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Case Report

Persistent Hyperinsulinemic Hypoglycemia of Infancy: A Rare Case with Multiple Anomalies

Zohre Sadat Sangsefidi[1], Rahim Vakili[2], Ahmadreza Zarifian[3], Nona Zabolinejad[4], Abdolreza Norouzy[1], Fatemeh Ghafouri-Taleghani[1], Bahare Imani[2]*

1. Department of Nutrition, Mashhad University of Medical Sciences, Mashhad, Iran
2. Department of Pediatrics, Mashhad University of Medical Sciences, Mashhad, Iran
3. Student Research Committee, Medicine Faculty, Mashhad University of Medical Sciences, Mashhad, Iran
4. Department of Pathology, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

***Background*:** Few cases of persistent hyperinsulinemic hypoglycemia of infancy (PHHI) have been reported, so far. The main concern in the management of PHHI is to prevent severe hypoglycemia, which can lead to coma, brain damage and mental retardation. Total or subtotal pancreatectomy is normally required for the infants, despite the availability of medical therapies.

***Case report*:** In this report, we present the case of a three-day-old male infant with hypoglycemia and seizure, admitted to a hospital in Mashhad with the diagnosis of PHHI. Further evaluations revealed multiple congenital disorders including dextrocardia, posterior communicating aneurysm, atrial septal defect, ventricular septal defect, situs inversus and asplenia. Maximal doses of diazoxide, octreotide and intravenous glucose were prescribed for the infant. The patient was referred to our hospital and subtotal pancreatectomy was performed. In addition, due to frequent hypoglycemic episodes, a near-total pancreatectomy was conducted six days after the first surgery. The patient died eight months after total pancreatectomy at the age of nine months with no follow-ups.

***Conclusion*:** Infants with PHHI are at a high risk of severe neurological damage due to severe hypoglycemia, unless immediate and adequate medical interventions are carried out. Considering the co-occurrence of different congenital anomalies and PHHI in the present case, further assessment of concomitant congenital disorders is highly recommended in PHHI patients.

Keywords Hyperinsulinism, Persistent Hyperinsulinemia Hypoglycemia, Neonate

Introduction

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is a rare disorder, with few cases being reported. The main aim of PHHI management is to prevent severe hypoglycemia, which can lead to severe complications such as coma, brain damage and mental retardation (1). High-dose glucose infusion and medication therapy using diazoxide, octreotide and nifedipine are the major steps in management of PHHI.

Pancreatectomy should be considered in case of resistance or treatment failure in PHHI patients (2, 3). Total or at least subtotal pancreatectomy is normally required for the infants, despite the availability of medical therapies (1). Moreover, hyperinsulinemia may be associated with cardiomyopathy (4, 5).

Co-occurrence of congenital cardiac diseases and PHHI has been reported in several infants (4, 6, 7). In fact, management of PHHI can be challenging due to other concomitant congenital disorders such as congenital heart defects and abdominal anomalies. Consequently, infants with PHHI require greater attention and supervision.

In the present report, we present the case of an infant with PHHI and several congenital disorders. The patient did not respond to medical treatments and underwent pancreatectomy.

Case presentation

The patient was a pre-term (36 weeks of gestation) male infant with a birth weight of 3.7 kg. He was the third child born to a consanguineous couple. The mother had a prior history of preeclampsia during her pregnancy. However, no history of congenital anomalies was reported in the family.

On the third day of life, he was admitted to a hospital in Mashhad with hypoglycemia (blood

* *Corresponding author*: Bahare Imani, Department of Pediatrics, Dr. Sheikh Children Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985137276580; Fax: +985137277470; Email: imanibh@mums.ac.ir

sugar= 31 mg/dl), hyperinsulinemia (serum insulin level= 50 mu/l) and seizure. Initial clinical examination revealed heart murmurs. Tachypnea, respiratory distress and cyanosis were reported, as well. Low blood sugar level (31 mg/dl), insulin-to-glucose ratio of > 0.4 and decreased serum levels of free fatty acids and ketone bodies confirmed the diagnosis of PHHI.

