were diagnosed as classical SW 21-OHD CAH, while 14 were SV and 22 were NC 21-OHD CAH. Second-tier testing results of SW, SV and NC-21-OHD CAH patients diagnosed by NS are presented in Supplementary Table 1a, b and c, respectively.

The distribution of 21-OHD CAH forms by sex is shown in Table 1, and no differences in prevalence of forms were observed between the sexes. The incidence of classical 21-OHD in the screened population was 1:12,044. None of these babies was premature nor had low birth weight. Out of the 91 neonates diagnosed with classical CAH through screening, 17 (15%) were refugees, and all of these cases were of the classical SW type.

Table 1. The distribution of 21-OHD CAH forms by sex

	Female	Male	Total
Salt-wasting	38 (69%)	39 (67%)	**77**
Simple virilizing	5 (9%)	9 (16%)	**14**
Non-classical	12 (22%)	10 (17%)	**22**
Total	**55**	**58**	**113**

21-OHD CAH: 21-hydroxylase deficiency congenital adrenal hyperplasia

In all infants diagnosed with classic 21-OHD, the (21-DF + 17-OHP)/F ratio was above 2. Overall, the PPV, sensitivity and specificity of the current screening protocol for classical 21-OHD CAH was calculated as 2.5, 100 and 99.6%, respectively. There was no FN case.

Out of 113 patients diagnosed with CAH, a molecular diagnosis was achieved in 64 patients. Forty-five (70%) patients were homozygous, 14 (22%) were compound heterozygous carriers of *CYP21A2* pathogenic variants, and 5 (8%) patients had a single pathogenic allele identified. The distribution of a total of 149 detected alleles, according to their frequency and severity, is shown in Figures 2A and 2B.

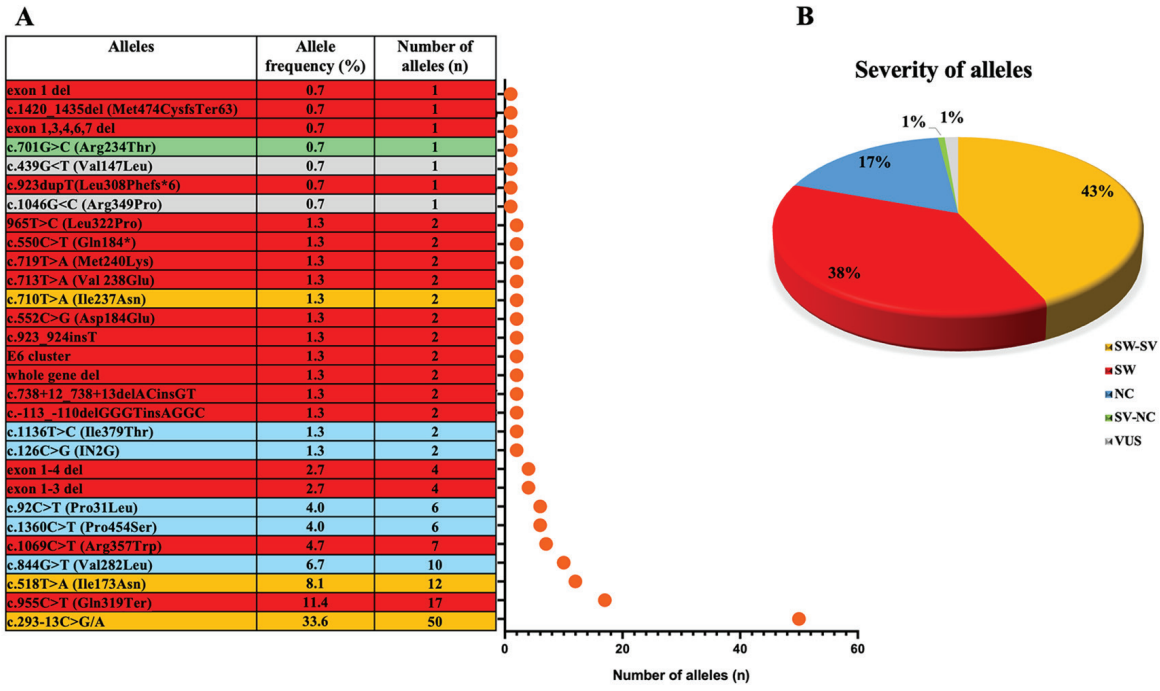
We were unable collect the number of patients with biochemically/genetically confirmed 11β-OHD from the centers.

Discussion

This audit presents the first evaluation of the nationwide neonatal CAH screening programme in Türkiye. The most significant finding of the analysis, as we previously recommended in our pilot studies, is the need to increase the cut-off values for FIA-17-OHP used in the first-tier screening. This approach will reduce the number of FP cases referred to the clinic in particular and thus decrease the number of cases subjected to second-tier testing, thereby lowering the screening costs.

In line with our previous findings (6,7), if the cut-off values of 50 ng/mL for neonates with a gestational age of 32-36 weeks and/or a birth weight of 1500-2500 g, and 17.5 ng/mL for those with a gestational age of ≥36 weeks and/or a birth weight of ≥2500 g, had been used for first-tier FIA-17-OHP measurements, the number of infants subjected to second-tier screening would have been 3,596 instead of 70,455. Even with this proposed approach, 95.1% of the samples subjected to second-tier screening would not have needed this step. This will result in significant savings in both workload and costs.

