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Case Report

Diazoxide and Continuous Glucose Monitoring as Treatment in a Neonate with Hyperinsulinemic Hypoglycemia due to HNF4A Mutation

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What is already known on this topic?
Neonatal hypoglycemia due to HNF4A mutations is usually diazoxide-responsive. It is crucial to closely monitor glucose levels in these children. However, continuous glucose monitoring systems are not indicated for neonatal age.

What this study adds?
Continuous glucose monitoring systems in a neonate with hyperinsulinemic hypoglycemia due to HNF4A mutation helped us to recognize hypoglycemia events with less finger pricks, and revealed diazoxide-induced hyperglycemia, facilitating treatment decisions -during hospitalisation and after hospital discharge- and establishment of a more physiological feeding pattern for our patient (exclusive breastfeeding). Further studies could establish the usefulness of CGM in these patients as an adjunct in clinical care.

Abstract
The transcription factor hepatocyte nuclear factor-4a plays a key role in insulin secretion and mutations in its encoding gene, *HNF4A*, have been associated with Monogenic diabetes (MODY 1) during adolescence or early adulthood and with transient hyperinsulinemic hypoglycemia during infancy. They are inherited as an autosomal dominant trait, therefore, *HNF4A* sequencing should be considered in every neonate presenting with macrosomia or persistent hypoglycemia after 24 hours from birth, especially when there is a family history of early-onset diabetes. Management of hyperinsulinism includes regular feeding, intravenous glucose and diazoxide, as first-line treatment. Blood glucose levels need regular monitoring to adjust treatment properly. Continuous glucose monitoring systems are not validated for neonates or patients with hyperinsulinism, so finger-prick blood tests are usually used before every meal. We present a case of diazoxide use in a female patient with neonatal hypoglycemia due to *HNF4A* mutation, where continuous glucose monitoring facilitated treatment decisions and detected hyperglycemia, as an adverse event early in the course. Notably, CGM use after hospital discharge contributed significantly to ongoing glucose monitoring and management. We recommend that further studies could establish CGM's usefulness as an adjunct in clinical care.
Keywords: HNF4A mutation, MODY 1, diazoxide, continuous glucose monitoring, hyperinsulinemic hypoglycemia

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Introduction
Hepatocyte nuclear factor 4A (HNF4A) is a transcription factor that plays an important role in pancreas and liver development, function and cell metabolism (1). Mutations in the *HNF4A* gene follow autosomal dominant inheritance pattern and are most commonly associated to Maturity-Onset Diabetes of Youth type 1 (MODY 1), but also to macrosomia and hyperinsulinemic hypoglycemia at birth or infancy (1, 2, 3). They can also cause a great heterogeneity of phenotypes, including extra-pancreatic manifestations, such as developmental delay, Fanconi syndrome, renal or hepatic findings (3). Hyperinsulinemic hypoglycemia has a reported incidence of 15% in *HNF4A* mutation carriers with an equal maternal and paternal inheritance, indicating that the pathogenesis of hyperinsulinism is independent of maternal glycemic control during pregnancy. Finally, hyperinsulinism is diazoxide-responsive but with a substantial variability in treatment necessity and duration that has been reported in case series (3,4).
Continuous glucose monitoring (CGM) systems measure interstitial glucose in a constant fashion every 1-15 minutes. The first commercial CGM was approved by FDA in 1999 for patients with type 1 diabetes mellitus. Since then, there has been a technological evolution in this field. Nowadays, most people with diabetes mellitus type 1 use CGMs, as they improve glycemic control, reduce hypoglycemia incidents and have a substantial impact on quality of life (5-7). CGM devices are not yet approved for use in neonates with congenital hyperinsulinism. However, there have been studies showing benefits of their use in detecting hypoglycemia and blood glucose trends and facilitated medications management, implying that CGMs could be applied as an adjunct to clinical care (8,9).
Having these potential benefits in mind, we decided to use a CGM device in a female macrosomic newborn with persistent hypoglycemia and a family history of HNF4A MODY, while initiating diazoxide therapy.
Case Report

