A congenital hypopituitarism infant presented with unexplained hypoglycemia
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Abstract

Congenital hypopituitarism may present with non-specific symptoms, so it is difficult to diagnose in newborn infants. If hypopituitarism cannot be recognized, recurrent hypoglycemia can occur, leading to permanent brain damage. At 14 hours of age, a 2.9 kg, female infant, born at 35 weeks of gestation, presented with respiratory distress caused by hypoglycemia. She had no risk factor to develop hypoglycemia, therefore, evaluation of her pituitary function was performed. The investigations revealed combined pituitary hormone deficiencies. This reported case illustrates unexplained hypoglycemia as a clue of congenital hypopituitarism.

Key words: Unexplained hypoglycemia, Congenital hypopituitarism, Septo-optic dysplasia,
Introduction

A female infant was born at 35 weeks of gestation to a 21-year-old, Gravida 2 Para 1, woman who had inadequate prenatal care. Her mother’s antenatal serology results were negative, and her group B Streptococcus (GBS) status was unknown. Her oral glucose tolerance test was normal. Pregnancy was complicated by premature labor pain. The infant’s mother did not receive intrapartum prophylaxis for GBS. She was delivered by spontaneous vaginal delivery with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively. She stayed with her mother at the postpartum unit.

At the age of 14 hours, she developed respiratory distress and turned blue. Physical examination revealed a respiratory rate of 60 - 70 breaths per minute; however, temperature, heart rate and blood pressure were within normal limits with oxygen saturation of 92% in room air. She weighed 2,984 g (75th percentile) with a length of 48 cm (75th percentile), and her head circumference was 33 cm (75th percentile). She had tachypnea, but no retraction, and with normal breath sound. No midline craniofacial was defected. Other examinations were unremarkable.

Complete blood count (CBC) showed a white blood cell (WBC) count of 9.7 x 10^9/µL (40% neutrophils, 52% lymphocytes and 8% monocytes), a hemoglobin level of 19.7 g/dL, and a platelet count of 181 x 10^9/µL. C-reactive protein (CRP) was 2.1 mg/L (normal < 5).

However, blood glucose was extremely low at 7.5 mg/dL. One intravenous bolus dose of 10% dextrose was given and then dextrose infusion was continued with a glucose infusion rate of 8 mg/kg/min. She was also put in an O₂ box and treated empirically with ampicillin and gentamicin.

The respiratory distress was resolved after plasma glucose was normalized. Twelve hours later, oxygen therapy was discontinued. She was started on bottle feeding and weaned off the dextrose infusion. Her plasma glucose was monitored, and all the results were more than 60 mg/dL.

Blood culture was negative, so antibiotic therapy was discontinued.

At 5 days of age, her thyroid function was checked and revealed a suboptimal serum free thyroxine (T4) level of 0.8 ng/dL (normal 1.6 - 3.8) and a thyroid-stimulating hormone (TSH) level of 3.8 mU/L (normal 1.7 - 9.1). She was, therefore, suspected to have secondary hypothyroidism. The combination of unexplained hypoglycemia and central hypothyroidism were clues for further evaluation of pituitary function.

After fasting for 5 hours, blood glucose slightly decreased to 41 mg/dL. At the same time, critical blood samples were collected, and the results revealed an abnormally low serum cortisol of 1.0 mcg/dL (normal > 18), negative serum ketone, and a normal serum insulin level of < 0.2 mIU/L, leuteinizing hormone (LH) < 0.1 mIU/mL, follicle-stimulating hormone (FSH) 0.24 mIU/mL. An adrenocorticotropic hormone (ACTH) stimulation test was done and showed abnormally low serum cortisol levels at 7.9 and 7.7 mcg/dL at 30 and 60 minutes, respectively (normal range > 18 mcg/dL). Unfortunately, her blood sample for growth hormone (GH) was missing. Magnetic resonance imaging (MRI) of the brain showed opened lip schizencephaly, partial corpus callosum dysgenesis, absent septum pellucidum, with hypoplasia of both optic nerves and hypoplasia of pituitary gland representing septo-optic dysplasia (SOD) (Figure 1). Ophthalmological examination showed bilateral optic disc hypoplasia. She was diagnosed with congenital hypopituitarism with SOD. Genetic tests were not performed due to lack of available resources.
The infant received hormone replacement therapy with hydrocortisone 10 mcg/m²/day and levothyroxine 10 mcg/kg/day.