Currently, in the second-tier of the screening programme, neonates with an LC/MS-MS-based (21-DF + 17-OHP)/F≥1 are referred to clinics for assessment for classical CAH. This cut-off value was determined based on the results of a previous study that retrospectively examined DBS samples (9). However, both in this current nationwide screening analysis and in previous pilot CAH screening trials in Türkiye, all patients diagnosed with classical CAH had a second-tier (21-DF + 17-OHP)/F ratio greater than 2 (6,7). If a (21-DF + 17-OHP)/F ratio of ≥2 had been used instead of ≥1



Alleles	Allele frequency (%)	Number of alleles (n)
exon 1 del	0.7	1
c.1420_1435del (Met474CysfsTer63)	0.7	1
exon 1,3,4,6,7 del	0.7	1
c.701G>C (Arg234Thr)	0.7	1
c.439G<T (Val147Leu)	0.7	1
c.923dupT(Leu308Phefs*6)	0.7	1
c.1046G<C (Arg349Pro)	0.7	1
965T>C (Leu322Pro)	1.3	2
c.550C>T (Gln184*)	1.3	2
c.719T>A (Met240Lys)	1.3	2
c.713T>A (Val 238Glu)	1.3	2
c.710T>A (Ile237Asn)	1.3	2
c.552C>G (Asp184Glu)	1.3	2
c.923_924insT	1.3	2
E6 cluster	1.3	2
whole gene del	1.3	2
c.738+12_738+13delACinsGT	1.3	2
c.-113_-110delGGGTinsAGGC	1.3	2
c.1136T>C (Ile379Thr)	1.3	2
c.126C>G (IN2G)	1.3	2
exon 1-4 del	2.7	4
exon 1-3 del	2.7	4
c.92C>T (Pro31Leu)	4.0	6
c.1360C>T (Pro454Ser)	4.0	6
c.1069C>T (Arg357Trp)	4.7	7
c.844G>T (Val282Leu)	6.7	10
c.518T>A (Ile173Asn)	8.1	12
c.955C>T (Gln319Ter)	11.4	17
c.293-13C>G/A	33.6	50

Figure 2. Distribution of the severity and frequency of *CYP21A2* variants detected in patients diagnosed in the first year of the nationwide neonatal CAH screening in Türkiye. **A)** Specific *CYP21A2* variants are indicated by allele frequency and allele numbers and highlighted in red, orange, blue, yellow and grey according to clinical severity representing salt-wasting, salt-wasting-simple virilising, non-classical, simple virilising-non-classical and variant of unknown significance, respectively. Prevalence of the variants are shown in the frequency dot plot graph on the right. **B)** A pie chart shows the frequency of all alleles detected in diagnosed CAH patients according to their clinical effects

SW: salt-wasting, SV: simple virilising, NC: non-classical, VUS: variant of unknown significance, CAH: congenital adrenal hyperplasia

as the referral criterion in the current screening, there would have been 563 referrals (about 1/6 of all referrals) instead of 3,429. This means that the recall rate in the screening would have been 0.051 % instead of 0.31 %. Therefore, the PPV would have increased by up to 16 %.

An additional concern is the detection of NC CAH cases through NS. The detection of some NC CAH cases can be explained by the low cut-off values used in first-tier 17-OHP measurements. NC CAH cases identified through screening do not reflect the true prevalence of NC-CAH and these neonates should be monitored without treatment unless a clear indication for treatment arises.

One area that requires improvement is the recall time. The success of screening depends on detecting the patient before symptoms develop. In SW CAH, symptoms are expected to begin after the first week of life. DBS samples in the current screening are collected after 72 hours postnatally. If the neonate is discharged before 72 hours, a heel-prick blood sample is taken by contacting the family through their affiliated primary healthcare provider. Delays in processes, such as reaching the family or the family's attendance at the healthcare facility, can prolong the recall time in some cases. This particularly creates challenges in reaching the babies of migrant families living in Türkiye, who constitute approximately 1/7 of all screened neonates. Since the second-tier screening uses LC-MS/MS with very low hormone interference, we recommend a pilot study to analyse false positives and false negatives in DBS samples collected before discharge. If there is no negative impact on screening results, moving the DBS collection to before discharge may shorten the recall time. As we suggested in previous pilot studies, referring neonates with very high first-tier test results (i.e., FIA-17-OHP > 90 ng/mL) to clinical evaluation without undergoing second-tier testing would also shorten the time to diagnosis, especially in SW cases.

Patients were diagnosed with classic CAH based on clinical findings (ambiguous genitalia and/or salt loss) in addition to a positive screening test, and the diagnosis was confirmed by biochemistry and further hormone testing. Inadequacies in accessible genetic testing, such as the inability to perform multiplex ligation-dependent probe amplification testing in all patients as molecular evidence, or that only the 10 most common mutations leading to 21-OHD were examined,

may have led to the failure to find the pathogenic second *CYP21A2* allele in some patients.

