

Hypoglycemia and jaundice in newborns with pituitary stalk interruption syndrome

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Abstract

Pituitary stalk interruption syndrome (PSIS) is a rare disease associated with either isolated growth hormone deficiency (GHD) or combined pituitary hormone deficiency (CPHD). In older children and adults, most patients experience short stature or hypogonadism. Neonatal PSIS is extremely rare and is difficult to recognize due to absence of dwarfism. However, when this condition occurs in newborns, it is often life-threatening. Here, we collected patients with neonatal PSIS to clarify its characteristics to improve its early diagnosis.

The patients included in this study were treated at the pediatric endocrine department of Shandong Provincial Hospital from January 2017 to July 2020. We obtained the clinical characteristics, endocrine hormone levels, pituitary magnetic resonance imaging (MRI) and further genetic data for all the patients. Hormone therapy was first given at the time of diagnosis, and the patients received regular follow-up.

Three neonatal patients were identified in our clinic. The characteristics of these patients included hypoglycemia and jaundice, as well as CPHD, which included features such as micropenis and hypothyroidism. Genetic etiology was still hard to discover. All the patients responded well to alternative therapy, and the longest follow-up period was 3 years. Regular replacement ensures good prognosis.

Sustained hypoglycemia and jaundice in newborns, indicate the presentation of PSIS. Early recognition is of great importance to avoid a life-threatening crisis.

Abbreviations: ACTH = adrenocorticotropic hormone, BS = blood sugar, BSEP = bile salt export pump, COR = cortisol, CPHD = combined pituitary hormone deficiency, E2 = estrogen, FSH = follicle-stimulating hormone, GH = growth hormone, GHD = growth hormone deficiency, HH = hypogonadotropic hypogonadism, LH = luteinizing hormone, MRI = magnetic resonance imaging, PSIS = pituitary stalk interruption syndrome, T = testosterone, TSH = thyroid stimulating hormone.

Keywords: combined pituitary hormone deficiency, hypoglycemia, jaundice, newborn, pituitary stalk interruption syndrome

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1. Introduction

Pituitary stalk interruption syndrome (PSIS) is a rare congenital abnormality of the pituitary that is responsible for anterior pituitary deficiency and was first reported by Fujisawa in 1987.^[1] PSIS has an estimated incidence of approximately 1 in 200000.^[2] Neonatal PSIS patients are rarely reported.^[2] PSIS is associated with either isolated growth hormone deficiency (GHD) or combined pituitary hormone deficiency (CPHD),^[3] which is a hormone deficiency that affects at least 2 anterior pituitary hormone lineages. The clinical manifestations associated with endocrine hormone deficiency, differently depending on the age of onset. In older children and adults, most patients experience short stature or hypogonadism.^[4] Neonatal PSIS is extremely rare and is difficult to diagnose due to absence of dwarfism, but delayed diagnosis could lead to life crisis.^[4–6] So, early identification of the clinical characteristics is of great importance for clinic. Here, we report 3 cases of neonatal PSIS in our department.

2. Methods

2.1. Patient population

The patients included in this study were treated at the pediatric endocrine department of Shandong Provincial Hospital from January 2017 to July 2020. We obtained the clinical characteristics, endocrine hormone levels, and pituitary magnetic reso-

nance imaging (MRI) and genetic data of all the patients. The clinic data for these patients were obtained by retrospective review. This study was approved by the Ethics Committee of the Shandong Provincial Hospital (NO. 2018–031). Informed consent for publication was obtained from all the patients' guardians.

2.2. Personal history and physical examinations

We obtained the personal history of these newborns from parents and medical records from local hospitals; the obtained data included:

1. perinatal characteristics, such as delivery mode, gestational age, birth weight, Apgar scores, and other anoxic history; and
2. clinical manifestations, including hypoglycemia, jaundice, convulsion, and so on (Table 1).

Physical examinations included measurement of the length, weight, and head circumference. Systematic physical examinations were performed to collect the clinical malformations, such as micropenis, cryptorchidism, and midline abnormalities.

