Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Neonatology

Effective Management of a Diffuse form of a Congenital Hyperinsulinism Due to a ABCC8 Mutation with a Combination of Diazoxide and Somatostatin Analogue (A Case Report)

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DOI: https://doi.org/10.36347/sjmcr.2025.v13i03.043 | **Received:** 20.02.2025 | **Accepted:** 24.03.2025 | **Published:** 27.03.2025

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Abstract **Case Report**

Congenital hyperinsulinism (CHI) is a rare genetic disorder characterized by inappropriate and excessive insulin secretion, leading to severe, recurrent hypoglycemia in neonates, with significant neurological risks. We report a clinical case of a male neonate with a severe form of CHI, diagnosed through genetic analysis, who presented with diazoxide-resistant hypoglycemia and was successfully managed with the somatostatin analog, octreotide. Genetic testing revealed a homozygous mutation in the ABCC8 gene, confirming a diffuse form of CHI. Despite initial treatment with diazoxide, the neonate continued to experience severe hypoglycemic episodes. The addition of octreotide allowed for glycemic stabilization, reduced the need for continuous glucose infusion, and eventually led to the discontinuation of diazoxide. This case underscores the effectiveness of octreotide as a second-line treatment in managing diazoxide-resistant CHI and highlights the importance of early genetic diagnosis, personalized treatment strategies, and the potential of octreotide in avoiding the need for pancreatic surgery. Further research is needed to solidify the long-term safety and efficacy of octreotide in treating CHI and to optimize management protocols for this challenging condition.

Keywords: Congenital Hyperinsulinism, Neonatal Hypoglycemia, Diazoxide-Resistant Hypoglycemia, Octreotide, ABCC8 Gene Mutation.

INTRODUCTION

Congenital hyperinsulinism (CHI) is a rare, heterogeneous genetic disorder characterized by excessive insulin secretion by pancreatic beta cells, leading to recurrent, persistent and often severe hypoglycemia, particularly in newborn and infants, with a high risk of neurological complications with cerebral sequelae. The various forms of ICH represent a clinically, genetically and morphologically heterogeneous group of diseases. CHI may be isolated or occur as part of a genetic syndrome. Octreotide is an effective therapeutic option for patients with congenital hyperinsulinism resistant to diazoxide, although its use requires monitoring to manage potential side effects. It offers a valuable alternative to surgery, controlling hypoglycemia and improving patients quality of life [1, 2]. We report a clinical case of a severe form of congenital hyperinsulinism with neonatal onset, resistant to diazoxide and responsive to octreotide, outlining the circumstances of diagnosis and the difficulty of management.

CASE REPORT

Jad is a male newborn Parents first cousins (1st degree consanguineous marriage), mother with no pathological history, notably no diabetes, mother of a 3-year-old child in good health with good psychomotor development. Delivery at 38 SA by cesarean section due increased uterine height in relation to gestational age, with fetal weight estimated at 4900g, good adaptation to extrauterine life. Birth weight was 5065 grams (> 95th percentile), height 55 cm (> 95th percentile), head circumference 35 cm (50th percentile). At the 44th hour of life, the newborn presented hypoglycemia at 0.20 g/L, with generalized cyanosis, for which he was hospitalized at our unit. Clinical examination revealed no facial dysmorphia, no hepatomegaly and no micropenis. During hospitalization, the newborn presented with repeated, anarchic and profound hypoglycemia of up to 0.10 g/L, requiring very high intravenous glucose intakes in excess of 10 mg/kg per minute. The hypoglycemic workup showed insulinemia at 45.8 mIU/mL (1.9-23 mIU/mL), C-peptide at 3.77 ng/mL (1.1-4.4 ng/mL)

(confirmed on 2 hypoglycemic assays), with an insulinemia/glycemia ratio greater than 4. Glucagon test was positive (rapid rise in blood glucose after glucagon injection). ACTH was normal, cortisol levels normal. Growth hormone (GH) and insulin-like growth factor (IGF1) were normal. Lactate, ammonia and liver function tests were normal. Abdominal ultrasound and abdominal (pancreatic) CT and MRI scans were normal. Cerebral MRI revealed peri-rolandic white matter abnormalities, extending bilaterally to the corticospinal fascicles, with a sequelae-like appearance. Genetic testing by an analysis of coding and flanking intronic regions of the KCNJ11 gene, and the coding all coding and exon/intron boundaries of the ABCC8 gene, by Sanger sequencing. The boy was found to be homozygous for an ABCC8 mutation leading to a diffuse form CHI (MIM256450). The genetic diagnosis of autosomal recessive congenital hyperinsulinism was confirmed. c18F-DOPA positron emission tomography (PET/CT) was not performed, diagnosis of diffuse form was proven genetically.

