Real-Time Continuous Glucose Monitoring in a Newborn with Congenital Hyperinsulinism

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Abstract

Congenital hyperinsulinism, also known as persistent hyperinsulinemic hypoglycemia of infancy, is the most frequent cause of severe, recurrent, and persistent hypoglycemia in children. The signs and symptoms of hypoglycemia are particularly difficult to recognize in this age group, which can lead to serious neurological impairment or even death. Continuous glucose monitoring provides real-time information about the interstitial fluid glucose levels throughout the day and has proven to be useful in preventing asymptomatic hypoglycemia. Despite this, there are only a few studies in the literature describing the use of continuous glucose monitoring systems in neonatal hypoglycemia, particularly in children with congenital hyperinsulinism. In this case report, the authors present their experience with a real-time continuous glucose monitoring system in a neonate with severe congenital hyperinsulinism, who underwent near-total pancreatectomy with the identification of a novel missense variant in the *ABCC8* gene. The use of a real-time continuous glucose monitoring system allowed for a better glycemic control as well as the prevention and treatment of asymptomatic hypoglycemia. In addition, it allowed for the improvement in the quality of life of the child and his parents, as it reduced the number of daily finger prick blood samples, with growing satisfaction and confidence in the device in the detection of hypoglycemia.

Keywords: Blood Glucose/analysis; Congenital Hyperinsulinism/complications; Hypoglycemia/diagnosis; Hypoglycemia/prevention & control; Infant, Newborn; Monitoring, Physiologic/methods

Introduction

Hypoglycemia is the most frequent metabolic disorder found in neonates, particularly in the first 48 hours of life.[1] Congenital hyperinsulinism is the most common cause of persistent hypoketotic hypoglycemia in neonates and infants, beyond the first week of life.[2,3] Early recognition, diagnosis, and treatment are necessary to prevent or minimize neurologic damage from recurrent or prolonged episodes of hypoglycemia.[4] Mutations in key genes, which are involved in the regulation of insulin secretion from pancreatic β-cells, underlie the molecular basis of congenital hyperinsulinism. Until now, mutations in 14 different genes that lead to the dysregulated secretion of insulin have been described and the mutation of *ABCC8* gene is the most common, affecting 40% of these patients.[5-7]

Continuous glucose monitoring system (CGMS) was initially developed for the management of diabetes mellitus.[3] Real time-CGMS (RT-CGMS) is only approved in children older than 4 years and adults with type 1 diabetes. The use of RT-CGMS in younger children with type 1 diabetes and non-diabetics is off-label.[8] In children with type 1 diabetes, RT-CGMS allows for the improvement in the glycemic control and prediction of unwanted episodes of hypoglycemia, by showing the trend of interstitial glucose levels. Therefore, RT-CGMS can be an option in identifying hypoglycemic episodes, particularly in neonates and infants in whom the symptoms of hypoglycemia are difficult to recognize and can be potentially life-threatening.[7] However, there are rather few studies that describe the use of RT-CGMS in children with neonatal hypoglycemia, particularly with congenital hyperinsulinism.[3]

Case Report

Male newborn born from a first gestation, with normal routine prenatal evaluation, at 39 weeks gestational age by operative vaginal delivery, with a birth weight of 4,400 g (weight *z*-score 2.01, based on the Fenton growth chart of 2013), large-for-gestational-age. The newborn had an Apgar score of 9 and 10 at 1 and 5