Study Limitations

One limitation of this audit is the inability to reliably determine steroid hormone cut-off levels that define subgroups of 21-OHD in diagnosed patients. This is due to the differences in the variants carried by the patients and the relatively small number of diagnosed cases. Furthermore, although second-tier CAH screening strategy would facilitate identification of cases with 11β-OHD, we were unable collect the number of patients with biochemically/genetically confirmed 11β-OHD from the centers. Therefore, we could not include data on the prevalence of 11β-OHD in this study.

Conclusion

As the Neonatal CAH Screening Scientific Committee, we believe that implementing the aforementioned changes during the early phase of the nationwide expansion of screening will enhance its long-term effectiveness and cost-efficiency, while also reducing laboratory and clinical workload. Furthermore, we consider that such audits in newborn screening programmes are crucial for improving preventive healthcare services.

Ethics

Ethics Committee Approval: The study was carried out with the written permission of the Scientific Committee of the TDPH.

Informed Consent: Heel-prick blood samples were collected from live-born babies after written consent from the parents was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Tülay Güran, Concept: Tülay Güran, Elif Yürüker, Ahmet Anık, Müge Atar, Emine Çamtosun, Elif Eviz, Mehmet İsakoca, Eda Mengen, Büşra Gürpınar Tosun, İhsan Turan, Aylin Kılınç Uğurlu, Edip Ünal, Doğuş Vurallı, Gülay Can Yılmaz, Yüksel Hakan Aydoğmuş, Şükran Darcan, Design: Tülay Güran, Şükran Darcan, Data Collection or Processing: Tülay Güran, Elif Yürüker, Ahmet Anık, Müge Atar, Emine Çamtosun, Elif Eviz, Mehmet İsakoca, Eda Mengen, Büşra Gürpınar Tosun, İhsan Turan, Aylin Kılınç Uğurlu, Edip Ünal, Doğuş Vurallı, Gülay Can Yılmaz, Yüksel Hakan Aydoğmuş, Şükran Darcan, Analysis or Interpretation: Tülay Güran, Literature Search: Tülay Güran, Writing: Tülay Güran.

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Click the link to access Supplementary Table 1a-c: https://https://d2v96fxpocvxx.cloudfront.net/1dda20c2-8b22-466b-a98e-85ecfb39ceaf/content-images/1aff00b7-0745-4e1e-afd7-00ef6e379fa3.pdf

BRIEF REPORT

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Iodinated Contrast-Induced Hypothyroidism in An Infant after Enteral Contrast Enema: A Case-Report and Systematic Review

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What is already known on this topic?

Data on the effects of iodinated contrast media (ICM) on thyroid function in children is scarce. After the Food and Drug Administration warning on the use of ICM in 2022, this topic has attracted more attention. Most recent studies have focused on the effect of topical or intravascular administration of ICM on thyroid function. However, data about the effect of enteral ICM administration on thyroid function are lacking.

What this study adds?

This is the first study to provide a systematic review of the current literature on enteral ICM-induced hypothyroidism in infants. The case-report and overview of the available literature highlights the potential severity of this iatrogenic hypothyroidism and suggests that future studies and clinical guidelines on this specific topic would be beneficial.

Abstract

Excessive iodine intake may trigger the Wolff-Chaikoff effect, which results in downregulation of thyroid hormone synthesis to prevent hyperthyroidism. Failure to recover euthyroidism after the Wolff-Chaikoff effect may be seen in infants, and especially premature infants, and may result in prolonged iodine-induced hypothyroidism. We describe a rare case of a preterm infant who developed severe iodinated contrast-induced hypothyroidism after the use and prolonged stasis of enteral iodinated contrast media (ICM). In addition, a systematic literature search was performed to evaluate all available data on this condition. This systematic literature search was performed in

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PubMed and Embase. Studies describing the effect of enteral ICM on thyroid function were considered eligible. The primary outcome was to determine the frequency of contrast-induced hypothyroidism in infants after administration of enteral ICM. The premature infant in our center developed severe iodinated contrast-induced hypothyroidism after enteral ICM. In total, only two studies met our eligibility data, reporting eight patients. Of these eight patients, four premature infants developed contrast-induced hypothyroidism after enteral administration of ICM. Data on severity, length and frequency of contrast-induced hypothyroidism after exposure to enteral ICM is very scarce. The present case-report and literature search highlights the potential severity of this iatrogenic hypothyroidism and suggests that future studies and clinical guidelines on this specific topic would be beneficial. We recommend standardized monitoring of thyroid function after exposure to enteral ICM in newborns to prevent delayed diagnosis of severe contrast-induced hypothyroidism until evidence based recommendations can be made.
Keywords: Hypothyroidism, iodinated contrast media, contrast induced hypothyroidism.

Introduction

Thyroid hormones are essential in fetal intrauterine and neonatal postnatal brain development, growth and metabolism (1). Untreated persistent neonatal hypothyroidism can cause serious brain damage, including mental retardation and impaired motor function (1). Therefore, newborn screening (NBS) programs for congenital hypothyroidism (CH) are in place to detect thyroid dysfunction as early as possible in life and to prevent brain damage by timely start of levothyroxine treatment (2). Depending on the type of NBS program, only primary CH, or primary and central CH may be diagnosed. Primary CH is caused by abnormal thyroid gland development or thyroid hormone biosynthesis, with an estimated incidence of 1:3000-4000 live births (3).