A 22-days old female neonate was admitted to our Pediatric Department for investigation and management of persistent hypoglycemia. According to her perinatal history, she was a near-term neonate, born on 36th gestational week with cesarian section, due to premature onset of labor, with macrosomia (weight: 3680 gr - 99th percentile, length: 51 cm - 99th percentile). From family history, her mother and maternal grandfather were previously diagnosed with HNFA4 MODY employing a MODY targeted gene panel Next Generation Sequencing and identified to be heterozygotes for the likely pathogenic variant c.956_958delTGC, p.Leu319del in exon 8 of the *HNF4A* (NM_175914.4)_gene. Her mother had no need for anti-diabetic medication, but with an elevation of glycated hemoglobin levels from 4.9% at first trimester to 5.9% at third trimester of gestation. The newborn, during the 1st hour of life, presented with hypoglycemia (Dextro stick: 32 mg/dl) and was fed without improvement (Dextro stick: 29 mg/dl, 20 minutes after feeding), so she was transferred to the Neonatal Intensive Care Unit and was fed with a mixed diet with full-term formula and a glucose polymer. Concomitantly, she received intravenous glucose with a maximum flow of 7.5 mg/kg/min, in order to achieve glucose levels above 60 mg/dl. The hypoglycemia incidents persisted during the second day of life, so the full-term formula was replaced by a formula for premature neonates, which contains higher glucose concentration. Since the third day of life, she remained normoglycemic, and she was discharged from the neonatal unit with instructions for pre-prandial blood glucose measurements and frequent feeding (every two hours) with formula for preterms. However, while at home, the neonate continued to experience frequent hypoglycemic episodes, which were confirmed by capillary glucose measurements using a glucometer. According to the parents, the infant appeared notably drowsy during these episodes. As a result, on the 22nd day of life, she was admitted to our Pediatric Department.

At initial presentation, the neonate was in general good condition, mildly lethargic but with no other findings from physical examination. Laboratory results revealed normal thyroid function, normal IGF-1 and ammonia levels, whereas glycated hemoglobin could not be quantified due to elevated levels of HbF. During the first hours of hospitalization, a hypoglycemia incident occurred and a critical sample confirmed hyperinsulinemic hypoglycemia with no presence of ketones (Table 1). A blood sample was also sent for *HNF4A* gene sequencing, given the family history of HNF4A MODY. A CGM was placed, after parents' consent, and the neonate continued receiving mixed feeding with preterm formula and breastfeeding every 2 hours. However, during the next few hours the CGM sensor showed a 30% time in hypoglycemia, while many hypoglycemia incidents were reversed with feeding and one needed intramuscular administration of glucagen (Figure 1). The next day, intravenous infusion of dextrose was initiated with a maximum flow of 18.8 mg/kg/min and diazoxide treatment at a low dose of 5 mg/kg/day twice-daily. Due to persistence of hypoglycemia, on 5th day of hospitalisation, diazoxide dose was titrated to 10 mg/kg/day, at which the patient was responsive and consequently, on eighth day intravenous glucose administration was discontinued and breastfeeding and full-term instead of preterm formula was recommended. On 12th day of admission, the patient was discharged from hospital, with diazoxide treatment (10 mg/kg/day) and continuous glucose monitoring, while we were informed about the result of the genetic test, which confirmed that our patient carries the maternal *HNF4A* gene variant, c.956_958delTGC, p.Leu319del. This variant has been reported in a family with two of its members presenting young onset diabetes, whereas another family member presented with macrosomia and neonatal hypoglycemia (10, 11).

Ten days after discharge from hospital, she had diazoxide-induced hyperglycemia incidents (maximum glucose: 262 mg/dl) (Figure 2), which were, at first, partly attributed to the change in the mode of diazoxide administration as parents were advised to use a more precise insulin syringe to quantify the amount of diazoxide given instead of the dosometric pipe accompanying the commercial diazoxide kit. The next days, hyperglycemia insisted, so we kept reducing the dose until we temporarily interrupted diazoxide for two days, but, due to reappearance of hypoglycemia, diazoxide was initiated again. CGM helped us managing the treatment dose, as the glucose levels of the patient seemed to be dependent from many factors, such as her first vaccination or mother's effort for exclusive breastfeeding, during which the baby was continuously offered breast milk. Up to date, at three months of age, we continue adjusting diazoxide dosing once or twice per week, as her hyperinsulinism has not been resolved yet, targeting glucose concentrations within the normal range of 70-140 mg/dl.

In all extreme glucose values detected by CGM (either hypoglycemia or hyperglycemia), capillary blood glucose measurements were performed to verify glucose values and guide clinical decisions, both during hospitalization and after discharge at home. Moreover, the patient was closely monitored throughout the entire course of diazoxide therapy for the most common adverse effects, such as fluid retention, hypertrichosis, gastrointestinal disturbances, and pulmonary hypertension. No serious adverse events were observed, the only side effect noted was moderate hypertrichosis.