2.3. Biochemical measurements

The liver function and biochemical indices included blood sugar (BS), serum sodium, serum potassium, total bilirubin, direct bilirubin, indirect bilirubin, gamma-glutamyltransferase, total serum bile acid, and blood ammonia. Endocrine hormone levels were measured, including the thyroid stimulating hormone (TSH), free triiodothyronine, free thyroxine, adrenocorticotropic hormone (ACTH), cortisol (COR), growth hormone (GH), insulin-like growth factor-1, follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), and estrogen (E2). Hypoglycemia was defined as BS below 2.2 mmol/L.^[7] Hyperbilirubinemia

was defined as serum bilirubin higher than the normal reference range. TSH deficiency was defined as low serum T4 (<11.5 pmol/L) associated with low or normal serum TSH (<0.64 μ IU/ml). For the diagnosis of ACTH deficiency, we used serum COR levels measured at 8–9 AM. Complete ACTH deficiency was defined as a serum COR level less than 2.2 g/dL (60.8 nmol/L) associated with low ACTH.^[3] Basal COR concentration of 2.2~8.0 g/dL (60.8 nmol/L–221.1 nmol/L) and low ACTH suggested partial ACTH deficiency.^[3] GHD was diagnosed without formal GH provocative testing in a newborn with hypoglycemia who did not attain a serum GH concentration above 5 μ g/L and had deficiency of at least one additional pituitary hormone.^[8] Basal LH less than 0.7 IU/L indicated idiopathic hypogonadotropic hypogonadism (HH), and LH \geq 0.7 IU/L indicated delayed pubertal development or partial idiopathic HH. The basal FSH less than 1.2 IU/L confirmed HH.^[9] In patients with basal FSH of at least 1.2 IU/L, the peak LH < 2.8 mIU/ml and FSH < 3.7 mIU/ml in the sex hormone stimulation test before puberty, indicating HH.^[10] LH < 5.8 mIU/ml and FSH < 4.6 mIU/ml after puberty are significant for the diagnosis of male HH.^[9]

2.4. Pituitary and brain MRI

MRI was performed with sagittal, coronal, and axial T1- and T2-weighted sequences. All the MRI results were reviewed by the same investigator who was unaware of the corresponding clinical or endocrine data. The anterior pituitary height was measured and compared to normal values for the age of the patient. The normal height of pituitary gland was 3.5 ± 0.5 mm in children under 1 year old.^[11] The pituitary stalk was considered to be interrupted when not visible over its entire length and was considered thin when its size was below 1 mm with a very spindly appearance.^[4,5] The pituitary stalk was considered absent when it was not visible at all.

Table 1
Clinical characteristics of the patients with pituitary stalk interruption syndrome.

	Patient 1	Patient 2	Patient 3
History			
Gestational, w	40.6	37.5	39
Mode of delivery	Caesarean section	Caesarean section	Caesarean section
Reasons for caesarean section	reduced foetal heart rate	amniotic fluid III pollution, oligohydramnios, umbilical cord around neck and torsion for 50 circles	oligohydramnios
Apgar (1 min/5 min)	8/9	8/10	8/9
Birth weight, kg	3.5	2.45	2.4
Clinic			
Gender	Male	Male	Female
Age at diagnosis, d	22	32	33
Weight at diagnosis, kg	3.6	3.4	3.17
Hypoglycaemia	Yes	Yes	Yes
Convulsions	Yes	No	Yes
Jaundice	Yes	Yes	Yes
Micropenis	Yes	Yes	–
Microorchidia	Yes	Yes	–
Hyponatremia	Yes	No	No
Associated malformations	Patent ductus arteriosus	Congenital microphthalmia	No
MRI			
Pituitary stalk	Not visible	Not visible	Not visible
Anterior pituitary	Not visible	Hypoplastic	Hypoplastic
Posterior pituitary	Not visible	Ectopic	Not visible
Molecular analysis	No variation	NHS	No variation

Kg = kilogram.