Acquired hypothyroidism in the neonatal period is rare. One of its potential causes is the excessive exposure to iodine via the skin (disinfectants/antiseptics containing iodine), gastrointestinal tract or intravenously (iodinated contrast medium; ICM) (4,5,6,7). Iodine is crucial for thyroid hormone synthesis. Many radiological diagnostic procedures involve ICM, resulting in potential excessive iodine exposure to the thyroid gland. Physiologically, the thyroid responds with downregulation of thyroid hormone synthesis to prevent hyperthyroidism, a phenomenon called the Wolff-Chaikoff effect (8). After a few days, escape from the Wolff-Chaikoff effect should occur, resulting in normalization of thyroid hormone synthesis. However, failure to escape the effect may result in prolonged hypothyroidism. Previous studies have shown that both topical and intravenous ICM administration may cause transient thyroid dysfunction, particularly in preterm infants as a result of a failed escape from the Wolff-Chaikoff effect (9,10,11). It is thought that prematurity is a risk factor for prolonged hypothyroidism after exposure to ICM because of immaturity of the escape mechanism (12). Especially during the neonatal period, when brain development is dependent on sufficient thyroid hormone concentrations, prolonged hypothyroidism should be prevented.

In 2022, the United States Food and Drug Administration (FDA) released a medication safety communication recommending thyroid function evaluation for children under the age of three years within three weeks after intravascular administration of ICM (12). The FDA statement resulted in increased attention to this subject. Subsequently, the Pediatric Endocrine Society (PES) and American College of Radiology (ACR) published statements questioning this recommendation due to lack of evidence and proposed a more individualized approach, identifying high-risk patient groups, like premature newborns (2,5). The current recommendations address intravenous ICM administration and overlook enteral ICM administration. Here we describe a case of prolonged hypothyroidism in a premature infant after enteral ICM exposure, and summarize the results of a systematic literature study into the reported number of cases of contrast-induced hypothyroidism in infants after enteral ICM administration.

Methods

A literature study was conducted according to the preferred reporting items for systematic reviews and meta-analysis guidelines (available at https://www.prisma-statement.org). In accordance with the guidelines, our systematic review protocol was registered in the international prospective register of systematic reviews with the number CRD42023393923. Informed consent was obtained for publication from parents of the patient that is described in the case-report. The Medical Ethics Review Committee of Amsterdam University Medical Centers is registered with the US Office for Human Research Protections as IRB00013752. The FWA number assigned to Amsterdam UMC is FWA00032965.

Literature Search

All scientific publications reporting on enteral ICM administration in newborns were considered eligible for review. A medical information specialist (RdV) searched electronic databases (PubMed and EmBase) from inception to

January 23, 2023. The following terms were used (including synonyms and closely related words) as index terms or free-text words: Iodinated contrast media, "Thyroid function", "Hypothyroidism" and "Neonates". Language restrictions were not applied and duplicates were excluded by RvD using Endnote X20.0.1 (Clarivate[tm]), following the Amsterdam Efficient Deduplication and Bramer-methods (13). Studies were screened by two independent authors using Rayyan (LDES, AGHP) (14). Full texts of the selected articles were retrieved for further review. Any disagreements were resolved by consultation with an expert specialist (JPMD). The reference lists of included articles were reviewed for additional relevant studies. Inclusion criteria were pediatric patients under the age of one year, enteral administered ICM and clearly described follow-up of thyroid function. Animal studies, duplicates, conference abstracts, studies reporting on intravenous or topical ICM administration and previous published data were excluded. The full search strategies for all databases are available as Supplementary Material 1.

Primary Outcome

The primary outcome was to determine the reported number of cases of contrast-induced hypothyroidism in infants after enteral administration of ICM. This outcome was illustrated with a case-report from our own center.

Data Extraction and Validity Assessment

Two authors (LDES, AGHP) independently extracted the data, and evaluated the methodological quality and risk of bias. Disagreements were resolved through discussion; if no consensus could be reached, a third reviewer was consulted (JPMD).

All included articles were assessed for methodological quality and risk of bias using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case-reports, Case series and cohort studies (15). For each tool several questions regarding methodological quality of the study need to be answered with "Yes", "No", "Unclear" or "Not applicable". Each answer option was scored and summed up. The maximum score for case-reports was 24 points. "High" quality was defined as 19 points or higher, "Moderate" as 14 to 18 points, and "Low" as 13 points or lower. For case series the maximum score was 30 points. "High" quality was defined as 24 points or higher, "Moderate" as 17 to 23, and "Low" as 16 points or less. Publications scored as "high" or "moderate" quality were included in this systematic review.

Statistical Analysis

Statistical meta-analysis of data obtained in the systematic review was not performed due to the low number of included articles.

Results

1. Case-report

The patient is a girl, born small for gestational age through Cesarean section at gestational age of $26^{6}/_{7}$ weeks (birthweight 550 g, Z-score -1.7) (16). The pregnancy was complicated by fetal growth restriction due to placental insufficiency. Prenatal fetal ultrasound revealed dilated intestinal loops. The first weeks of life were complicated by multiple gastro-intestinal problems including meconium plug requiring ileostomy creation on day 2 (D2), and a jejunal intestinal perforation on D6 for which surgery was performed with overstitching of the perforation (Figure 1). Postoperatively, on D8 minimal enteral feeding was started. However, an increase in feeding volumes resulted in a high-output stoma. In addition, failure to grow and difficulties with distal stoma refeeding were observed. A fistulogram was performed on D79 using 20 mL of omnipaque (240 mg I/mL) to visualize the distal bowel patency, showing no stenosis, obstruction or dilated bowel loops (Figure 2A).

