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CASE REPORT

Persistent hypoglycemia in Shashi-Pena Syndrome: a pediatric case report

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Abstract

Hyperinsulinemia is the leading cause of persistent and recurrent hypoglycemia in infancy. This case report presents the diagnostic and treatment challenge of hyperinsulinemic hypoglycemia in an infant with a genetic syndrome. We describe a patient born at term, small for gestational age, with genetic stigmata, who remained hospitalized in neonatal ICU due to low weight and complications. We also describe the clinical evolution up to two years of age of the child. With the suspicion of genetic syndrome, genetic testing was performed, confirming Shashi-Pena syndrome.

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INTRODUCTION

Persistent hypoglycemia is a challenging condition. Hyperinsulinemia is the primary cause of persistent and recurrent hypoglycemia in childhood. This article describes a case of severe hypoglycemia in an infant diagnosed with Shashi-Pena Syndrome after genetic testing. Since there is variability in the presentation and severity of symptoms in individuals with the syndrome, this case report aims to help understand Shashi-Pena syndrome and the treatment of hyperinsulinemic hypoglycemia.

CASE REPORT

A 2-year-old female infant, the daughter of Caucasian and non-consanguineous parents, was taken to our clinic. Her mother was a 19-year-old primiparous diagnosed with gestational hypothyroidism treated with levothyroxine. She did not drink alcohol, smoke, or use illicit substances during pregnancy. The last prenatal ultrasound examination revealed type 2 intrauterine growth restriction and the decision was made to terminate the pregnancy with a cesarean section. A girl was born weighing 1985g (Z score -2.77), with a length of 42.5cm (Z score -3.16) and a head circumference of 32cm (Z score -1.13). She was in good general condition and did not require neonatal resuscitation. Physical examination revealed a nevus flammeus on the glabella, long arched eyebrows, synophrys, a thin upper lip, an ogival palate, a lingual frenulum, micrognathia, deep plantar creases, generalized hypertrichosis lanuginose, and axial hypotonia. Due to her low birth weight and asymptomatic hypoglycemia, she was referred to the neonatal intensive care unit. Figure 1 shows the patient with Shashi-Pena syndrome shortly after birth.

In the neonatal period, the infant had significant trouble feeding orally due to incoordination of sucking, swallowing, and breathing, requiring a feeding tube. She had recurrent episodes of hypoglycemia and was prescribed a maximum infusion rate of 12 mg/kg/min to maintain normal blood glucose levels. The infant also had persistent diarrhea, requiring the introduction of extensively hydrolyzed infant formula, with a good response.

Since the newborn had uterine growth restriction, was small for gestational age and had recurrent episodes of hypoglycemia, imaging tests were performed with the following results: brainstem auditory evoked potential (bilateral hearing disorder); Doppler echocardiogram (patent ductus arteriosus and small interatrial communication); urinary tract ultrasound examination (horseshoe kidneys); magnetic resonance imaging of the head (hypoplasia of the cerebellar vermis and dilation of the fourth ventricle, findings suggestive of Dandy-Walker malformation); electroencephalogram (frequent epileptiform activity in the frontal, central, and temporal regions of the brain).

Figure 1. Patient with Shashi-Pena syndrome shortly after birth: A) Lateral decubitus; B) Ventral decubitus.

Since hypoglycemia persisted beyond the neonatal period, the patient was started on prednisolone 2.5 mg/m2 daily, initially alone and later associated with GH, without improvement. At eight months of age, a critical sample was collected during an episode of glycemia <50 mg/dL, and a glucagon stimulation test was performed (essential for diagnosing hyperinsulinemic hypoglycemia). At 12 months, the patient was started on diazoxide (5 mg/kg/day), resulting in adequate glycemic control.

Molecular analysis by exome sequencing found pathogenic variant chr2:25.749.716 G>A in heterozygosity in the ASXL2 gene, confirming a genetically determined condition known as Shashi-Pena Syndrome (OMIM # 617190).