Table 2**Biochemical index of the patients with pituitary stalk interruption syndrome at the early onset.**

Parameters	Normal	Patient 1	Patient 2	Patient 3
Glucose, when born, mmol/L	3.9–6.3	0.4	2.1	0.9
Glucose, mmol/L	3.9–6.3	2.07	2.65	2.71
TBIL, $\mu\text{mol/L}$	3.5–23.5	123.2	126	141
DBIL, $\mu\text{mol/L}$	0.5–6.5	47.1	37.8	18.5
IBIL, $\mu\text{mol/L}$	1–17	76.1	87.8	123
GGT, U/L	7–45	547	174	245
TBA, $\mu\text{mol/L}$	0–12	110	67.1	58.5
Serum sodium, mmol/L	135–145	129	137	135.8
Serum potassium, mmol/L	3.5–5.5	4.90	1.76	5.25
TSH, $\mu\text{IU/ml}$	0.64–6.27	0.008	7.67	9.81
FT3, pmol/L	3.5–6.5	2.99	3.65	4.35
FT4, pmol/L	11.5–22.7	17.0	9.76	10.4
ACTH, pg/ml	7.2–63.3	1.65	31.3	19.9
COR, pg/ml	172–497	42.4	34.3	16.9
GH, ng/ml	0.09–6.29	<0.03	6.18	4.45
IGF-1, ng/ml	–	<25	Not done	25.7
FSH, mIU/ml	1.5–12.4	0.11	0.15	0.20
LH, mIU/ml	1.7–8.6	<0.10	<0.10	<0.10
Testosterone, mIU/ml	0.12–0.21	<0.03	<0.03	<0.50
E2, pg/ml	12.4–233	Not done	Not done	< 5
Blood ammonia, $\mu\text{mol/L}$	3–47	50.0	70.0	67

ACTH = adrenocorticotropic hormone, COR = cortisol, DBIL = direct bilirubin, E2 = estrogen, FSH = follicle-stimulating hormone, FT3 = free triiodothyronine, FT4 = free thyroxine, GGT = gamma-glutamyltransferase, GH = growth hormone, IBIL = indirect bilirubin, IGF-1 = insulin-like growth factor-1, LH = luteinizing hormone, TBA = total serum bile acid, TBIL = total bilirubin, TSH = thyroid stimulating hormone.

2.5. Follow-up

When the diagnosis of PSIS was established, hormone replacement therapy was given at the first time. Each patient was followed up every 3 months, continuing until the present time. Height and weight measurements were obtained at each visit. Biochemical measurements were also performed. Evaluation of anterior pituitary function was repeated during follow-up visits.

3. Results

3.1. Patient 1

3.1.1. Clinical characteristics. A Chinese newborn was experiencing failure to thrive. He was sent to the hospital for intermittent cyanosis and convulsions on the 2nd day after birth and was diagnosed with neonatal hypoglycemia, brain hematoma, brain damage, pneumonia, and suppurative meningitis. Continuous positive airway pressure was used during his second hospitalization, and a diagnosis of multiple organ dysfunction syndrome was rendered. Hyperbilirubinemia, hypothyroidism, electrolyte disorder, such as hyponatremia, hypoglycemia and metabolic acidosis were also found. Supplements to improve electrolyte disorders, ceftizoxime and meropenem to prevent infection, and euthyrox were administered. However, hypoglycemia and hyponatremia were still difficult to be corrected, which were thought to be the main reasons for the convulsions. He struggled to suck milk and to maintain oxygen saturation and was sent to our hospital with a resuscitation airbag and stomach tube. His weight was only 3.6 kg at 22 days old. Physical examination showed systemic mild jaundice, with no special facial features. Moist rales were heard in both lungs, and a micropenis was observed that was shorter than 0.5 cm. His sucking reflex was also reduced.

3.1.2. Endocrine hormone testing and additional examination. Endocrine hormone testing, genetic analysis, and MRI scan of the patient were shown in Table 2, Table 1, and Figure 1,

respectively. Abdominal ultrasound showed bilateral testicular sheath fluid and bilateral testicular volume were low.

3.1.3. Management and outcome. In addition to symptomatic treatments, such as antibiotics, hormone supplements, including hydrocortisone (12.5 mg/d, 55.3 mg/m²/d), 9 α -flucortisone (0.1 mg/d), and euthyrox (2.5 $\mu\text{g/d}$, 7 $\mu\text{g/kg/d}$), were also immediately administered. He could suck milk by himself with no more convulsions a few days later, and an obvious response was observed with improvement in electrolyte disorder in 7 days. The jaundice disappeared 3 months later, but there was still intermittent hypoglycemia. GH (0.4 U/d, 0.14 u/kg/d) was used when he was 30 days old, and his glucose levels finally increased to within normal range. Later, we tried to use human chorionic gonadotrophin to improve the micropenis when he was 4 months and 15 days old, and after 10 injections, his T levels increased from < 0.03 ng/mL to 1.62 ng/mL, and the penis length went from less than 0.5 cm to 1 cm. Therefore, clinical improvement had been completely achieved. Hypoglycemia, hyponatremia, and jaundice did not recur during follow-up (Table 3). When 2.9 years old, he was 104 cm (>P97) with normal thyroid and COR levels.

