Persistent Hyperinsulinemic Hypoglycemia with Pancreatic Teratoma in Infancy: A Case Report

Authors' Contribution:
Study Design **A**
Data Collection **B**
Statistical Analysis **C**
Data Interpretation **D**
Manuscript Preparation **E**
Literature Search **F**
Funds Collection **G**

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Conflict of interest: None declared

Patient:	**Female, 6-month-old**
Final Diagnosis:	**Hyperinsulinemic hypoglycemia with abdominal teratoma**
Symptoms:	**Hypoglycemia**
Medication:	**—**
Clinical Procedure:	**Surgery removal**
Specialty:	**Endocrinology and Metabolic**

Objective: Unusual clinical course

Background: Pediatric intraabdominal pancreatic teratomas have been rarely reported. This is the first case of severe hyperinsulinemic hypoglycemia in a 6-month-old infant secondary to an intraabdominal teratoma. The hypoglycemia resolved after surgical removal.

Case Rreport: A 6-month-old infant was seen in a pediatric emergency department with complaints of lethargy and abnormal eye movements. She was diagnosed with hyperinsulinemic hypoglycemia and started on diazoxide. A CT and MRI of the abdomen revealed a 165×77×72 mm cyst with a 51×45×30 mm solid structure connecting to the wall of the cyst by a stalk, raising suspicion of a fetus in fetu. The mass had no connection to her pancreas. Following total excision of the intraabdominal mass, her hypoglycemia resolved. Histopathological examination showed immature fetal pancreatic tissue consistent with a mature teratoma. Whole exon sequencing of the infant's peripheral blood showed a negative mutation of ABCC8 and presence of heterozygous variations of HNF1β and IRS1 genes.

Conclusions: This is the first case report of an infant with severe hyperinsulinemic hypoglycemia secondary to a pancreatic teratoma. The heterozygous variations of HNF1β and IRS1 genes likely played a role in the embryogenesis, causing a pancreatic teratoma and hyperinsulinemic hypoglycemia.

MeSH Keywords: Hyperinsulinism • Hypoglycemia • Infant, Newborn • Teratoma

Abbreviations: **MRI** – magnetic resonance imaging; **US** – ultrasound; **CT** – computed tomography; **FIF** – fetus in fetu; **MCT** – mature cystic teratoma; **HNF1**β – hepatocyte nuclear factor-1 beta; **IRS1** – insulin receptor substrate 1

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Background

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is a rare genetic disorder in newborns and infants. It is commonly due to mutations of genes that regulate insulin secretion from the beta cells of the pancreas, resulting in focal or diffuse pancreatic hyperplasia [1–5]. The incidence of PHHI is about 1 in 35 000 live births, but it is more prevalent in countries with a high consanguinity rate [1,2]. Severe cases usually present in the newborn period, whereas diagnosis of less severe forms may be delayed until 3 to 6 months of age. PHHI presents with an inappropriately high insulin level in the face of hypoglycemia and an absence of ketosis. Hyperinsulinism suppresses ketone production and gluconeogenesis, making infant brains even more vulnerable to hypoglycemic damage [1–4]. Prompt diagnosis and treatment is therefore crucial to prevent irreversible brain damage. We are presenting a case of severe hyperinsulinemic hypoglycemia with an abdominal mass in a 6-month-old infant.