The patient had recurrent respiratory infections (at 4, 7, 10, 12, 13, and 15 months), requiring hospitalization in the pediatric ward on four occasions. The imaging pattern in the right upper lobe between episodes prompted an investigation of immunodeficiency. Her complete blood count was normal, immunoglobulin levels were within the percentiles for her age, and flow cytometry immunophenotyping revealed a decrease in the CD19+CD20+ B and CD16+CD56+ NK lymphocyte counts. The patient was then kept without medication.

A control Doppler echocardiogram performed at one year and three months of age showed a patent ductus arteriosus, an enlarged left atrium, and a globular left ventricle. The patient was referred to a referral hospital, where cardiac catheterization was indicated without the need for drug therapy.

She could not catch up on growth during the first two years of life. The patient also had developmental delays: she could not sit without support, say words, or feed herself. She is currently under multidisciplinary monitoring and attends weekly supplementary therapies. Figure 2 shows the patient with Shashi-Pena syndrome: A) At five months of age; B) At one year and four months.

DISCUSSION

Shashi-Pena syndrome is caused by pathogenic variants in heterozygous form in the ASXL2 gene. It is a genetically determined condition that can be inherited as an autosomal dominant trait or secondary to a “de novo” mutation, a variant that appears in an individual for the first time and is not inherited from one of the parents.[1,2]

Figure 2. Patient with Shashi-Pena syndrome: A) At five months of age; B) At one year and four months of age.

The prevalence of the syndrome is estimated at 45 cases worldwide. Shashi-Pena syndrome was first described in 2016 and is characterized by facial dysmorphisms (macrocephaly, nevus flammeus in the glabella region, hypertelorism, and arched eyebrows), congenital cardiac abnormalities, hypoglycemia, feeding difficulties, bone mineral density alterations, seizures, hypotonia, and global developmental delay.[1-4]

Our patient presents dysmorphisms and phenotypic alterations compatible with Shashi-Pena syndrome. However, she did not present macrocephaly and was a small-for-gestational-age newborn (by weight and length), which goes against what is reported in the current literature.[1-4]

Congenital hyperinsulinemic hypoglycemia was an important finding in this case. Hyperinsulinism can be transient (<6 months) or persistent (> six months) and is the primary cause of persistent and recurrent hypoglycemia in children. When it starts in the neonatal period and continues after that, it is named congenital hyperinsulinism.[5-7]

Small-for-gestational-age (SGA) newborns with intrauterine growth restriction (IUGR) and/or signs suggestive of a genetic syndrome are at higher risk of neonatal hypoglycemia due to alterations in metabolic pathways (glycogenolysis, gluconeogenesis, mitochondrial fatty acid oxidation or ketogenesis).[6,7] The signs and symptoms of hypoglycemia vary and include agitation, irritability, pallor, cyanosis, hypothermia, lethargy, apnea, and seizures.[7]

The investigation of neonatal hypoglycemia (plasma levels < 50mg/dL) requires that the following parameters be tested at the time of hypoglycemia: blood glucose, blood gas (arterial or venous), lactate, electrolytes (sodium, potassium, and chloride), insulin, ammonia, cortisol, GH, C-peptide, beta-hydroxybutyrate, free fatty acids, acylcarnitine, and amino acid profile. A partial urine sample must also be collected to assess the presence of ketonuria and/or reducing substances.[6,7]

If hypoglycemia occurs with metabolic acidosis, glycogenosis, gluconeogenesis disorders, and hypopituitarism must be investigated. If hypoglycemia occurs without metabolic acidosis, hyperinsulinism and fatty acid oxidation disorders must be considered.[6,7]

It is essential to determine the cause of hypoglycemia since treatment varies according to the underlying disease. In the case of hyperinsulinemic hypoglycemia, the drug of choice is diazoxide.[8] As reported in the literature, A somatostatin analog (octreotide) should be considered for patients with refractory hypoglycemia.[9]

CONCLUSIONS

The signs and symptoms seen in patients diagnosed with the same genetic syndrome may vary. The primary purpose of this case report was to contribute to the spectrum of phenotypes and genetic variations of Shashi-Pena syndrome. Only 13 cases have been reported in the literature since 2016. This is the first time that diazoxide has been administered to a patient with persistent hypoglycemia secondary to Shashi-Pena syndrome, helping to maintain adequate glycemic control.