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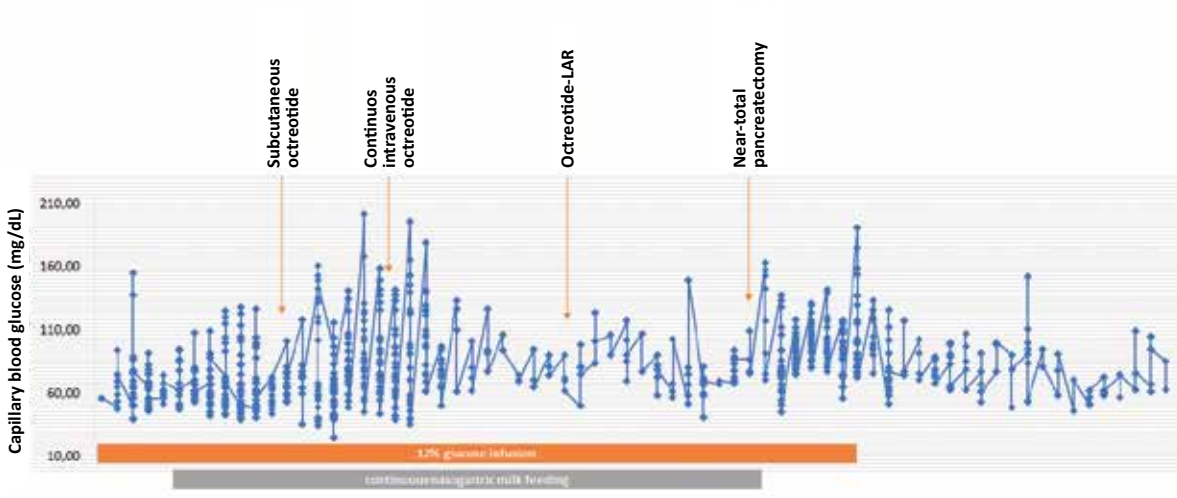
minutes, respectively. He had an unremarkable physical examination, with no dysmorphisms, no organomegaly, normal male external genitalia, and a normal sized penis. Newborn screening was negative for congenital hypothyroidism, inherited disorders of metabolism, fatty acid beta-oxidation disorders, aminoacidopathies and organic aciduria and cystic fibrosis. The family history was unremarkable, with no previous neonatal deaths and no known individuals with global development delay. There was no history of gestational diabetes or parental consanguinity.

As he was large-for-gestational-age, routine glycemia testing was started. Asymptomatic hypoketotic hypoglycemia (serum glucose 23 mg/dL, reference values ≥ 40 mg/dL and ketone bodies 0.2 mg/dL, reference values < 0.6 mg/dL) was detected on the first hour of life. As hypoglycemia persisted, he was started on a 12% glucose infusion, requiring a high infusion rate (GIR) (maximum rate of 7 mg/kg/min). Despite continuous intravenous glucose supplementation and oral feeding (145 mL/kg/day), his blood sugar levels still fluctuated between 25 mg/dL and 70 mg/dL. On the fourth and ninth days of life, an endocrine assessment during episodes of hypoglycemia showed a normal thyroid hormone level with thyroid stimulating hormone 6.16 µIU/mL (reference values 0.7-4.17 µIU/mL), free thyroxine 18.7 pmol/L (reference values 11.45-17.63 pmol/L) and an appropriate counter-regulatory hormone response to hypoglycemia. However, he had an inappropriately normal serum insulin level (8.1 µIU/mL, reference values 3-25 µ/dL). Plasma lactate (1 mmol/L, reference values < 0.5-2 mmol/L) and ammonia (150 µmol/L, reference values < 180 µmol/L), urine amino acids, and urine organic acids were normal.

On the 15th day of life, due to the persistence of hypoglycemia, off-label RT-CGMS (insulin pump system MiniMed Paradigm™ VEO™, Medtronic), intravenous glucagon (10 µg/kg), and oral diazoxide (15 mg/kg/day) were started. During the intervening period, the infant was kept under serial finger prick measurements (Fig. 1). As of the 30th day of life, he maintained severe asymptomatic hypoglycemia (confirmed with finger prick measurements of 25-49 mg/dL), initiated continuous nasogastric milk feeding (150 mL/kg/day), subcutaneous injections of octreotide (5 µg/kg/day), followed by octreotide infusion (maximum of 12 µg/kg/day) on the 37th day of life, with a slight improvement in his glycemic profile and a gradual reduction of the GIR (4 mg/kg/min). A genetic test was offered and accepted by his parents. The study revealed a heterozygous mutation of two *ABCC8* variants (a nonsense pathogenic variant and a new missense variant). With these results, as this mutation is associated with poor response to oral diazoxide, it was gradually suspended. On the 44th day of life, monthly intramuscular administration of octreotide long-acting release (octreotide-LAR) was started (5 mg/month).