3.2. Patient 2

3.2.1. Clinical characteristics. Another Chinese newborn came to the hospital for hypoglycemia. He was hospitalized for 32 days from the 2nd day after birth, with neonatal hypoglycemia, pneumonia, and jaundice in the local hospital. His lowest blood glucose reading was 2.1 mmol/L.

Physical examination showed mild jaundice and the anterior fontanelle was 3.0 \times 3.0 cm. In addition, he presented with ocular hypertelorism with congenital microphthalmia, low ear position, right temporal depression, and small penis shorter than 0.5 cm.

3.2.2. Endocrine hormone testing and additional examination. Endocrine hormone testing, genetic analysis, and MRI scan

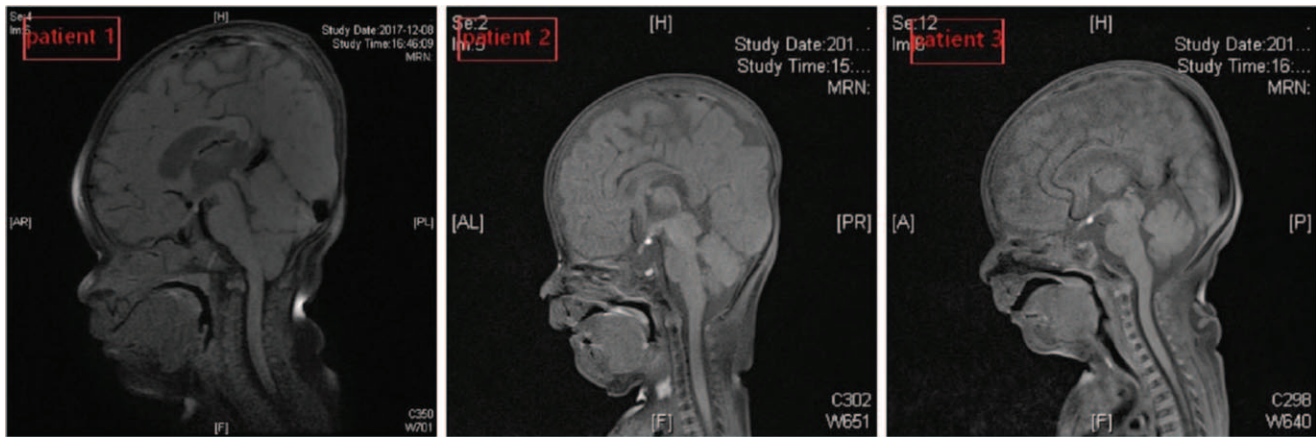


Figure 1. Magnetic resonance imaging (MRI) scan of the pituitary in our patients. Patient 1: The sagittal image showed that no pituitary was found in the pituitary fossa, the pituitary stalk was not seen, and the hyperintense signal disappeared in the posterior pituitary. Patient 2: The sagittal image showed that the anterior pituitary was slightly lower, the pituitary stalk could not be seen clearly, and posterior pituitary ectopia as well as bilateral lateral ventricle widening. Patient 3: The sagittal image showed that the anterior pituitary was slightly lower, the pituitary stalk was not seen, and the hyperintense signal disappeared in the posterior pituitary.

of the patient were shown in Table 2, Table 1, and Figure 1, respectively. We found a mutation in the *NHS* gene, which was closely associated with microphthalmia.