Case Report

This full-term, 3370 gm infant was delivered by Cesarean section. The pregnancy was uneventful except for right hydronephrosis and a 30 mm amniotic surface cystic lesion of the placenta on prenatal ultrasound (US) at 25 weeks' gestation. Physical exam was normal at 4 weeks of age. At the age of 2 months she presented with abdominal distention. An US and magnetic resonance imaging (MRI) of the abdomen revealed a retroperitoneal 15-cm pure cystic mass (Figure 1A) displacing the left kidney inferiorly and a right grade III hydronephrosis. Laboratory work-up to rule out possible malignancy included alpha-fetoprotein, human chorionic gonadotropin, and neuron sensitive enolase, which were normal. The blood glucose concentration was 91 mg/dL. Since she was in significant respiratory distress, 700 mL of cystic fluid was aspirated under US guidance. Biochemical analysis was not consistent with urine, and no malignant cells were detected. Within a 3-day period, 400 mL of fluid reaccumulated and was again aspirated, leaving a smaller cystic mass on US. At age 3 months a repeat US of the abdomen revealed the presence of a small, solid component within one of the bibulated cysts (25×25×9 mm and 28×27×13 mm in diameter) (Figure 1B). A voiding cystourethrogram revealed a right ureteropelvic junction stenosis and grade III hydronephrosis. At age 5.5 months she was seen by a pediatric neurologist for concerns of staring spells. An MRI of the brain and EEG were normal. A week later she presented to the pediatric emergency department with lethargy, sleepiness, and abnormal eye movements. Laboratory studies revealed a blood glucose concentration of 23 mg/dL and a simultaneous insulin level of 18.8 µU/mL (which should be undetectable with hypoglycemia). Blood ketones were negative, and

cortisol concentration was 25.7 µg/dL (5–10 µg/dL). She was given an intravenous bolus of 10% dextrose and was admitted to the pediatric intensive care unit with the diagnosis of hyperinsulinemic hypoglycemia. She required a 15% dextrose infusion via central line to maintain a blood glucose concentration above 70 mg/dL. Concomitant oral diazoxide was started and increased to 15 mg/kg/day. She demonstrated an abnormally elevated response to glucagon administration during a hypoglycemic episode with a rise in blood glucose concentration from 37 to 96 mg/dL. This confirmed the diagnosis of hyperinsulinemic hypoglycemia. Despite a good oral intake (breastmilk and formula) and the diazoxide, she required 6.25 mg/kg/min glucose infusion to maintain a blood glucose concentration above 70 mg/dL. An MRI and CT of the abdomen showed a cystic mass of 104×61×48 mm in diameter with a 50×40×36 mm heterogeneous solid component (Figure 1C). At 6 months of age a through-cut biopsy was performed. Histopathological examination showed ductal structures within a myxoid stroma with no atypical cells and a low level of mitosis. A decision was made to surgically excise the intra-abdominal mass. Surgical findings are depicted in Figure 2.

Histopathological findings

The entire solid mass consisted of fetal pancreatic tissue similar to that at 3 months' gestation, based on embryologic staging of pancreatic ductal and acinar structures. Almost 95% of the mass consisted of islets of Langerhans. The immune-histochemical testing revealed an abundance of insulin-secreting beta cells with scattered areas of glucagon and few somatostatin-secreting cells, which are seen in the early embryologic stage of development (Figure 3).