REFERENCES

1. Shashi V, Pena LDM, Kim K, Burton B, Hempel M, Schoch K, et al. De Novo truncating variants in ASXL2 are associated with a unique and recognizable clinical phenotype. Am J Hum Genet [Internet]. 2017 Jan 5; [cited 2024 Feb 17]; 100(1):179. DOI: https://doi.org/10.1016/j.ajhg.2016.12.004. Available from: https://pubmed.ncbi.nlm.nih.gov/27693232/.
2. Cuddapah VA, Dubbs HA, Adang L, Kugler SL, McCormick EM, Zolkipli-Cunningham Z, et al. Understanding the phenotypic spectrum of ASXL -related disease: Ten cases and a review of the literature. Am J Med Genet A [Internet]. 10 mar 2021; [cited 2024 Feb 17]. DOI: https://doi.org/10.1002/ajmg.a.62156. Available from: https://pubmed.ncbi.nlm.nih.gov/33751773/.
3. Wang Y, Tan J, Wang Y, Liu A, Qiao F, Huang M, et al. Diagnosis of Shashi-Pena Syndrome caused by chromosomal rearrangement using nanopore sequencing. Neurol Genet [Internet]. 23 nov 2021; [cited 2024 Feb 17]; 7(6):e635. DOI: https://doi.org/10.1212/nxg.0000000000000635. Available from: https://pubmed.ncbi.nlm.nih.gov/34841066/.
4. Liberatore Junior RD, Negri AA, Martinelli Junior CE, Kochi C, Silva IN, Collett-Solberg PF. Hipoglicemia hiperinsulinêmica da infância: Análise de dados clínicos de uma amostra brasileira. Arq Bras Endocrinol Amp Metabol [Internet]. 2012 Dez; [citado 2024 Fev 17]; 56(9):666-71. DOI: https://doi.org/10.1590/s0004-27302012000900011. Disponívl em: https://www.scielo.br/j/abem/a/H5wLBKy8YfMXH9vMXP3frJp/.
5. Arnoux JB, Verkarre V, Saint-Martin C, Montravers F, Brassier A, Valayannopoulos V, et al. Congenital hyperinsulinism: current trends in diagnosis and therapy. Orphanet J Rare Dis [Internet]. 2011; [cited 2024 Feb 17]; 6(1):63. DOI: https://doi.org/10.1186/1750-1172-6-63. Available from: https://pubmed.ncbi.nlm.nih.gov/21967988/.
6. Marinho PC, Sá AB, Gouveia BM, Serpa JB, Moraes JRS, Sodré RS, et al. Hipoglicemia neonatal: revisão de literatura. Braz J Health Rev [Internet]. 2020; [citado 2024 Fev 17]; 3(6):16462-74. DOI: https://doi.org/10.34119/bjhrv3n6-068. Disponível em: https://ojs.brazilianjournals.com.br/ojs/index.php/BJHR/article/view/20050.
7. Pediatric Endocrinology. Williams textbook of endocrinology. Moscow: GEOTAR-Media; Publishing Group eBooks; 2020.

8. Flanagan SE, Kapoor RR, Mali G, Cody D, Murphy N, Schwahn B, et al. Diazoxide-responsive hyperinsulinemic hypoglycemia caused by HNF4A gene mutations. Eur J Endocrinol [Internet]. 2010 May; [cited 2024 Feb 17]; 162(5):987-92. DOI: https://doi.org/10.1530/eje-09-0861.

9. Yuan M, Shan Y, Xu F, Yang L, Sun C, Cheng R, et al. A newborn with a pathogenic variant in ASXL2 expanding the phenotype of SHAPNS: a case report and literature review. Transl Pediatr [Internet]. 2023 Jan; [cited 2024 Feb 17]: 0. DOI: https://doi.org/10.21037/tp-22-220. Available from: https://pubmed.ncbi.nlm.nih.gov/20164212/.