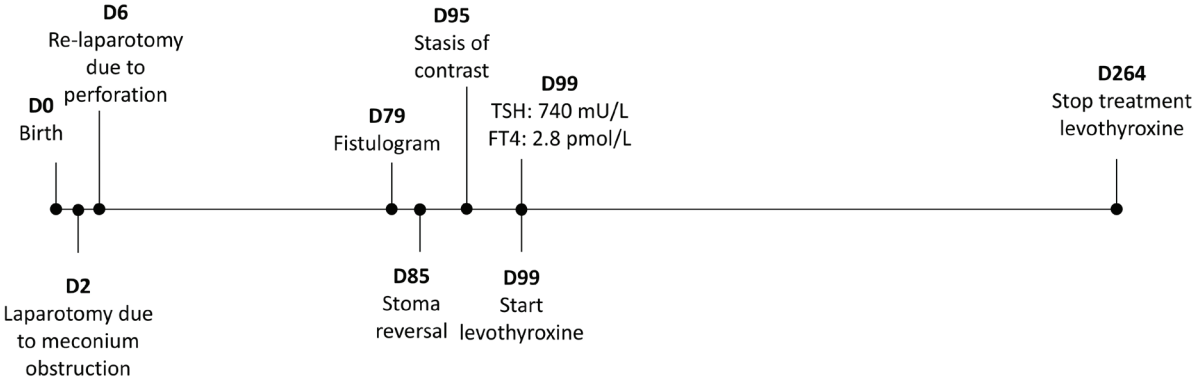

Figure 1. Timeline of a neonatal patient who developed iodinated contrast induced hypothyroidism

TSH: thyroid-stimulating hormone, fT4: free thyroxine

Surgical stoma reversal was done on D85. Postoperatively, bilious retentions persisted and there was no defecation. The patient developed a severe systemic inflammatory response syndrome (SIRS), resulting in respiratory insufficiency requiring high respiratory pressures, hypotension, electrolyte imbalances, and extreme soft tissue edemas necessitating circulatory support (Figure 2B). The chest X-ray on D95 showed ICM stasis in the rectum (Figure 2C). Rectal irrigation was started on D98 due to constipation. On D98 a chest X-ray was taken to check for pulmonary abnormalities, showing signs of osteopenia (Figure 2D). With no clear cause for the clinical deterioration, the pediatric endocrinologist was consulted regarding the osteopenia and suspicion of adrenal insufficiency as a possible cause of the circulatory insufficiency. Central adrenal insufficiency was ruled out via a low-dose cosyntropin stimulation test. Additional endocrinological laboratory test on D99 revealed severe primary hypothyroidism with an extremely elevated thyroid-stimulating hormone (TSH) level of 740 mU/L (local age-specific reference range 0.7-8.4 mU/L) and very low free thyroxine (fT4) level of 2.8 pmol/L (local age-specific reference range 11.9-25.6 pmol/L). Prior to this, the NBS result for CH was normal, as were previous thyroid function tests (fT4 concentration 15.0 pmol/L at D58). Treatment with levothyroxine was started immediately (D99) at a daily dose of 25 mcg (6.62 mcg/kg/day). Within two days after start of levothyroxine treatment, circulatory and respiratory status improved and treatment with inotropic drugs could be stopped. During follow-up, levothyroxine dose was titrated based on thyroid function testing. At D264 levothyroxine treatment could be stopped with normal thyroid function at further follow-up.