Discussion

The clinical manifestations of our patient were indicative of the typical phenotype of *HNF4A* gene mutations, including macrosomia, hypoglycemia since first day of life, need for intensive neonatal care with intravenous glucose administration and diazoxide-responsive hyperinsulinism. In our case, there was a known family history of HNF4A MODY, so the diagnosis was obvious. It is important for clinicians to consider HNF4A sequencing in every patient with neonatal hyperinsulinemic hypoglycemia and macrosomia, especially when there is a family history suggestive of maturity-onset diabetes of the youth (12). Conversely, when there is a known *HNF4A* mutation in family history, it is important to screen for macrosomia and hypoglycemia at birth and during the first 24 hours (2). Having in mind that HNF4A mutations follow an autosomal dominant pattern of inheritance (2), in cases of neonatal hypoglycemia, it is crucial to seek both father and mother's history of diabetes, and not only mother's glycemic control during pregnancy.

We have no data from mother's neonatal history, so it is possible that she had no hypoglycemia incidents, or they were too mild and transient to be identified. In a recent systematic review, Perge et al. highlighted that mutations in *ABCC8, HNF4A, HNF1A* and *GCK* genes can give a biphasic phenotype in the same person with both neonatal hypoglycemia and diabetes after adolescence or a reverse phenotype in the same family, as probably in our case (13). If we accept that mother had not manifested hyperinsulinemic hypoglycemia, the presence of hypoglycemia in our neonate could suggest a difference in genotype-phenotype correlation with a worsening of phenotype in subsequent generations within the same family. However, this has not been extensively documented and studied yet.

Diazoxide is first-line treatment for hyperinsulinemic hypoglycemia, as it reduces insulin secretion, and most carriers of HNF4A mutations are responsive (14). In our case, we started with a low-dose of 5 mg/kg/daily, but soon titrated to 10 mg/kg/daily, in order to achieve normoglycemia. On the 20th day of treatment, while at home, CGM revealed substantial hyperglycemia. After excluding technical problems at administration, we decided to reduce diazoxide dose, as diazoxide-induced hyperglycemia is a well-defined, although difficult to identify, adverse event. The main pathogenetic mechanisms behind diazoxide-induced hyperglycemia are the inhibition of insulin secretion by beta-cells and the increase of epinephrine release which results in increased glycogenolysis (14). There are also case reports of diazoxide-related hyperosmolar hyperglycemic state in children with hyperinsulinism, suggesting that it is crucial to closely monitor glucose levels in these children (15-17).

Although CGM is increasingly being used off-label in neonates with hyperinsulinism, its accuracy at extreme glucose values remains limited. A meta-analysis in preterm infants reported low sensitivity for detecting hypoglycemia (39%), but higher sensitivity for hyperglycemia (87%), with overall specificity exceeding 95% (18). Similarly, a study in postoperative neonates

demonstrated a mean absolute relative difference (MARD) of 10.8%, with 100% sensitivity and 93.9% specificity for hyperglycemia above 150 mg/dL (19). Moreover, it is well acknowledged that CGM systems may tend to overreport hypoglycemia on the first day of sensor insertion, due to sensor stabilization, warm-up effects or even a local inflammatory response and tissue microhaemorrhages (20). These findings highlight the need for cautious interpretation of CGM data, particularly during the initial calibration phase and in hypoglycemic ranges. In our case, to address these limitations, all extreme glucose readings—both low and high—were verified with capillary blood glucose measurements throughout hospitalization and after discharge, ensuring accurate interpretation and safe clinical decision-making.

Our report demonstrates the usefulness of continuous glucose monitoring in titration of diazoxide dose and in adopting a more physiological feeding pattern in a patient with hyperinsulinemic hypoglycemia due to *HNF4A* mutation. Although off indication, Win et al. used also real-time CGM in neonates with hyperinsulinemic hypoglycemia and compared glucose values (sensor and blood) giving a mean absolute relative difference of 11% (8). Gariepy et al. used CGM in children with hyperinsulinism, showing a major help in detecting hypoglycemic incidents and in guiding medical management (9). Saif et al. have also described a case of a neonate with hyperinsulinism, where CGM helped to identify hypoglycemic episodes, overcoming the difficulty in recognizing hypoglycemia symptoms in such a young patient and avoiding frequent pricks (21). In our case, CGM use after hospital discharge was proved particularly valuable for ongoing monitoring and individualized management. It enabled early identification of diazoxide-induced hyperglycemia and supported "real-time" dose adjustments based on daily variations, such as changes in feeding routines or physiological stressors like vaccination. This real-world application of CGM outside the hospital setting provided a more comprehensive view of the patient's glucose profile, helping to optimize therapy and support safe transition to exclusive breastfeeding. Our case highlights its potential as a valuable outpatient management tool in infants with hyperinsulinism.