Jad was treated with diazoxide at a dose of 15 mg/kg per day in 3 doses, intravenous carbohydrate intake replaced by enteral intake. After 5 days of treatment, blood glucose monitoring revealed persistent hypoglycemic episodes reaching 1.1 mmol/l, requiring emergency re-sugaring with failed 6-hour fasting tolerance test and the need for continuous nutritional support enriched with carbohydrates, and bolus injections of glucagon (0.02 mg/kg) were combined to stabilize blood glucose levels, we concluded that this was a diazoxide-resistant form. The ineffectiveness of this treatment led us to combine it with a somatostatin analogue, octreotide (Sandostatine ®), at a dose of 10 µg/kg/d in three subcutaneous injections, with dose escalation in 10 µg/kg increments over two weeks up to a dosage of 50 µg/kg/d. This enabled the therapeutic objective of maintaining blood glucose > 3.3 mmol/l, passing the 6 hours fasting test, stopping continuous enteral intake, and progressively reducing the dose of diazoxide until discontinuation. The evolution was marked by the appearance of hypertrichosis (Figure1), especially on the forehead, as a complication due to diazoxide. A cardiac echocardiography performed before starting diazoxide and in the month following its introduction showed no cardiac side effects, and after 2 months of treatment with octreotide, no side effects were noted, in particular no signs of ulcero-necrotizing enterocolitis.

Figure 1: Photos showing secondary hypertrichosis due to treatment in our patient

DISCUSSION

Congenital hyperinsulinism (CHI) is a rare genetic disorder characterized by inappropriate insulin secretion, leading to severe hypoglycemia and the risk of irreversible neurological sequelae. CHI is the most common cause of persistent hyperinsulinemic hypoglycemia in infants and children. Its incidence is estimated at one case in 50,000 per year in Western countries, and one case in 2,500 in certain Middle Eastern populations due to high rates of consanguinity [3].

Histologically, there are three forms of CHI : a focal form (40% of cases), linked to isolated hyperfunction of certain islets of Langerhans, the rest of the parenchyma is normal, a diffuse form (60% of cases), in which there is hyperactivity of all beta cells distributed throughout the gland, without any normal territory and is characterized by nucleomegaly of some islet cells, CHI is termed ‘atypical’ if the tissue histology is not characteristic of either of these forms [4–6].

Hyperinsulinemic hypoglycemia can be transient, persistent or as an accompanying symptom in several syndromes. Usually, transient hyperinsulinemic hypoglycemia is secondary (caused by increased pancreatic b-cells function because of maternal diabetes mellitus) [4]. In these conditions hypoglycemia usually settles within a few days after delivery and rarely requires treatment with Diazoxide and prolongs several months [5]. Hyperinsulinemic hypoglycemia may also be present in several overgrowth syndromes (Beckwith–

Wiedemann, Perlman, Sotos, Kabuki, Usher, Timothy, Costello, Trisomy 13, mosaic Turner) [4-7]. Mutations of several genes responsible for CH are identified (Table 1) [4–8]. with ABCC8 by far the most frequently incriminated [7].

Table 1 – Most frequent genes mutations responsible for CH.

- ABCC8 gene, encoding SUR1 subunit of pancreatic b-cell ATP-sensitive potassium channels (KATP channels)
- KCNJ11 gene, encoding KIR6.2 subunit of KATP channels.
- GLUD1 gene, encoding glutamate dehydrogenase, also associated with hyperinsulinism/hyperammonemia syndrome.
- GCK gene, encoding glucokinase (activation of GCK lowers the threshold of glucose-stimulated insulin secretion).
- HADHSC gene, encoding short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD)
- SLC16A1 gene, encoding monocarboxylate transporter 1 (associated with exercise-induced hyperinsulinism).
- HNF4A gene, encoding hepatocyte nuclear factor 4a.
- UCP2 gene, encoding mitochondrial uncoupling protein 2 Insulin receptor gene.