**Discussion**

Patients with hypopituitarism may present with signs and symptoms of various severity that depend on the etiology, age onset, and hormone deficiency.

In the neonatal period, congenital hypopituitarism may present with non-specific symptoms including hypoglycemia, lethargy, apnea, seizures, and prolonged jaundice that could be related to neonatal complications, with or without midline craniofacial defect or genital abnormalities. Therefore, it is difficult to diagnose congenital hypopituitarism in the newborn. Postnatal complications such as hypoglycemia, hyponatremia and recurrent sepsis were found in 52% of patients with hypopituitarism, however only 23% were diagnosed with hypopituitarism in the neonatal period.
Hypoglycemia is the most common feature of congenital hypopituitarism that is associated with ACTH deficiency, leading to cortisol deficiency, or growth hormone deficiency. If hypopituitarism cannot be recognized, infants have recurrent hypoglycemia resulting in permanent brain damage. Infants who typically received basic neonatal care, have hypoglycemia after the first 4 to 5 postnatal days, or develop hypoglycemia with no risk factor such as intrauterine growth retardation, or infant of a diabetic mother, should be evaluated for hypopituitarism.

Usually newborns who have non-specific symptoms may have to be evaluated to exclude sepsis. If they have non-specific symptoms with additional clues such as midline craniofacial or central nervous system defect, unexplained hypotension, nystagmus, optic nerve hypoplasia, hypoplastic genitalia in boys, prolonged jaundice, polyuria, hypematremia, unexplained hypoglycemia, low total thyroxine and inappropriately normal TSH or abnormal MRI brain scan including ectopic posterior pituitary or interrupted pituitary stalk, the newborns should have pituitary function investigations.

Clinical manifestations of congenital hypopituitarism can be an isolated growth hormone deficiency or combined pituitary hormone deficiencies. For the diagnosis, a full endocrinological evaluation must be done, including serum growth hormone, thyroid function, and adrenocortical status. LH, FSH, and/or testosterone levels should be evaluated as well in patients less than 6 months of age.

In neonates with suspected or diagnosed hypopituitarism, it is important to obtain an MRI of the brain and pituitary, as there is a correlation between the neuro-radiological abnormalities and the severity and evolution of the endocrinopathy.

Congenital hypopituitarism can associated with birth trauma, birth asphyxia and midline craniofacial defect. The most common craniofacial defect is SOD. The incidence of SOD is 1 in 10,000 newborns. There are three criteria to diagnose SOD. First, patients have underdeveloped optic nerves or optic nerve hypoplasia (ONH). The second criterion is the presentation of midline forebrain defects such as agenesis of the corpus callosum and absent septum pellucidum. The last aspect, they have pituitary hypoplasia with variable hypopituitarism. It is important to note, however, there are only 30% of patients with SOD showing all criteria, and 66% have hypopituitarism, and 60% present an absent septum pellucidum. Cerebellar hypoplasia, schizencephaly and aplasia of fornix are abnormalities that can be found in patient with SOD.

The etiology of this order is unknown. It might be a combination of environmental factors and genetic factors such as gene HESX1, OTX2, SOX2 mutations.

The endocrine abnormalities seen in patients with SOD are of various degrees from partial pituitary insufficiency to panhypopituitarism. GH deficiency is the commonest endocrine defect at 70%. In patients with SOD, the incidence of central hypothyroidism, adrenocorticotropic hormone deficiency, and diabetes insipidus are 43%, 27% and 5% respectively. When they are adolescents, they may have either sexual precocity or failure to develop in puberty. Patients with SOD may have pituitary hormone deficiencies which evolve over time, so they require long term follow-up and treatment.