While awaiting surgery, the infant was continued on RT-CGMS and medical management. The parents were educated on the identification and treatment of hypoglycemia.

At 2 months of age, as the infant was unresponsive to medical treatment, he underwent a near-total pancreatectomy (95%). Histological analysis of the pancreatic specimen showed a diffuse beta cell hyperplasia in the body and tail of the pancreas (Fig. 2). Octreotide infusion and GIR were gradually suspended (on the 60th and 65th days of life, respectively), and normoglycemia was achieved, although with occasional episodes of hypoglycemia (confirmed with finger prick measurements).



LAR - long acting release; RT-CGMS - real time continuous glucose monitoring system.
The blue dots represent finger prick measurements. The high glucose levels observed in this figure are explained by postprandial hyperglycemia.

Figure 1. Distribution of the total of finger prick blood glucose levels and the different treatment changes performed during the admission.

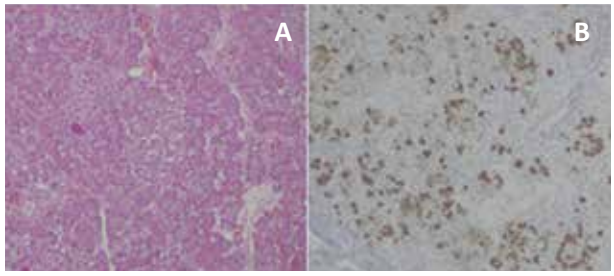


Figure 2. Histology images of diffuse beta cell hyperplasia in our infant. A - hematoxylin eosin, x10; B - immunohistochemistry for insulin, x10.

Serial analytical evaluations have been performed regularly along admission, and insulin was always abnormally normal/high before surgery: 20.1 µIU/mL (14th day of life), 23.3 µIU/mL (24th day of life), 81.2 µIU/mL (30th day of life), 5.9 µIU/mL (58th day of life), and 8.7 µIU/mL (65th day of life).

In our case, the use of RT-CGMS showed a good similarity with capillary blood glucose levels. Before surgery, the mean of capillary blood glucose measurements was 84 mg/dL ± 17 mg/dL and the mean of sensor glucose levels was 86 mg/dL ± 17 mg/dL. After surgery, the mean of finger prick blood glucose readings was 74 mg/dL ± 16 mg/dL and the mean of sensor glucose levels was 83 mg/dL ± 15 mg/dL. Furthermore, during the hypoglycemic episodes the correlation was equally good (Fig. 3).

Presently, at 5 months of age, he is still using RT-CGMS and is prescribed monthly intramuscular administration of octreotide-LAR, with good glycemic control (interstitial glucose 76 ± 19 mg/dL, 50-124 mg/dL). His psychomotor development is appropriate to his age. His parents observed a good correlation between the measurement of interstitial glucose and capillary blood glucose values and, as such, they have been relying on RT-CGMS for the correction of hypoglycemia.

Discussion

We describe a case of a newborn with congenital hyperinsulinism and the use of RT-CGMS in the diagnostic and therapeutic approach of this illness.