Insulin inhibits glycogenolysis and promotes peripheral glucose utilization. Glucose enters the beta cell via the transporter (GLUT2) and is then phosphorylated by glucokinase. Glucose metabolism in the beta cell leads to increased ATP production. The increase in the ATP/ADP ratio causes closure of the pancreatic potassium channel, made up of two subunits, the sulfonylurea receptor SUR1 (regulatory protein), encoded by the ABCC8 gene, and KIR6.2 (potassium channel) encoded by KCNJ11 gene, both located in the 11p15.1 region. This closure of the potassium channel causes membrane depolarization, leading to the opening of the calcium channel, resulting in massive calcium entry into the cell and insulin exocytosis. Diazoxide inhibits insulin secretion by opening the potassium channel. Somatostatin acts on calcium and potassium channels. Thus, diazoxide and somatostatin are medical treatments for CHI [5].

The most common causes of CH are ‘‘channelopathies’’, which refer to the pancreatic b-cell ATP-sensitive potassium channels (KATP channels) defects, and less frequently subgroup of CH is ‘‘metabolopathies’’ caused by different genes mutations (GK, GDH or SCHAD or insulin receptor gene) [4-7].

Genetic diagnosis and genetic counselling are of crucial importance for newborns and infants with CHI and their families, as the search for a genetic cause may have implications for patient management, screening of symptomatic and non-symptomatic relatives, and genetic counselling. A distinction will be made between syndromic CHI, which accounts for around 10% of patients with CHI, and isolated CHI, the latter depending on whether the patient responds to diazoxide treatment. Isolated, diazoxide-sensitive hyperinsulinism, the genetic cause is found in less than 50% of cases. Isolated, diazoxide-resistant hyperinsulinism A genetic cause is found in around 95% of cases [9]. In the case of an infant with diazoxide-resistant CHI, genotype determination is urgently required to assess the indication for surgery (screening for a focal form with persistent hypoglycemia curable by targeted partial pancreatectomy). The majority (82%) of cases with unresponsiveness to Diazoxide are related to the mutations of the ABCC8 or KCNJ11 genes [10]. In cases such ours, the molecular analysis alone provides an informative genetic diagnosis for the clinical management of CH patients with recessively inherited pathogenic mutations.

Focal forms are homogeneous, sporadic and due to the association of a heterozygous mutation of paternal origin in the sulfonylurea receptor gene (SUR1 gene) or the KIR6.2 gene (located at 11p15.1) with a loss of allele of maternal origin in the 11p15 region limited to the cells of the hyperplastic region, the SUR1 and KIR6.2 genes, 5 Kb apart in the 11p15.1 region, code for the two potassium channel subunits involved in insulin secretion [4-12].

Diffuse forms are heterogeneous, with familial or sporadic cases, autosomal recessive, or dominant transmission, making genetic counseling difficult. Five mutations have been identified in congenital diffuse IH. A mutation in the SRU1 or KIR6.2 gene is often responsible for recessive inheritance, more rarely for dominant inheritance. SCHAD (fatty acid oxidation enzyme) deficiency has recently been identified in autosomal recessive inheritance. The GLUD1 genes encoding glutamate dehydrogenase (GDH) and glucokinase (GK) have been reported to be dominantly inherited. However, 50% of infants with diffuse ICH have no identified mutations [1].

The clinical presentation is heterogeneous, but identical for all forms. Newborns with CHI present with moderate to severe, persistent hypoglycemia; clinical severity varies with age at onset of hypoglycemia,

hypoglycemia may manifest as lethargy, apnea, hypotonia, tremulousness, abnormal movements, cyanosis, irritability, poor feeding, and hypothermia. hypoglycemia is often severe, revealed by seizures in half of cases [3]. Hypoglycemia in the neonatal period is often due to the various etiologies of transient hyperinsulinism, and the diagnosis of CHI is evoked by early hypoglycemia, before the seventy-second hour of life, occurring in a full-term neonate, without a timetable, profound (below 2 mmol/l), not accompanied by elevated ketone bodies, persistent despite sufficient glucose intake, and responding to the injection of 0.5 mg glucagon. Distinguishing between hyperinsulinemic and non-hyperinsulinemic hypoglycemia is not biochemically possible before H48 of life. However, if the newbom requires continuous carbohydrate intake > 8 to 10 mg/Kg/min (12 to 15 g/Kg/d) to normalize blood glucose levels, a mechanism involving insulin is involved, and HI is highly probable [13].