Genetic evaluation

Her karyotype was 46 XX with no deletion, duplication, or aberrant methylation profile of one or more sequences of the KvDMR and H19DMR domains in the 11p15 BWS/Russell-Silver syndrome region. Chimerism testing of the surgically removed material and the blood sample of the infant was performed by using an AmpFlSTR Identifiler PCR Amplification kit (Applied Biosystems, Warrington, UK). Briefly, we used 17 different STR markers located at 2p23-2per, 2q35-37.1, 3p21.31, 4q28, 5q21-31, 5q33.3-34, 7q11.21-22, 8q24.3, 11p15.5, 12p12-pter, 13q22-31, 16q24-qter, 18q21.3, 19q12-13.1, 21q11.2-q21, Xp22.1-22.3, and Yp11.2. The analysis showed that the surgical material and the baby were genetically identical. The zygocity testing of the surgical material demonstrated homozygocity at the centromeric region. Whole exon sequencing (WES) of the infant's peripheral blood showed negative mutation of the ABCC8 gene and heterozygous variation of hepatocyte nuclear factor-1 beta (HNF1β), (exon 1 (rs747555052),
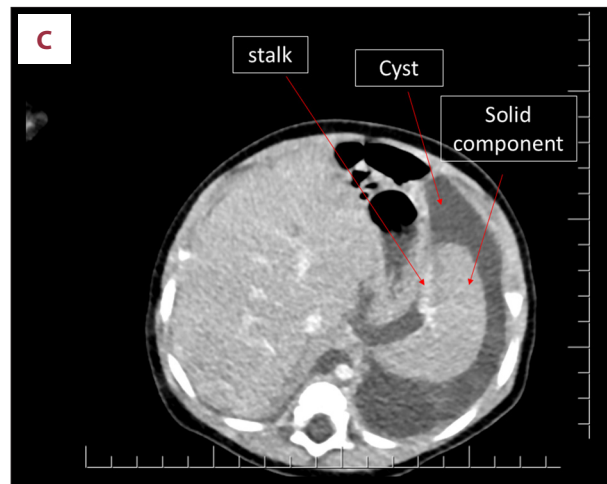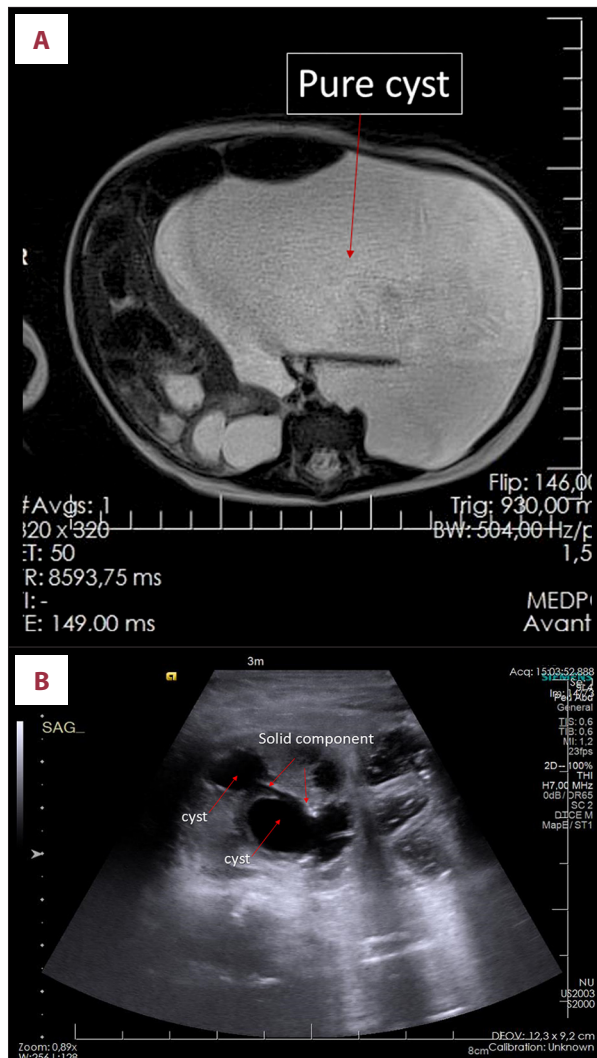
Figure 1. MRI and US findings of the intraabdominal lesion. (**A**) MRI at 2 months of age, a pure cystic lesion. (**B**) US of the abdomen at 3 months of age showing a vague small solid component within 1 of the bilobulated cysts of 25×25×9 mm and 28×27×13 mm in diameter. (**C**) CT at 6 months of age showing a 50×40×36 mm solid component within a 104×61×48 mm cystic lesion connecting with a 2-cm stalk. Please note that this image has a striking similarity to a prenatal US image of a fetus.

c.79G>C, p.V27L) and insulin receptor substrate 1 (IRS1) (exon 1 (rs779584301), c.1860 C>T, p.P454S) genes.