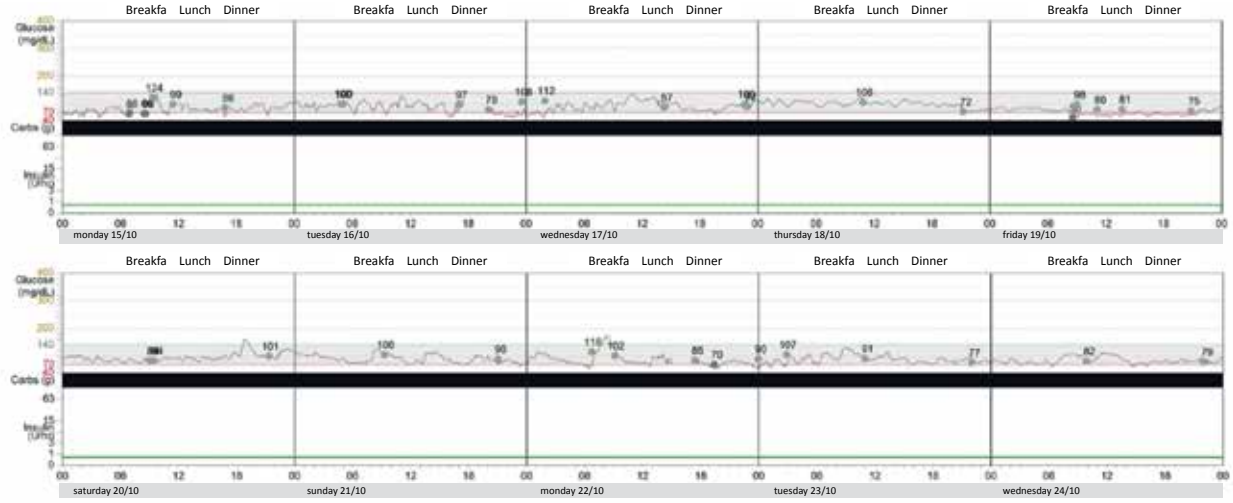
Congenital hyperinsulinism is the most common cause of persistent hypoketotic hypoglycemia in neonates and infants, which results from the inappropriate secretion of insulin.[4,8]

Newborns are very vulnerable to any condition that impairs the establishment of normal glucose homeostasis. Congenital hyperinsulinism is a clinically and genetically heterogenous disease, whose signs and symptoms of hypoglycemia are challenging to recognize, particularly in this age group, and its clinical presentation ranges from mildly symptomatic hypoglycemia to life-threatening events.[2]

Capillary blood sampling is the most common procedure performed in newborns to assess serum glucose. If carried out incorrectly, capillary blood sampling can cause pain and inaccurate test results, leading to repeated sampling. Furthermore, hypoglycemic episodes may go unrecognized between capillary blood glucose measurements.[12]

The RT-CGMS gives a 24-hour trend of interstitial glucose levels, providing information about the trend, frequency, and duration of hypoglycemia, which can help identify and prevent unwanted periods of hypoglycemia and achieve a better glycemic profile.[7]

There are rather few studies where CGMS has been used for congenital hyperinsulinism. A published study included a total of 102 newborns at risk of neonatal hypoglycemia, between December 2006 and February 2009, and determined the usefulness and reliability



Carbs- carbohydrates.
The light gray tracing corresponds to the sensor data and the gray dots represent finger prick measurements. The infant experienced numerous hypoglycemic episodes thought the days, which were backed up by finger prick measurements.

Figure 3. Ten day summary report from a real-time continuous glucose monitoring system.

of CGMS. The authors concluded that CGMS detects many more episodes of low glucose concentration than intermittent blood glucose measurement.[10] Recently, other authors presented their good experience with CGMS in a case report of a 2-month-old female with congenital hyperinsulinism.[7] In cases like those, CGMS can be an option to identify hypoglycemic episodes, particularly in younger age groups in which hypoglycemia can be difficult to identify and can be potentially life-threatening. Although RT-CGMS is only approved in children older than 4 years and adults with type 1 diabetes, it can be valuable in younger children.[8] In our case, CGMS helped to predict and prevent these episodes and thereby to achieve the best therapeutic outcomes.

From our experience, a good similarity was found between RT-CGMS and finger prick measurements. We must note that the mean of the glucose levels after surgery was slightly lower because the infant was under 12% glucose infusion and there was continuous nasogastric milk feeding, which was needed before surgery. As shown in Fig. 3, the use of RT-CGMS detected several episodes of hypoglycemia, confirmed by a finger prick test, also with a good similarity. Consequently, during admission, we gradually trusted the interstitial glucose readings to adjust the therapy glucose levels.

Moreover, RT-CGMS offers frequent glucose readings and trend arrows that allow treatment adjustments, predicting and preventing hypoglycemic episodes. In the future, the use of RT-CGMS can possibly reduce the finger prick measurements for glucose values assessment.

In this case, the use of RT-CGMS improved the quality of life of our patient by reducing the number of daily finger prick measurements. In addition, his parents felt that using RT-CGMS improved their confidence in detecting asymptomatic hypoglycemia episodes, which reduced they anxiety.