3.2.3. Management and outcome. Typical hypoglycemia was observed with CPHD, including decreased COR, cryptorchidism and hypothyroidism, confirming a diagnosis of PSIS, which was consistent with the MRI. Hormone supplementation immediately followed the diagnosis, including hydrocortisone (5 mg/d, 22.8 mg/m²/d) and euthyrox (6.25 µg/d, 1.91 µg/kg/d). The child responded well, and the hypoglycemia improved. The jaundice was also significantly decreased one month later. During follow-up, the boy was hospitalized twice with recurrent hypoglycemia and infection. He was finally treated with GH (1.5 U/d, 0.14 u/kg/d) for short stature, he was 93 cm (P50) when 2.5 years old. (Table 3)

3.3. Patient 3

3.3.1. Clinical characteristics. The third Chinese newborn was hospitalized in neonatal intensive care unit for poor reaction and

convulsions only 17 hours after birth in the local hospital, diagnosed with sepsis, hypoglycemia, hypoglycemic encephalopathy, blood coagulation disorder, and neonatal jaundice. Her blood glucose was 0.9 mmol/L at that time. Ten days later, she was hospitalized again in our department for hypoglycemia. No abnormalities were identified during physical examination, except for low auricular position and jaundice.

3.3.2. Endocrine hormone testing and additional examination. Endocrine hormone testing, genetic analysis, and MRI scan of the patient were shown in Table 2, Table 1, and Figure 1, respectively.

3.3.3. Management and outcome. After the diagnosis of PSIS and application of hydrocortisone (2 mg/d, 9.52 mg/kg m²) and euthyrox (12.5 µg/d, 3.94 µg/kg/d), the hypoglycemia and jaundice had resolved soon. During follow up, her hormone levels were stable (Table 3). She was also treated with GH (0.5 U/d, 0.158 u/kg/d), and her insulin-like growth factor-1 level

Table 3

Biochemical index of the patients with pituitary stalk interruption syndrome in the last follow-up.

Parameters	Normal	Patient 1	Patient 2	Patient 3
Glucose, mmol/L	3.9–6.3	4.98	4.99	5.24
TBIL, µmol/L	3.5–23.5	8.64	8.14	14.2
DBIL, µmol/L	0.5–6.5	1.66	1.50	2.00
IBIL, µmol/L	1–17	6.98	6.64	12.2
GGT, U/L	7–45	9.00	11.0	12.0
TBA, µmol/L	0–12	1.40	1.54	1.59
Serum sodium, mmol/L	135–145	137	134	139
Serum potassium, mmol/L	3.5–5.5	4.54	4.40	4.30
TSH, µIU/ml	0.64–6.27	<0.005	0.016	0.120
FT3, pmol/L	3.5–6.5	4.94	5.17	4.82
FT4, pmol/L	11.5–22.7	12.4	20.5	12.5
ACTH, pmol/L	7.2–63.3	2.97	3.46	3.32
Cor, nmol/L	172–497	335	316	378
IGF-1, ng/ml	–	248	172	155
FSH, mIU/ml	1.5–12.4	<0.10	Not done	Not done
LH, mIU/ml	1.7–8.6	<0.10	Not done	Not done
Testosterone, ng/mL	0.12–0.21	0.04	Not done	/

ACTH = adrenocorticotropic hormone, COR = cortisol, DBIL = direct bilirubin, FSH = follicle-stimulating hormone, FT3 = free triiodothyronine, FT4 = free thyroxine, GGT = gamma-glutamyltransferase, IBIL = indirect bilirubin, IGF-1 = insulin-like growth factor-1, LH = luteinizing hormone, TBA = total serum bile acid, TBIL = total bilirubin, TSH = thyroid stimulating hormone.

improved correspondingly. She measured 74 cm (<P3) when she was 1.5 years old, without enough caught up.

4. Discussion

The pituitary gland regulates growth, reproduction, stress response, and metabolism by secreting hormones in response to signals from the hypothalamus. The clinical consequences of pituitary hormone deficiency are diverse, including short stature, hypothyroidism, hypercortisolism, hypogonadism, and so on.^[5,12,13] There are some late-onset reports of PSIS,^[5,14] while PSIS manifested in newborns is rarely reported. However, the manifestations of neonatal PSIS are complex and serious, even life-threatening.^[3–6] The diagnosis is often delayed in newborns, likely due to its low prevalence.^[15,16] Therefore, it is very valuable to identify the clinic characteristics of PSIS in newborns. From our 3 patients, we observed that persistent hypoglycemia and jaundice were the clinical characteristics easy to be detected, sometimes accompanied by hyponatremia and even convulsions, which provide clues of neonatal PSIS.

