# Case Report

# Persistent Hyperinsulinemic Hypoglycemia of Infancy Associated with Congenital Neuroblastoma: A Case Report

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*The authors report a rare case of persistent hyperinsulinemic hypoglycemia of infancy (PHHI) with congenital neuroblastoma without feature(s) of Beckwith-Wiedemann syndrome. A term newborn with a birth weight of 3,900g developed hypoglycemia one hour after birth and required up to 20 mg/kg/min of intravenous glucose infusion to maintain euglycemia. Investigations during the critical period revealed an inappropriately high insulin level. An abdominal CT scan revealed a normal pancreas, right suprarenal mass, and liver nodules. A condition of stage 4S neuroblastoma was suspected and supported by an increased ratio of urine vanillylmandelic acid to creatinine. The bone marrow smear was normal. She underwent near total pancreatectomy at the age of 2 months. The suprarenal mass and liver nodules were not found during the operation or during repeated abdominal CT scans at 3 month of age. Spontaneous regression of neuroblastoma was suspected. The pathology of the pancreas was compatible with PHHI.*

***Keywords:*** *Persistent hyperinsulinemic hypoglycemia, Infancy, Congenital neuroblastoma*

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**Case Report**

A term female newborn was born after an uneventful pregnancy without history of maternal diabetes. Her birth weight was 3,900g. Her Apgar scores at 1 and 5 minutes were 8 and 9, respectively. Her blood glucose level at one hour after birth was 30 mg/dL. She required up to 20 mg/kg/min of intravenous glucose infusion to maintain euglycemia. Physical examination showed a large abdominal for gestational age newborn with mild hepatomegaly. The rest of the physical examination was normal.

Investigations during the critical period showed inappropriately high insulin levels: insulin (I), 49 mU/L; blood sugar (BS), 6 mg/dL; I/BS ratio, 8.1 with negative urinary ketone; and other hormonal levels were normal. An abdominal CT scan revealed normal appearance of the pancreas, an 8 mm right suprarenal mass, and an enlarged liver with heterogeneous attenuation at posterior segment of the right lobe (Fig. 1).

A condition of stage 4S neuroblastoma was suspected. This was further supported by an increased ratio of urine vanillylmandelic acid (VMA) to creatinine, which was 26.3 mg/g Cr (Normal < 18.8 mg/g Cr). The bone marrow smear, complete blood count, and liver panels were normal. She was treated by hydrocortisone, octreotide, and total parenteral nutrition, which were complicated by three episodes of *Staphylococcus aureus* sepsis. She depended on glucose infusions despite receiving medication. Subsequently, she underwent a near total pancreatectomy at the age of 2 months. Suprarenal mass and liver metastases were not found during the operation or on a repeated abdominal CT scan at the age of 3 months (Fig. 2). Pathology of the pancreas revealed a diffuse hyperplasia of islet cells forming a ductuloinsular complex with giant and bizarre nuclei, which was compatible with PHHI (Fig. 3A-B). On immunocytochemistry,

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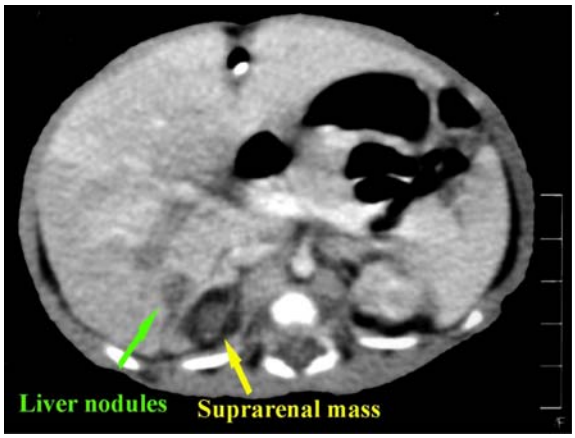


**Fig. 1** Abdominal CT scan showed an 8 mm right suprarenal mass and an enlarged liver with heterogeneous attenuation at the posterior segment of liver, consistent with neuroblastoma with liver metastasis