Postoperatively she had marked hyperglycemia, but after 24 h her blood glucose normalized with complete resolution of her hyperinsulinemic hypoglycemia. At age 8.5 months she was diagnosed with a congenital hiatal hernia and underwent corrective surgery at 11 months. Histologic examination of the surgical material showed mature squamous epithelium and was thought to be residue of the previously removed mature teratoma. The patient is currently 2.5 years of age and has had no subsequent episodes of clinical or biochemical hypoglycemia.

Discussion

The mechanism of action was initially unclear in this case of hyperinsulinemic hypoglycemia with teratoma in this 6-month-old infant. Insulinoma is a very rare cause of hyperinsulinemic

hypoglycemia in childhood [6] and therefore had not been considered due to her age and the presence of an intra-abdominal mass without connection to her normal appearing pancreas. The solid component of the mass connected to the wall of the cyst by a 2.5-cm stalk raised the suspicion of a case of fetus in fetu (FIF). The differential diagnoses included pancreatic heterotopias, mature cystic teratoma (MCT), and FIF. Pancreatic heterotopia is a rare congenital anomaly in which there is pancreatic tissue with no anatomic connection to the pancreas itself [7]. Pancreatic heterotopia is commonly an incidental finding in adults and very rarely reported to cause hyperinsulinemic hypoglycemia [8]. In MCT the presence of various tissue types in a cystic mass is characteristic. The presence of mature pancreatic tissue in mediastinal teratomas has been reported; however, none of the cases resulted in hyperinsulinemic hypoglycemia [8–11]. Although diagnostic criteria have been proposed for FIF [12], the differentiation between MCT and FIF is still controversial [13–16]. All cases of FIF occur in identical twins and are always genetically identical to the host. It has been reported that MCT and FIF could be differentiated by zygosity [16]. Teratomas are always homozygous at or near the centromeric regions [17]. Although this mass fulfilled the diagnostic criteria of FIF [12], it was homozygous at the centromeric region, confirming the diagnosis of an MCT. The presence of a squamous epithelium in a small region was also consistent with a teratoid maturation.
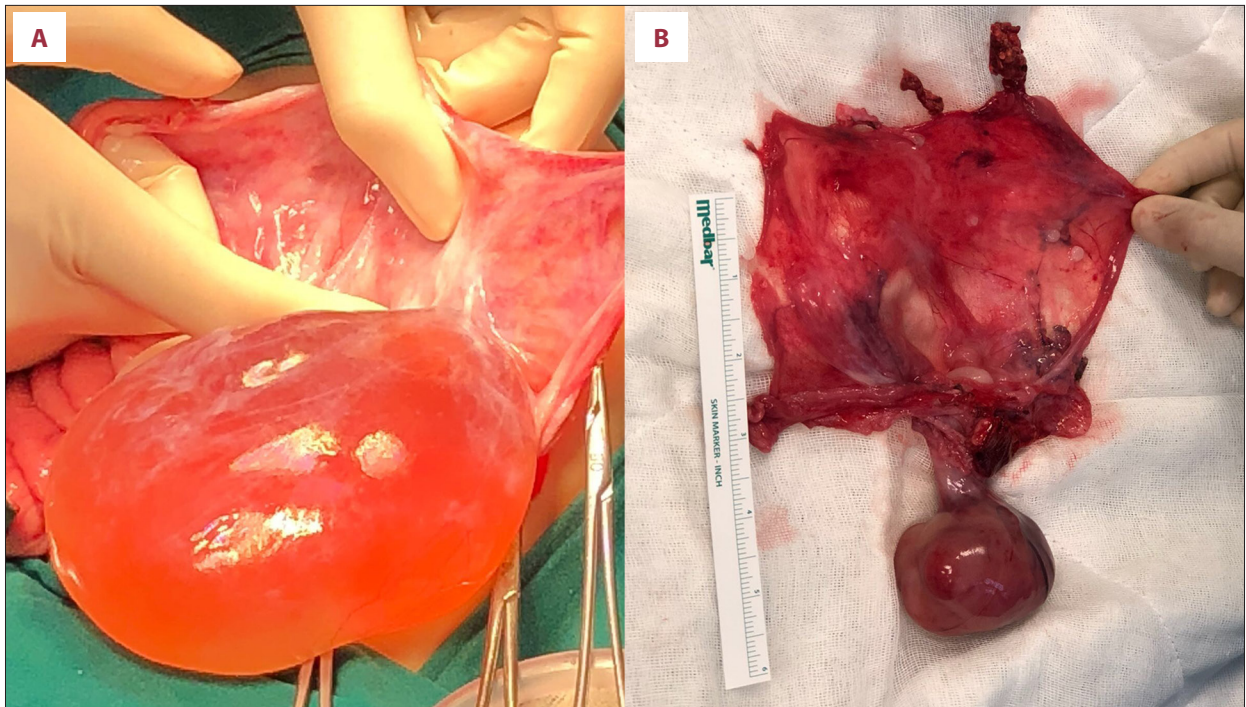
Figure 2. During laparotomy, a clear serous fluid-filled intact sac with a solid component was detected (**A**). The spleen and pancreas appeared normal and were easily detached from the cyst sac. The left adrenal gland was removed as it could not be detached from the wall of the cyst. The wall of the cyst was cut open exposing the solid component connected to the wall of the cyst with a stalk. A homogenous, smooth, ovoid shaped rubbery solid component connected to the cyst wall with a 2.5-cm stalk was removed (**B**).