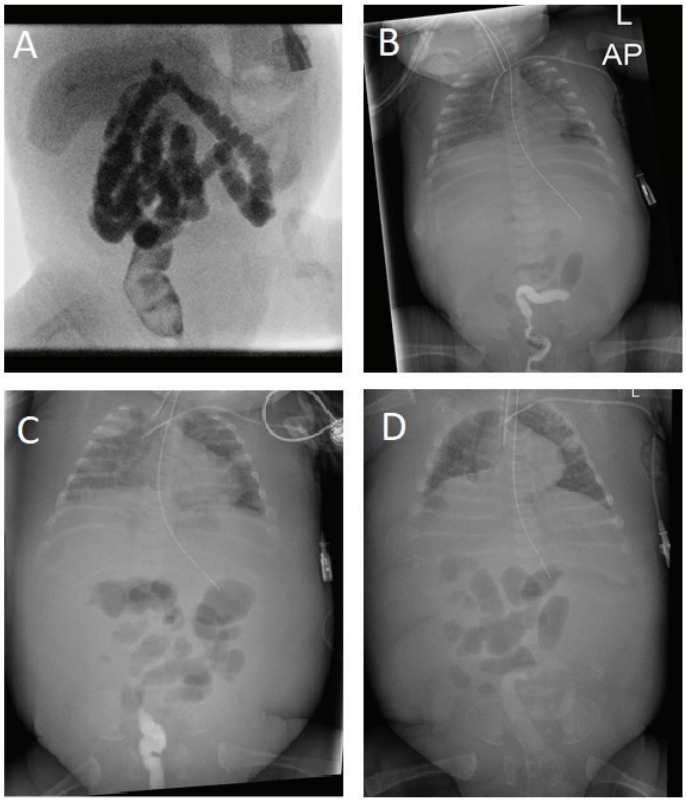

Figure 2. Radiological images of a neonatal patient who developed iodinated contrast induced hypothyroidism. **A)** D79, fistulogram. Contrast enema omnipaque 240 mg I/mL, 20 mL administered via the ileostomy. Normal diameter and appearance of the bowel loops and colon. **B)** D86, X-ray of the thorax and abdomen. Seven days after contrast enema. Pulmonary markings that indicate bronchopulmonary dysplasia. Distended abdomen, with abnormal bowel gas, and residual intraluminal contrast in the distal recto sigmoid. Edematous soft tissue. **C)** D95, X-ray of the thorax and abdomen. Sixteen days after contrast enema, intraluminal contrast is still visible. **D)** D98, X-ray of the thorax and abdomen. Nineteen days after contrast enema. This was after rectal irrigation and only subtle appearance of intraluminal contrast is visible

The girl's primary hypothyroidism was thought to be acquired, especially because of the normal fT4 concentration on D58. In retrospect, the ICM administered on D79 was still visible on the chest X-ray on D95, indicating gastro-intestinal stasis of ICM for 19 days. This prolonged exposure to ICM was judged to be the most likely cause of the hypothyroidism. Since iodine-induced hypothyroidism is almost always a transient problem, that the thyroid function remained normal after stopping levothyroxine treatment is further proof for this diagnosis.

2. Systematic Review

The systematic literature search in PubMed and Embase resulted in 2012 unique articles. After title and abstract screening 1984 articles were excluded. The remaining 28 articles underwent full-text screening, resulting in exclusion of 26 articles. Reasons for exclusion were intravenous contrast administration (n = 12), topical povidone use (n = 4), studies without original data (n = 9), and incomplete information (n = 1). Ultimately, two studies were included, reporting eight patients with thyroid function follow-up after exposure to enteral ICM (Figure 3). Study characteristics are summarized in Table 1 (17,18).

Risk of Bias

Risk of bias was assessed using the JBI Critical Appraisal Checklist for case-reports, case series and cohort studies (15). Results are shown as Supplementary Material 2. The quality of the case-report by Lombard et al. (18) was scored as high and the case series of Ares et al. (17) was scored as moderate.

Study Characteristics of Contrast Induced Hypothyroidism

The two eligible studies, published in 2008 and 2009, included one case-series and one case-report. The case series of Ares et al. (17) described seven newborns from a neonatology department during a one-year period. The infants received Gastrografin, a contrast enema with an iodine concentration of 370 mg/mL. The indication for Gastrografin administration was treatment for uncomplicated meconium ileus in three patients, and use as contrast medium for radiological imaging in four patients. All had normal NBS results for CH. Six out of seven patients were born preterm (range 27-36 weeks gestational age). Hypothyroidism was defined as increased TSH levels (local reference range 0.5-6.15 mU/L) and normal to decreased fT4 levels (local reference range 0.70-1.64 µg/dL). Normal total T4 levels were defined as >6.5 µg/dL. Three of the seven reported patients developed contrast-induced hypothyroidism (Table 1). All three patients with hypothyroidism were born premature. The first diagnosed patient was treated with Gastrografin for meconium ileus, exhibiting elevated TSH levels and decreased fT4 levels on D6 after administration. In the second case, Gastrografin was administered as contrast enema, resulting in increased TSH and normal fT4 levels observed 13 days later. In the third case, Gastrografin was administered as contrast medium. TSH levels were increased, but the total T4 level was elevated. The duration between Gastrografin administration and thyroid function evaluation was not specified. The three infants diagnosed with contrast-induced hypothyroidism were all treated with levothyroxine for one month after which levothyroxine treatment was stopped. In one patient the TSH level was high after cessation of levothyroxine treatment resulting in restarting levothyroxine treatment and further follow-up by a pediatric endocrinologist. In summary, Ares et al. (17) reported that three out of seven infants who received Gastrografin, all premature born, were diagnosed with, and treated for iodine-induced hypothyroidism.