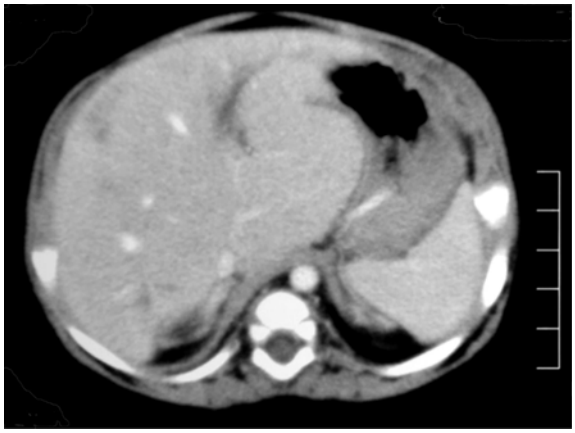

**Fig. 2** A repeated abdominal CT scan at the age of 3 months revealed no suprarenal mass or liver metastasis

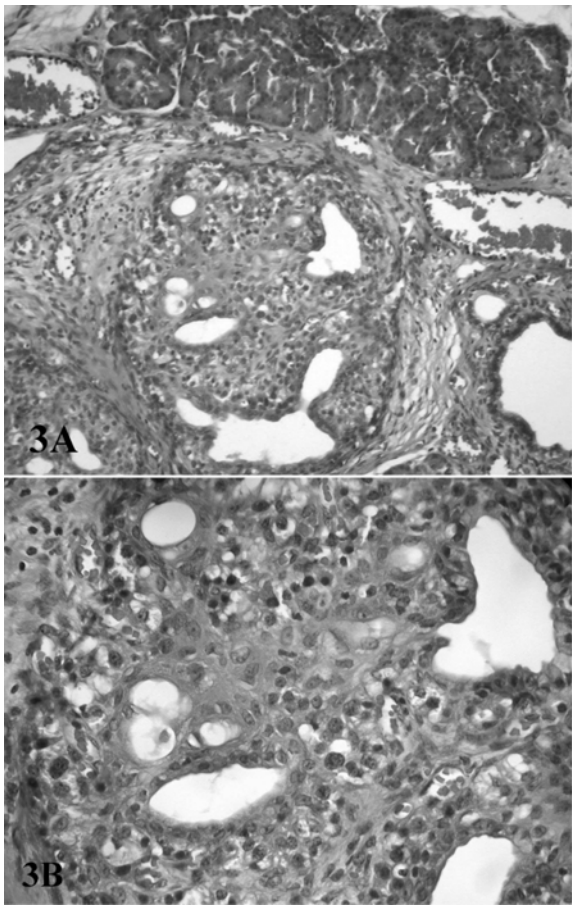


**Fig 3A-B** Diffuse islet cell hyperplasia forming ductuloinsular complexes with giant and bizarre nuclei

hypertrophic islet cells were positive for insulin staining (Fig. 3C).

After the operation, she continued to have hypoglycemia despite a decreased level of insulin, and required nifedipine and hydrochlorothiazide to improve glycemic control.

## Discussion

This case presented the classic features of PHHI: intractable nonketotic hypoglycemia with inappropriately high insulin level[1,2]. PHHI has been known to be associated with Beckwith-Wiedemann syndrome (BWS)[3,4]. Classically, children with BWS are identified at birth by macroglossia, overgrowth, and abdominal defect. Additionally, they may have some or all of the following features: hypoglycemia, hemihypertrophy, ear anomalies, midface hypoplasia, nevus flammeus, cardiomegaly, enlarged placenta, long umbilical cord, and/or polyhydramnios. Diagnosis of BWS during the neonatal period requires three primary criteria or two primary criteria plus one or more other criteria[5]. Patients with BWS have increased risk of embryonal cancers of infancy and childhood, especially in those who have hemihypertrophy[6]. The most common tumors include Wilms' tumor, adrenocorticol carcinoma, and hepatoblastoma; however, neuroblastoma has been less commonly reported. The relative risk (RR) of Wilms' tumor in BWS was 816 (95% confidence interval [CI], 359-1,156) and hepatoblastoma 2,280 (95% CI, 928-11,656), whereas the RR of neuroblastoma in BWS was 197 (95% CI, 22-711)[6].