There are fourteen different genes (*ABCC8, KCNJ11, CACNA1D, SLC16A1, GLUD1, GCK, HADH1, UCP2, HK1, PGM1, PMM2, HNF1A, HNF4A,* and *FOXA2)* responsible for the molecular basis of congenital hyperinsulinism, which dysregulate insulin secretion from pancreatic β-cells.[5,10,11] We describe a new missense mutation involving the *ABCC8* gene. The identification of the genetic subtype of congenital hyperinsulinism is helpful as this information can guide clinical management. The *ABCC8* and *KCNJ11* genes encode the proteins SUR1 and Kir6.2, respectively, which play a vital role on the activity of ATP-sensitive potassium (K_{ATP}) channel. Oral diazoxide is a K_{ATP} channel opener, which inhibits the influx of calcium and prevents insulin release.[12] In this clinical case, we gradually suspended oral diazoxide because patients with the most common genetic mutations (*ABCC8* and *KCNJ11* genes) are unlikely to respond to diazoxide treatment.[5]

Histologically, diffuse forms account for about 60% of all congenital hyperinsulinism cases and are associated with homozygous/compound heterozygous *ABCC8* and *KCNJ11* mutations. In diffuse disease, like in our case report, patients are typically unresponsive to medical treatment and require a near-total pancreatectomy.[5,8]

In conclusion, the use of RT-CGMS should be considered in the approach of persistent neonatal hypoglycemia, particularly in infants with congenital hyperinsulinism. Close follow-up is needed to monitor growth, neurodevelopment, and the endocrine/exocrine pancreatic functions, particularly in this case where near-total pancreatectomy was done.

WHAT THIS CASE REPORT ADDS

- Hypoglycemia can be challenging to identify and can be potentially life-threatening in younger age groups.
- A real-time continuous glucose monitoring system can be an option in identifying and preventing hypoglycemic episodes in children with congenital hyperinsulinism, instead of intermittent measurements.
- A real-time continuous glucose monitoring system offers frequent glucose readings and trend arrows that allow for treatment adjustments.
- A new missense pathogenic variant in the *ABCC8* gene has been associated with congenital hyperinsulinism.
- Near-total pancreatectomy is reserved for severe cases, where medical therapy has failed.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Consent for publication

Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Monitorização Contínua em Tempo Real da Glicose num Recém-Nascido com Hiperinsulinismo Congénito

Resumo

O hiperinsulinismo congénito, também conhecido com hipoglicemia hiperinsulinémica persistente da infância, é a causa mais frequente de hipoglicemia grave, recorrente e persistente no início da infância. Os sinais e sintomas da hipoglicemia são particularmente difíceis de reconhecer neste grupo etário, o que pode conduzir a alterações neurológicas graves ou mesmo à morte. A monitorização contínua da glicose fornece informação em tempo real sobre os níveis da glicose intersticial ao longo do dia, permitindo prevenir episódios de hipoglicemia assintomática. São poucos os estudos descritos na literatura sobre o uso da monitorização contínua da glicose em tempo real na hipoglicemia neonatal, particularmente em crianças com hiperinsulinismo congénito. Neste caso clínico, os autores descrevem a sua experiência com a monitorização contínua da glicose em tempo real num recém-nascido com hiperinsulinismo congénito grave, submetido a pancreatectomia quase total, com identificação de uma nova variante *missense* envolvendo o gene *ABCC8*.

Com a utilização da monitorização contínua da glicose em tempo real foi possível adquirir um melhor controlo glicémico, assim como prevenir e tratar episódios de hipoglicemia assintomáticos. Adicionalmente, permitiu melhorar a qualidade de vida da criança e dos cuidadores, através da redução do número de glicémias capilares diárias e da maior satisfação e confiança no dispositivo na deteção de hipoglicémias.

Palavras-Chave: Glicemia/análise; Hiperinsulinismo Congénito/complicações;Hipoglicemia/diagnóstico; Hipoglicemia/prevenção e controlo; Monitorização Fisiológica/métodos; Recém-Nascido