The mechanisms of hypoglycemia include deficiencies in glucose-inducing hormones, such as GH, adrenocortical hormone, and thyroxine. They play roles in elevating BS by liver glycogen gluconeogenesis, fatty tissue lipolysis, fatty acid oxidation, and so on. Children with PSIS cannot produce enough glucose-inducing hormones, ultimately resulting in hypoglycemia. The degree of hypoglycemia depends on the type and extent of hormone deficiency in the anterior pituitary. Prolonged jaundice in PSIS remains uncertain. Even isolated primary hypothyroidism typically is associated with unconjugated hyperbilirubinemia,^[17] cholestasis is also recognized as the primary cause of the jaundice.^[18] Analysis of data strongly correlates the presence of cholestasis with a profoundly collapsed plasma COR level.^[16] In 9 children with cholestasis due to hypopituitarism, liver biopsy analyses revealed decreased expression of canalicular transport proteins (namely, bile salt export pump, multidrug resistance protein 3, and multidrug resistance-associated protein 2) that are involved in bile secretion.^[19] Accordingly, glucocorticoids have been shown to regulate transcription of genes encoding bile salt export pump and multidrug resistance protein 3 through different receptors (glucocorticoid receptor and farnesoid X receptor), either directly or through the transcription factor C-terminal binding protein.^[20] All the 3 patients presented with especially elevated total bilirubin, in particular total serum bile acid and gamma-glutamyltransferase. Therefore, we think that prolonged jaundice maybe caused by both reduced COR and hypothyroidism. The mechanisms of hyponatremia may be as follows: ACTH deficiency reduces the secretion of aldosterone and COR. Decreased aldosterone reduces kidney sodium retention. Reduction of COR, inadequate thyroid hormone which causes accumulation of adhesion proteins, and the unbalanced ACTH/antidiuretic hormone result in water retention and dilutive hyponatremia.^[21,22]

Children with PSIS may present with either isolated pituitary hormone deficiency or CPHD, and the younger the onset age, the greater possibility of developing CPHD.^[4,15] Wang et al found that the prevalence of deficiency was 100%, 97.2%, 88.2%, and 70.3%, respectively, for GH, gonadotrophin, corticotrophin, and thyrotrophin.^[23] All 3 of our patients (3/3) manifested hypothyroidism, hypogonadism and hypoadrenocorticism. Only one patient (1/3) presented GHD at the beginning, while the other

2 patients (2/3) developed GHD during follow-up. Based on their reduced levels of central endocrine hormones, all 3 patients had CPHD. It should be paid attention that, other more hormone deficiency will occur during the follow-up.^[15]

To date, PSIS is considered a part of the broad spectrum of holoprosencephaly, and this syndrome belongs to the spectrum of midline abnormalities and is often associated with other midline extra-pituitary malformations, such as septo-optic dysplasia, central cleft lip and palate, and omphalocele.^[5,24] In our patients, malformations such as micropenis (2/2), microorchidia (2/2), and congenital microphthalmia (1/3) were observed. PSIS diagnosed during the neonatal period has a particularly severe hormonal and radiological phenotype.^[4] Findings in MRI include interrupted or thin pituitary stalk, absent or ectopic posterior pituitary, and anterior pituitary hypoplasia or aplasia.^[25–27]

Hormone therapy is effective. Growth responds especially well to GH (0.1–0.2 U/kg/d) therapy, in particular during the first year.^[28,29] The dose of recombinant human GH was 0.16 to 0.24 mg/kg/qw.^[3] Hydrocortisone was 8 to 12 mg/m²/d, and levothyroxine dose is similar to that used in congenital primary hypothyroidism.^[3] Micropump infusion of gonadorelin can be used in the treatment of hypogonadism in patients with PSIS.^[30,31] Induction of secondary characteristics by hormone replacement can be initiated with monthly T injection in men aged 12 to 13 years and oral E2 in women aged 11 to 12 years and then followed with E2 and progesterone. As soon as a PSIS diagnosis was established, we administered supplements in the order of hydrocortisone, thyroxine, GH, and sex hormones during follow-up. All the patients rapidly improved and grew well.

The limitation of the study is that cases enrolled are few due to the low prevalence. Despite the fact that PSIS is a rare disorder, early diagnosis is possible based on newborn hypoglycemia and prolonged jaundice. Furthermore, detection of the endocrine hormone levels and MRI image can be helpful. Early diagnosis leads to early supplementation. The appropriate hormone replacement therapy helps to prevent neonatal PSIS patients from suffering from life crisis and developing multisystem damage.

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