Further clinical examination revealed congenital heart defects in the infant including dextrocardia, posterior communicating aneurism (PCA), atrial septal defect (ASD) and ventricular septal defect (VSD). Moreover, abdominal ultrasonography indicated situs inversus and asplenia. At the time of hospital admission, PET scan was not available for further evaluation of the patient.

Since maximal doses of diazoxide (20mg/kg/q8h), octreotide (40mcg/kg/q12h) and high-rate glucose infusion (32mg/kg/24h) were ineffective in achieving normal blood sugar, the patient was referred to our hospital after 11 days of admission (at 15 days of age). At the time of admission, maximum nutrition tolerance of breast milk was 30 cc/kg/q2h*12 via percutaneous endoscopic gastrostomy (PEG). The infant's blood sugar was calculated to be 22 mg/dl.

Consequently, treatment with diazoxide (50mg/kg/q6h), octreotide (40 mcg/ kg/ q12h) and intravenous (IV) glucose (18mg/ kg/ 24h) was commenced. In spite of complete drug therapy with the highest recommended doses, the patient showed no response to the treatment; therefore, he was assigned as a candidate for pancreatectomy.

Nevertheless, we started feeding the patient with breast milk via PEG (30 cc/kg/q2h*12). On the third day of hospital admission, IV hydrocortisone (5.4mg/q6h) was added to the treatment. However, the patient was unresponsive and underwent subtotal (80%) pancreatectomy on the fifth day of hospitalization (at the age of 19 days). Pathologic reports of the resected specimen revealed abnormal large nuclei in the islet cells with bizarre, ovoid or crescent shapes, distributed throughout the pancreas (Figure 1).

Medical therapy was continued after surgery in order to control the patient's glycemic index. Despite the administration of diazoxide (50 mg/kg/q6h), octreotide (90mcg/kg/q12h), IV hydrocortisone (4.5 mg/q6h) and IV glucose (35 mg/kg/24h), hypoglycemic episodes continued. Eventually, near-total (95%) pancreatectomy was performed six days after the first surgery.

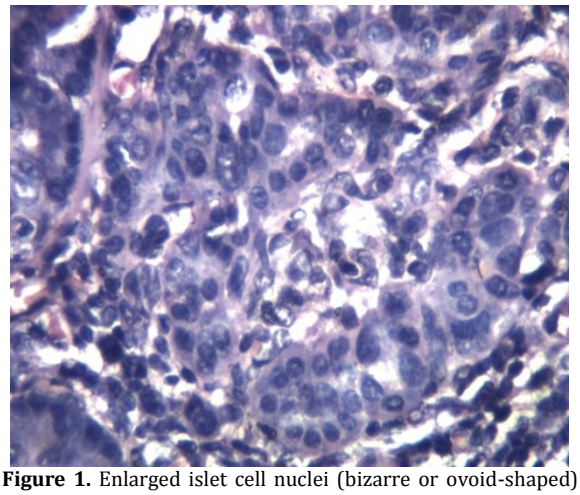

Figure 1. Enlarged islet cell nuclei (bizarre or ovoid-shaped) (hematoxylin and eosin staining × 400)

Doses of hydrocortisone and glucose were changed to 3 mg/q8h and 23 mg/kg/24h, respectively, and octreotide was interrupted five days after the second surgery. The regimen was nothing per oral (NPO) for one day before each surgery and breast milk feeding (5 cc/q2h*6) started a day after each surgery.

Hypoglycemic episodes continued and the patient did not respond to the interventions. Maximal nutrition tolerance of breast milk was 60 cc/kg/q2h*12 after the second surgery. After 19 days of hospitalization, the patient was transferred to another hospital in order to continue his therapeutic course. Medical therapy continued with diazoxide (25 mg/kg/d) and IV hydrocortisone (3 mg/d) for blood sugar control.