The most interesting point of this case is that the mature teratoma with immature fetal pancreatic tissue lacked the normal control mechanisms of insulin secretion. Having extra beta cells does not cause hyperinsulinemic hypoglycemia if the beta cell function is properly regulated. During the first trimester, beta cells have immature glucose sensing mechanisms [18]. The insulin secretion from the fetal pancreas during early stages of maturation responds to amino acid rather than to glucose concentrations, and at 12 to 22 weeks' gestation, basal insulin secretion from the fetal pancreas is 4-fold higher [19]. Therefore, immaturity of the fetal pancreatic tissue may be the reason for the uncontrolled insulin secretion and partial response to diazoxide treatment. Unfortunately, WES on the tumor tissue could not be performed due to the quality and quantity of the available DNA, and we cannot totally exclude the possibility of a mutation in the teratoma that could have caused uncontrolled insulin secretion. The WES of the peripheral blood, however, detected a heterozygous variation of HNF1β and IRS1 genes but no mutation of the ABCC8 gene. The heterozygous IRS1 variation detected in this case is known to be associated with type 2 diabetes and susceptibility to insulin resistance [20] and therefore could be a coincidental finding. However, the combination of heterozygous variations of the HNF1β and IRS1 genes may be a new finding for the pathogenesis of persistent hyperinsulinemic hypoglycemia in infants. HNF1β plays an important role in organogenesis, especially of the liver, kidney, and pancreas. Mutations in the HNF1β gene cause monogenic diabetes in youth type 5 (MODY5), renal cysts, genital malformations, and pancreas atrophy [21]. Mutations in the HNF1β gene have not been reported to cause hyperinsulinemic hypoglycemia. This infant had a right ureteropelvic junction stenosis and grade III hydronephrosis which could have been due to the detected