Conclusions

Mutations in *HNF4A* gene should be considered when investigating neonatal hypoglycemia, especially when there is a family history of early onset diabetes both in maternal and paternal history. CGMs could be useful in medical care of patients with hyperinsulinemic hypoglycemia treated with diazoxide. More studies are needed to support their usefulness in preventing both unaware hypoglycemia and treatment-induced hyperglycemia and help clinicians make decisions on diazoxide dosing in a timely manner.

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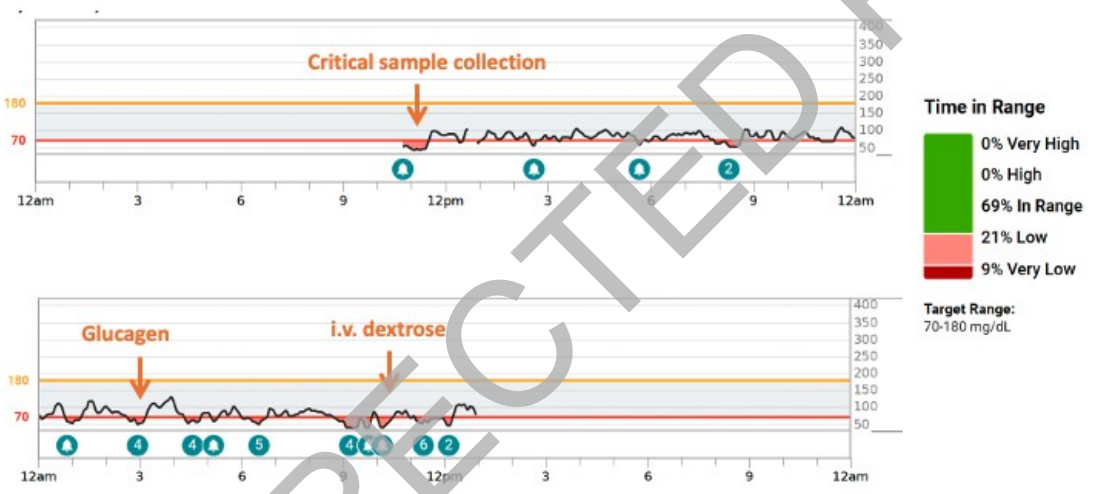

Figure 1. CGM data during the first day of application

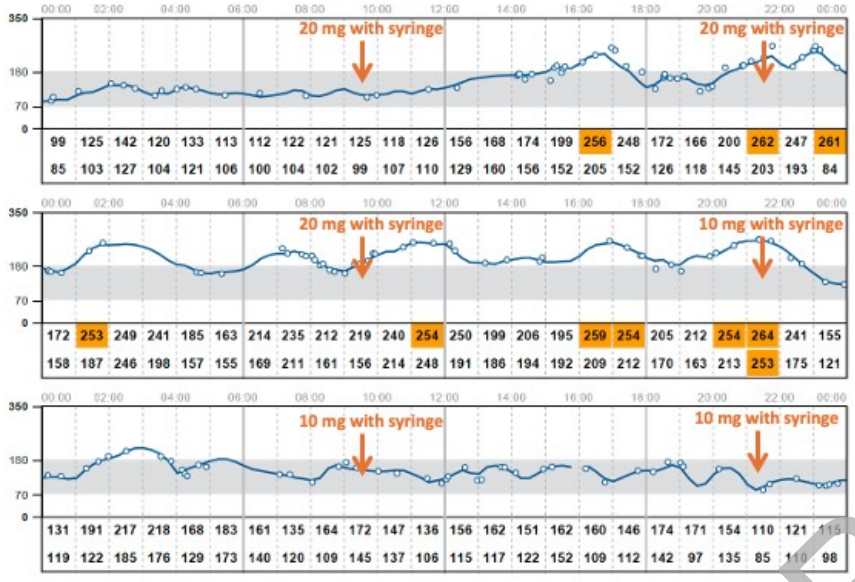

Figure 2. Diazoxide-induced hyperglycemia

Table 1. Critical sample results	
Glucose in EDTA (mg/dl)	**32**
Ketones (mmol/l)	**0.1**
Insulin (mIU/L)	**2.16**
Cortisol (µg/dl)	**15.40**
GH (ng/ml)	**19.758**
Lactic acid (mmol/L)	**4**
Ammonia (µg/dl)	**48**