Despite thorough explanation about the necessity and importance of hospitalization and treatment continuation to the parents, the infant was discharged after three days with parents' consent. His blood sugar upon discharge was 50 mg/dl. Finally, eight months later, at the age of nine months, the patient died most probably due to hypoglycemia and congenital heart failure.

Discussion

Prevention of severe hypoglycemia caused by PHHI is of utmost importance as it may lead to severe complications. PHHI has been categorized into two types: focal and diffuse PHHI. Most previous studies have shown that the majority of focal cases are treated after surgery, whereas hypoglycemia may continue after surgery in the diffuse type, which can be controlled by medical interventions. In some cases, symptoms of hypoinsulinemia may be observed in the diffuse type, which can lead to diabetes mellitus in the long run (8-15).

Palladino et al. reported an improvement in more than 90% of focal cases after surgery. The rate of hypoglycemia was 50% in diffuse cases after surgery, which was controlled by medical interventions. In 25% of cases with the diffuse type, hypoglycemia was improved after surgery without the use of medications, while the remaining 25% required insulin replacement therapy (1, 15). Additionally, Sawathiparnich et al. studied 10 patients with PHHI and reported that the majority of cases could be managed with intensive medical interventions (14).

In another study, Yasukura et al. reported the case of a female diagnosed with light nesidioblastosis (the initial term for PHHI), who had normal insulin and insulin-to-glucose ratio. IV glucose (0.7-2 mg/kg/min) and diazoxide were administered to prevent hypoglycemia; however, due to patient's unresponsiveness, total pancreatectomy (95%) was performed. Her blood sugar was controlled and she showed normal growth during a three-year follow-up after the surgery (16).

In a report by Semiz et al. in 2002, PHHI was diagnosed in a three-month-old male infant with symptoms of lethargy and seizure, blood sugar level of 24 mg/dl and insulin-to-glucose ratio above 0.3. They observed no response to maximal doses of prednisolone, glucagon, diazoxide, octreotide and glucose and eventually, pancreatectomy (80%) was performed. However, hypoglycemia continued after surgery and low-dose octerotide was administered for its management. The patient showed normal growth during a six-month follow-up after the surgery (17).

The correlation between other maternal disorders and PHHI has not been studied, so far. Few studies have reported PHHI cases with associated congenital cardiomyopathy. One of these studies reported a case of PHHI with left ventricular hypertrophy and arrhythmia (7). Since the infant did not respond to medical therapy, 95% pancreatectomy was performed. The infant was eventually expired at 70 days of age due to hypoglycemia and heart failure (7).

In line with the abovementioned study, our patient presented with PHHI and congenital defects including PDA, ASD, VSD, dextrocardia, absence of spleen and displacement of liver lobes. We managed hypoglycemia by medical therapy using diazoxide, octerotide, IV glucose and IV hydrocortisone, following the final surgery. This was in line with previous research by Semiz and Palladino et al. (15, 17) and in contrast with some other studies (16). In addition, in contrast with some studies, our patient died about eight months after the surgery due to congenital heart disease (7, 17).

We also managed the nutritional status of the infant via therapeutic approaches, while this was not achieved in the abovementioned studies. The co-occurrence of PHHI and different congenital anomalies was the main characteristic of this case. The main limitation of our study was lack of access to the patient, which left no chance for follow-up after the surgery.

Conclusion

Focal hypoglycemia is treated after pancreatectomy in the majority of patients, while it may recur in the diffuse type, requiring medical interventions. Hence, early diagnosis and intervention can significantly reduce complications in PHHI patients. In cases with PHHI, concomitant with different congenital disorders, treatment can be difficult. Therefore, it is strongly recommended to consider other congenital anomalies, especially cardiac disorders in all PHHI cases for determination of patient prognosis and survival, particularly in preterm infants.

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