variation of the HNF1β gene. About one-third of patients with an HNF1β mutation have pancreatic structural anomalies, but a pancreatic teratoma has never been reported with variations or mutations of the HNF1β gene [22]. The specific variation in the HNF1β gene detected in this infant has been reported previously and is considered to be a benign variant or variation of unknown significance [23,24]. This variation was located at the dimerization domain of the HNF1β protein, which is important for protein function and therefore might have impacted the embryogenesis of the pancreas, causing a pancreatic teratoma with uncontrolled insulin secretion and severe hyperinsulinemic hypoglycemia in this infant.
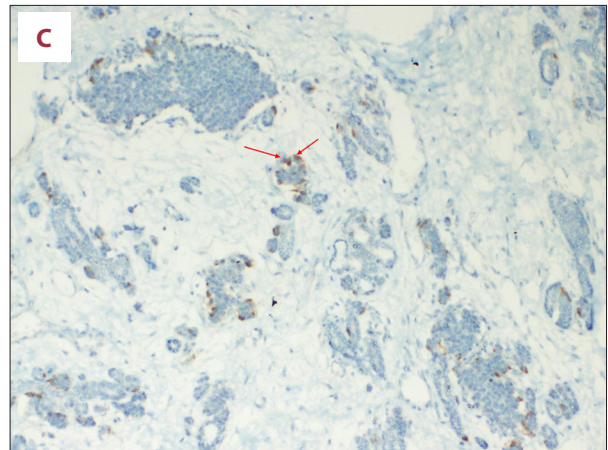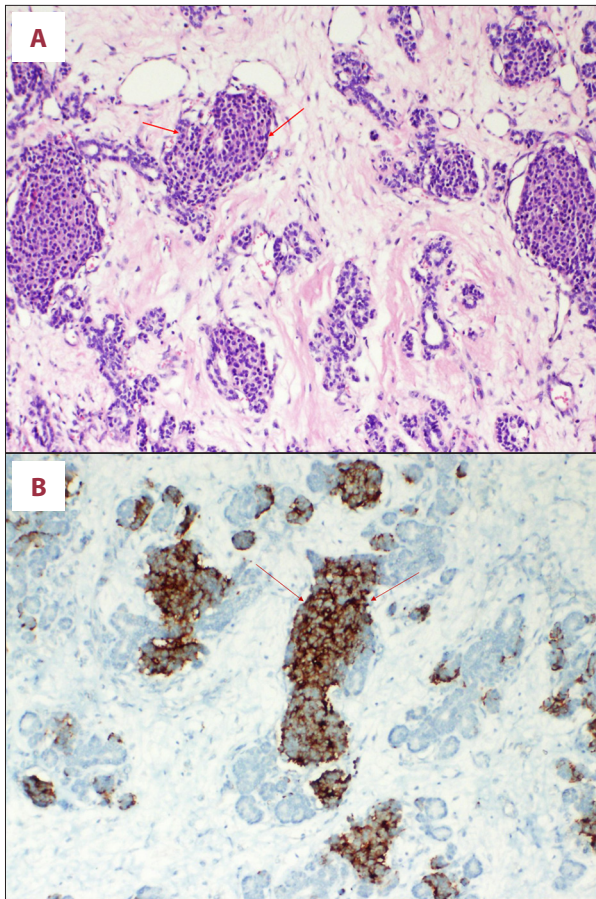
Figure 3. Histopathologic examination: Macroscopically, the surgical material consisted of a cystic mass with a diameter of 175×80×40 mm and a solid component with a diameter of 66×44×40 mm with a total diameter of 205×80×40 mm. (**A**) Pattern is that of a pancreatic tissue in early embryonic development with islets much higher in number than expected (Hematoxylene and Eosine X100 original magnification, shown in arrows). (**B**) Neuroendocrine islets showing extensive positivity for insulin (Anti-insulin antibody immunohistochemistry staining, ×100 original magnification, shown in arrows). (**C**) Neuroendocrine islets showing sparse glucagon positive cells (Anti-glucagon antibody immunohistochemistry staining, ×100 original magnification, shown in arrows).

Conclusions

The combination of heterozygous variations of HNF1β and IRS1 genes in this infant likely played a role in the embryogenesis in utero, causing a pancreatic teratoma and severe hyperinsulinemic hypoglycemia. Therefore, this should be considered in the pathogenesis of persistent hyperinsulinemic hypoglycemia in infants.

Conflict of interest

None.

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