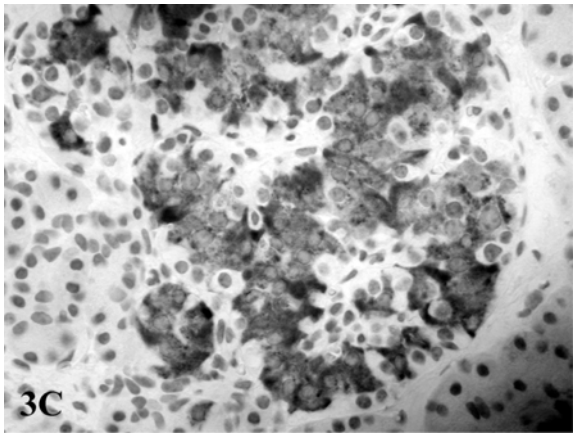


**Fig 3C** Hypertrophic insulin-producing cells on immunocytochemistry staining of insulin

Thus, the presented patient does not meet the criteria for diagnosis of BWS, which indicates that congenital neuroblastoma coexists with PHHI. The diagnosis of neuroblastoma stage 4S disease in the presented case was based on radiographic appearance: suprarenal mass, hepatomegaly with liver nodules, and an increased urinary VMA. Fifty percent of patients with congenital neuroblastoma were classified with stage 4S disease, which usually has a high rate of spontaneous regression and a good survival rate[7-9]. The tumors usually regress spontaneously, especially in infants under six months of age[7-9]. The time of spontaneous regression with complete remission has been reported in the range of 5-7 months[10]. Neither suprarenal mass nor liver metastasis was found in a repeated abdominal CT scan at the age of three months, which indicates very early spontaneous regression of neuroblastoma in the presented patient. The association of PHHI and neuroblastoma had been defined as a rare type of complex neurocristopathy, neoplasia of tissue originating in the neural crest[11]. The triad of congenital neuroblastoma, PHHI, and glomerulocystic disease of newborn has also been previously reported[12].

To maintain euglycemia, the presented patient required a high rate of glucose infusion and a combination of medication, which included octreotide and hydrocortisone. However, diazoxide, which was the drug of choice for initial treatment[1,2,13], was not available. Because of unresponsiveness to medication, the 95% pancreatectomy was performed. The patient still had hypoglycemia after the pancreatectomy, indicating the presence of diffuse lesions in the rest of the pancreas[13]. However, the hypoglycemia was less severe than during the preoperative period and can be controlled by nifedipine and hydrochlorothiazide. She is at risk of developing exocrine pancreatic enzyme deficiency and diabetes mellitus later in life[13].

Nesidioblastosis, which is defined as B cells budding from the pancreatic duct, was observed in the pancreases of patients with PHHI; however, it can also be found in those of normoglycemic neonates. Therefore, the presence of nesidioblastosis is not a pathognomonic sign or a characteristic of PHHI. In PHHI, the histology of the pancreas revealed two types of morphological B cell, a focal form and a diffuse form[14-16]. In the presented case, diffuse islet cell hyperplasia with bizarre nuclei and ductuloinsular complex, which refer to an endocrine cell cluster intimately associated with a ductule[17], were observed.

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## *รายงานผู้ป่วย persistent hyperinsulinemic hypoglycemia of infancy ร่วมกับ congenital neuroblastoma*

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*รายงานผู้ป่วย persistent hyperinsulinemic hypoglycemia of infancy (PHHI) ร่วมกับ congenital neuroblastoma ซึ่งเป็นภาวะที่พบได้น้อย โดยผู้ป่วยไม่มีลักษณะของ Beckwith-Wiedemann syndrome ทารกน้ำหนักแรกเกิด 3,900 กรัม มีภาวะน้ำตาลต่ำรุนแรงเมื่ออายุ 1 ชั่วโมงหลังคลอด และต้องการน้ำตาลทางหลอดเลือด 20 มก./กก./นาที การตรวจทางห้องปฏิบัติการพบระดับ insulin สูง ผลเอกซเรย์คอมพิวเตอร์ช่องท้องพบก้อนที่เหนือไตขวาและตับ ตับอ่อนปกติ ผู้ป่วยได้รับการวินิจฉัยเป็น neuroblastoma ระดับ 4S จากผลเอกซเรย์และระดับ vanillymandelic acid ต่อ creatinine ในปัสสาวะสูง ผลการตรวจไขกระดูกปกติ ผู้ป่วยได้รับการรักษาโดยผ่าตัด subtotal pancreatectomy เมื่ออายุ 2 เดือน ขณะผ่าตัดและเอกซเรย์คอมพิวเตอร์ช่องท้องเมื่ออายุ 3 เดือน ไม่พบก้อนที่เหนือไตหรือตับ ซึ่งเข้าได้กับ spontaneous regression ของ neuroblastoma ผลทางพยาธิวิทยาของตับอ่อนเข้าได้กับ PHHI*