Radiological diagnostic procedures, such as ultrasound, CT, and MRI, rarely detect the pancreatic nodules, as these lesions are usually very small [1-15]. Measurement of insulin gradients in blood samples taken from catheterized pancreatic veins (pancreatic venous catheterization) or multiple pancreatic biopsies during laparoscopy, used to differentiate between diffuse and focal forms of CH [4-29]. However, these methods are invasives and complicated [16]. for over than 20 years the PET scan has been successfully used to distinguish the forms [9-17]. Fluorine-18 labeled L'dihydroxyphenylalanine (18F-DOPA) is used [2-16]. The uptake of 18F-DOPA is increased in b-cells which produce higher rates of insulin. Both PET and genetics give information about the form (focal or diffuse) of CH, and thus may be helpful in choosing medical or surgical management, and the extent of the surgical intervention of CHI. However, The PET studies should not be performed under the age of 1 month to exclude patients with transient hyperinsulinism, or in patients with a genetically proven suspected diffuse form [11].

The cornerstone of clinical management is early diagnosis and the initiation of appropriate treatment for patients with all forms of HH (hyperinsulinemic hypoglycemia). The goal is to maintain plasma glucose levels above 3.3 mmol/L, as the brain is deprived of alternative substrates [1].

The medical treatment of hypoglycemia must be administered promptly due to the potential cerebral sequelae in the case of prolonged severe hypoglycemia. In newborns, this necessitates the placement of a central catheter to ensure substantial glucose administration, supplemented by continuous glucose infusion via a gastric tube. Continuous infusion of glucagon, either subcutaneous or intravenous, may also be required [18].

Diazoxide, is the first-line treatment. However, 30 to 50% of patients exhibit resistance to this medication, requiring alternatives such as octreotide [9], used for over 30 years for this indication, its off-label use in hyperinsulinism is supported by strong consensus within rare disease healthcare pathways, demonstrating efficacy in 60 to 70% of cases resistant to diazoxide [3]. Somatostatin analogs, are used when diazoxide is contraindicated, or as a second-line treatment in cases of resistance to the latter, to improve glycemic control and limit the need for nutritional support, which can lead to oral intake disorders. The combination of diazoxide and somatostatin analogues may allow for normalization of blood glucose levels, or at least partial improvement in glycemic control, which may require nutritional support. Diazoxide, if well tolerated, is not discontinued when introducing a somatostatin analogue, at least not initially, since the primary concern is achieving glycemic balance. The effect of discontinuing diazoxide would only be fully assessable after a week [9].

Octreotide is a synthetic analogue of somatostatin with a prolonged action, composed of eight amino acids, which inhibits insulin secretion by reducing cyclic AMP in β-cells through binding to somatostatin receptors 2 and 5 (SSTR2 and SSTR5) [18]. Activation of SSTR5 decreases the activity of the insulin gene promoter, inhibits calcium mobilization, and reduces acetylcholine activity [19]. Somatostatin also inhibits the KATP channel, leading to reduced insulin secretion. The recommended initial dose of octreotide is 5 to 10 µg/kg/day administered by subcutaneous injections (or continuous subcutaneous pump) at 6–8 hour intervals, with a maximum dose of 50 to 60 µg/kg/day. There is no international consensus on the maximum dose of octreotide, which ranges from 15 to 60 µg/kg/day [9-18]. Abdominal pain and diarrhea are commonly observed at the start of treatment, but these symptoms usually decrease within a few days. Regular abdominal ultrasounds should be performed, as the appearance of biliary sludge or even stones is frequent. These typically resolve with treatment using ursodeoxycholic acid and usually do not require discontinuation of treatment. In cases where medical treatment fails to control hypoglycemia, partial pancreatectomy (for focal forms) or subtotal pancreatectomy (for diffuse forms) is indicated [20, 21].

CONCLUSION

Congenital hyperinsulinism (CHI) is the leading cause of severe and persistent hypoglycemia in neonates. Diazoxide-resistant forms, which are typically treated as first-line therapy, require an alternative therapeutic strategy. Octreotide is a useful second-line treatment option in diffuse CHI, and aids the current management strategy to avoid surgery and thereby preserve pancreatic tissue.

We report the case of a neonate with diazoxide-resistant CHI, managed with octreotide. The favorable clinical outcome with octreotide, alongside glycemic

stabilization, highlights the effectiveness of this treatment in cases of resistance. This case underscores the diagnostic challenges, the importance of a multidisciplinary approach, and the need to further strengthen the data on the off-label use of octreotide.

This case emphasizes the effectiveness of octreotide in managing diazoxide-resistant CHI, despite its off-label use. A personalized approach, incorporating genetics, imaging, and multidisciplinary follow-up, is essential to prevent neurological and metabolic complications. Continued efforts should be made to improve access to innovative treatments and consolidate long-term safety data.

Conflicts of Interest: The authors declare no conflicts of interest.

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