Most importantly, neonates diagnosed with congenital hypopituitarism require lifelong follow-up by a multidisciplinary team. They need to receive hormone replacement therapy, and physicians must monitor clinical signs and symptoms, and hormone levels. Because they might have other anomalies such as SOD, cerebellar hypoplasia and schizencephaly. Visual assessment and neurodevelopmental support by qualified specialists are essential. If these patients present with syndromic hypopituitarism, genetic testing and counseling should be offered.

It must be recognized that postnatal hypothyroidism and hypoglycemia can cause brain injury. The baby’s outcomes should be determined by the associated neurologic abnormalities.
Our patient developed unexplained hypoglycemia that was a non-specific symptom when she was 14 hours of age. Her random free T4 measurement was low and the TSH was inappropriately low. These were the critical clues to evaluate pituitary function. She had pituitary hormones testing by fasting and an ACTH stimulation test, this importantly, revealed combined pituitary hormone deficiencies. Using her MRI brain findings, her condition was associated with SOD and schizencephaly. Unfortunately genetic testing was not available at that time. She now receives hormone replacement with hydrocortisone and levothyroxine and has follow up appointments with our multidisciplinary team.

**Conclusion**

In newborns, it is difficult to diagnose hypopituitarism. When they develop nonspecific symptoms, such as tachypnea or lethargy, but with significant clues like unexplained hypoglycemia and central hypothyroidism, pediatricians should consider evaluating pituitary function. With additional alternative findings by the MRI, a clear diagnosis of hypopituitarism can be made, and relevant treatment and management can begin. In this way, the best possible outcome will follow for the patient.

**Potential conflicts of interest**

None.

**References**

บทคัดย่อ
ผู้ป่วยทารกแรกเกิดที่มีภาวะบกพร่องในการหลั่งฮอร์โมนจากต่อมใต้สมองแต่กำเนิดได้ส่งผลแต่กำเนิดมีเพิ่มวัสดุการ อาการแสดงที่ไม่เฉพาะเจาะจง ทำให้การวินิจฉัยทำได้ยาก หากไม่สามารถวินิจฉัยอาการนี้ได้ ทำให้เกิดภาวะน้ำตาลในเลือดต่ำ ซึ่งส่งผลให้เกิดอันตรายกับสมองอย่างถาวร รายงานนี้นำเสนอผู้ป่วยแรกเกิดเพศหญิงอายุครรภ์ 35 สัปดาห์ น้ำหนักแรกเกิด 2.9 กิโลกรัม ที่มีอาการหายใจหอบเหนื่อยเมื่อทารกมีอายุ 14 ชั่วโมง ซึ่งมีสาเหตุมาจากภาวะน้ำตาลในเลือดต่ำ ผู้ป่วยรายนี้ไม่มีความเสี่ยงในการเกิดภาวะน้ำตาลในเลือดต่ำซึ่งจัดเป็นต้องตรวจสอบการทำงานของต่อมใต้สมอง ผลการตรวจพบว่าผู้ป่วยมีภาวะบกพร่องในการหลั่งฮอร์โมนหลายชนิดจากต่อมใต้สมอง รายงานนี้นำเสนอตัวอย่างผู้ป่วยที่มีภาวะน้ำตาลในเลือดต่ำที่ไม่สามารถอธิบายได้ ซึ่งเป็นข้อมูลสำคัญนำไปสู่การวินิจฉัยภาวะบกพร่องในการหลั่งฮอร์โมนจากต่อมใต้สมองแต่กำเนิด

คำสำคัญ: ภาวะน้ำตาลในเลือดต่ำที่ไม่สามารถอธิบายได้, ภาวะบกพร่องในการหลั่งฮอร์โมนจากต่อมใต้สมองแต่กำเนิด, Septo-optic dysplasia