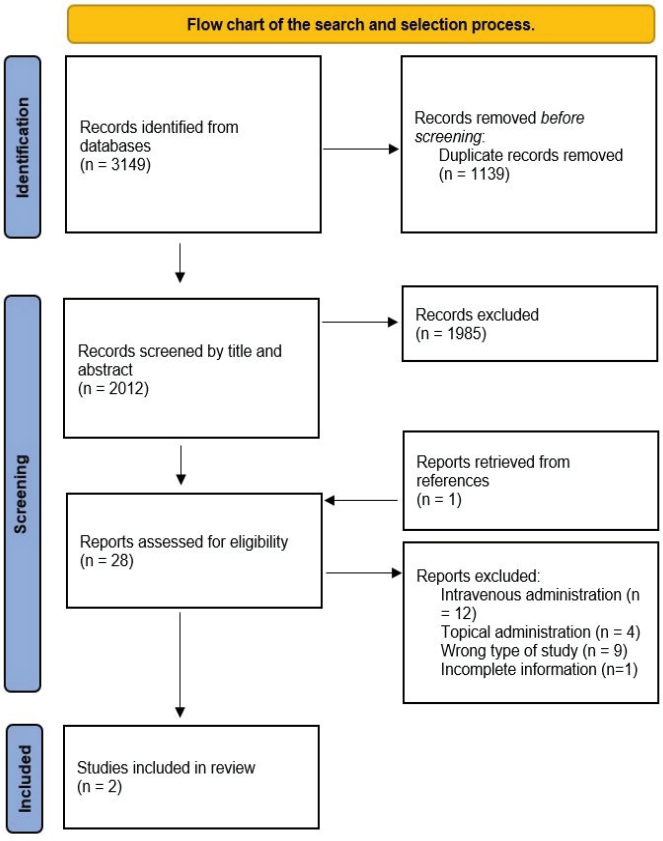

Figure 3. Flowchart of search and selection process

Lombard et al. (18) reported a case of a male infant, born at 27 weeks gestation. Due to failure to pass stools, he underwent a diagnostic test receiving a sodium ioxitalamate contrast enema with an iodine concentration of 120 mg/mL with a total volume of less than 20 mL. After 23 days the male infant developed jaundice and biochemical evaluation showed cholestasis. Sixty-six days after contrast administration thyroid function was evaluated because of

Table 1. Included studies in this systematic review on contrast induced hypothyroidism in neonates

Author	Year	Type of study	Premature	CIH	Type of contrast	Reason for use of iodinated enteral contrast	Laboratory values	Treatment levothyroxine
Ares et al. (17)	2008	Case-series	6/7, range 27-36 weeks GA	3/7	Gastrografin	Treatment uncomplicated meconium obstruction (n = 3) Radiological imaging (n = 4)	Case 1 TSH: 33.14 µUI/mL fT4: 0.51 µg/dL Case 2 TSH: 25.7 µUI/mL fT4: 1.06 µg/dL Case 3 TSH: 40.0 µUI/mL total T4: 3.4 µg/dL	3/7
Lombard et al. (18)	2009	Case-report	1/1, 27 weeks GA	1/1	Ioxitamalate (telebrix 12)	Meconium obstruction (n = 1)	TSH: 368 µUI/mL (local reference range 0.2-4.2 µUI/mL), fT4: 5.1 pg/mL (local reference range 9.3-17.0 pg/mL) fT3: 2 pg/mL (local reference 1.5-4.1 pg/mL)	1/1

TSH: thyroid-stimulating hormone, fT4: free thyroxine, GA: gestational age, CIH: contrast induced hypothyroidism

persistent cholestasis. Contrast induced hypothyroidism was diagnosed based on elevated TSH, decreased fT4 and normal fT3 levels (Table 1). Treatment with levothyroxine was started immediately. After 49 days treatment could be stopped, and TSH, fT4 and fT3 levels remained normal.

In total, four of the eight reported patients who received enteral ICM were diagnosed with contrast-induced hypothyroidism. The patients with reported iodinated contrast induced hypothyroidism were all born premature.

Discussion

We present a case of a preterm infant who developed iodine-induced hypothyroidism after enteral ICM administration via a fistulogram, followed by prolonged stasis of the ICM. Within twenty days after ICM administration the patient developed severe SIRS. Laboratory results showed an extremely elevated TSH level and a very low fT4, indicating severe primary hypothyroidism. Although it is uncertain whether the clinical symptoms prior to levothyroxine treatment were only caused by severe hypothyroidism, the patient recovered rapidly after initiation of treatment with levothyroxine. A systematic literature search was performed to evaluate this complication of enteral ICM. Only two studies reported on iodine-induced hypothyroidism after enteral ICM administration, including eight patients of whom four were diagnosed with ICM-induced hypothyroidism.

The FDA released a medication safety communication in March 2022 advising thyroid function monitoring within three weeks following intravascular administration of ICM in all children under the age of three years (12). This caution is rooted in the fact that especially infants are vulnerable to thyroid dysfunction after excessive intake of iodine, resulting in the Wolff-Chaikoff effect (8). The escape from the inhibitory impact of high iodine dosages, however, is not always successful in infants, and may cause clinical or subclinical hypothyroidism (19). It is thought that preterm infants might be especially at risk of developing ICM-induced hypothyroidism since the ability to escape from the Wolff-Chaikoff effect develops only between 36 and 40 weeks of gestation (20,21). Effects of ICM administration on thyroid function in children have therefore been a topic of debate in recent literature. Available literature primarily focused on intravenous administration, for example for cardiac interventions and evaluation of tip position of peripherally inserted central catheter or topical administration for disinfection (4,9,22). The results of these studies are contradictory and randomized studies with large sample sizes are lacking. The results of our systematic literature search showed that evidence on the effects of the use of enteral ICM on thyroid function in (premature) infants is limited. Nevertheless, it is important to raise awareness for the potential severe clinical consequences of late diagnosis of iodine-induced hypothyroidism after prolonged exposure to enteral ICM, as illustrated by our patient.

In patients with CH it is known that persistent low thyroid hormone concentrations have a major negative impact on brain development. Over recent decades, more and more countries have introduced NBS for CH. Since then, numerous studies have sought to compare the IQ scores of patients treated for CH with those who received no treatment. The benefits of early detection and treatment are indisputable from these studies (23,24). Notably, subsequent studies have found that the severity of hypothyroidism plays a significant role in the neurological outcome of these patients (3). In cases with acquired hypothyroidism, such as patients with contrast-induced hypothyroidism, the period of low thyroid hormones is relatively short and transient. However, one may hypothesize that, especially in preterm infants, even a relatively short period of severe hypothyroidism could negatively impact brain development with potential lifelong consequences.

We speculate that prolonged enteral exposure to ICM may result in increased iodine uptake, although it is unknown if intestinal permeability, the duration of stasis or the amount and concentration of the ICM contrast plays a role in development of hypothyroidism. Our case illustrated that the contrast remained in the bowel until rectal irrigation, nineteen days after fistulogram. The higher the iodine exposure, the likelier it is that the Wolff-Chaikoff effect occurs and premature infants are more likely to be unable to escape the inhibitory Wolff-Chaikoff effect, resulting in prolonged thyroid dysfunction. Therefore, stasis of ICM may be one of the risk factors contributing to the development of contrast-induced hypothyroidism.

Following the reported recent case in our center, speculation arose regarding the severity, length and frequency of this complication in infants since thyroid function monitoring was not standard care for those receiving enteral ICM. The results of the literature review showed only two previous publications describing four infants suffering from contrast induced hypothyroidism. However, the potential complication of enteral ICM-induced hypothyroidism have been reported in additional publications that were not included in our systematic review due to incomplete data (9,25,26,27,28). It has been suggested in some of these publications that monitoring of thyroid function after enteral administration of ICM is warranted until an evidence based guideline is available, and this suggestion has been made by the PES and ACR as well (27,28). Although

overall evidence is limited, the available data suggests that contrast induced hypothyroidism might be a more frequent complication after the use of enteral ICM then previously realized. Consequently, a local protocol was implemented as standard care in our hospital, consisting of standard testing of thyroid function and abdominal X-rays to detect stasis of contrast in infants after enteral ICM administration.

Study Limitations

This case-report and systematic review aimed to provide insights into the clinical presentation of iodine-induced hypothyroidism in infants following enteral ICM administration. However, several limitations must be acknowledged. The finding of this case-report might be specific to the individual patient described and may not be applicable to a broader population or different clinical setting. In addition, the urinary iodine excretion was measured 26 days after enteral ICM administration. At that time, urinary iodine levels were not elevated. However, we believe that urinary iodine levels would have been high shortly after prolonged (19 days) enteral exposure to ICM. In retrospect, earlier evaluation of urinary iodine excretion could have confirmed systemic exposure to high levels of iodine. The primary limitation of the systematic review is that none of the included studies specifically focused on the occurrence of contrast-induced hypothyroidism in infants. Furthermore, publication bias could impact results, as unreported negative cases make determining the number of cases of contrast-induced hypothyroidism challenging. Nevertheless, this is the first systematic review reporting on the effect of enteral ICM on thyroid function in infants.

Conclusion

We present a case-report of contrast-induced hypothyroidism after prolonged stasis of administered enteral ICM in a premature infant. Additional studies on the severity, length and frequency of this complication are lacking, as our systematic review only identified two studies reporting on enteral ICM-induced hypothyroidism with a very small sample size. Therefore we are unable to report the true number of cases of contrast-induced hypothyroidism in infants who were exposed to enteral ICM. In line with the PES and ACR statements, we recommend monitoring of thyroid function after the use of enteral ICM in all infants until an evidence-based guideline is available.

Ethics

Ethics Committee Approval: The Medical Ethics Review Committee of Amsterdam University Medical Centers is registered with the US Office for Human Research Protections (OHRP) as IRB00013752. The FWA number assigned to Amsterdam UMC is FWA00032965.

Informed Consent: Informed consent was obtained for publication from parents of the patient that is described in the case-report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Joep P. M. Derikx, L. W. Ernest van Heurn, Joost van Schuppen, Sandra E. Zoetelief, Wes Onland, Christiaan F. Mooij, Nitash Zwaveling-Soonawala, A. S. Paul van Trotsenburg, Concept: Adinda G. H. Pijpers, Joep P. M. Derikx, L. W. Ernest van Heurn, Joost van Schuppen, Wes Onland, Christiaan F. Mooij, Nitash Zwaveling-Soonawala, A. S. Paul van Trotsenburg, Design: Adinda G. H. Pijpers, Joep P. M. Derikx, Wes Onland, Christiaan F. Mooij, Data Collection or Processing: Adinda G. H. Pijpers, Laurens D. Eeftinck Schattenkerk, Ralph de Vries, Analysis or Interpretation: Adinda G. H. Pijpers, Joep P. M. Derikx, Laurens D. Eeftinck Schattenkerk, Christiaan F. Mooij, Literature Search: Adinda G. H. Pijpers, Laurens D. Eeftinck Schattenkerk, Ralph de Vries, Writing: Adinda G. H. Pijpers, Joep P. M. Derikx, Joost van Schuppen, Sandra E. Zoetelief, Wes Onland, Christiaan F. Mooij, Nitash Zwaveling-Soonawala, A. S. Paul van Trotsenburg.

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