Clinical Case Report

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Cholestasis caused by panhypopituitarism and acquired cytomegalovirus infection in a 2-month-old male infant

A case report

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Abstract

Rationale: Septo-optic dysplasia (SOD) is a rare congenital disorder that may cause jaundice in infants. However, it is usually prone to neglect and misdiagnosis in infants with cholestasis because endocrine disorder such as panhypopituitarism is rare in the cause of infantile cholestasis. We report a case of SOD concurrent with acquired cytomegalovirus (CMV) infection, who presented with prolonged jaundice as the first clinical sign.

Patient concerns: The patient was a 2-month-old male infant who presented with cholestasis, combined with fever and panhypopituitarism.

Diagnoses: He was diagnosed with SOD and acquired CMV infection.

Interventions: He was treated with hormone replacement therapy and ganciclovir.

Outcomes: After correction of the pituitary hormone deficiency and ganciclovir treatment, significant improvements of cholestasis, retinal lesions, and growth rate were seen in our patient.

Lessons: Although an endocrine disorder such as panhypopituitarism is rare in the cause of neonatal or infantile cholestasis, we must keep this reason in mind.

Abbreviations: CMV = cytomegalovirus, DBS = dried blood spots, MRI = magnetic resonance imaging, PCR = polymerase chain reaction, SOD = septo-optic dysplasia.

Keywords: cholestasis, cytomegalovirus, panhypopituitarism, septo-optic dysplasia

1. Introduction

Septo-optic dysplasia (SOD) is a rare congenital disorder affecting 1 in 10,000 live births. It is characterized by the presence of 2 or more of the following: optic nerve hypoplasia, hypothalamic–pituitary dysfunction, and midline brain abnormalities. Panhypopituitarism, a consequence of SOD, may cause cholestasis in neonates and infants. Neonatal or infantile cholestasis due to endocrine disorders is infrequent and poorly recognized. We report a case of SOD concurrent with acquired cytomegalovirus (CMV) infection, who presented with prolonged jaundice as the first clinical sign.

2. Case report

A 2-month-old formula-fed male Taiwanese infant was referred to our emergency department from a regional hospital with the chief complaint of prolonged jaundice and fever for 4 days. He was born to a 27-year-old, G1P1 mother at 41 weeks of gestational age, by vaginal delivery with a birth weight of 3.4 kg (25–50th birth weight percentile). His prenatal and perinatal history was uneventful, and the result of newborn screen was normal. His father has thalassemia. He had history of neonatal jaundice, neonatal hypoglycemia, and urinary tract infection with *Escherichia coli* at 5 days of age and had been successfully treated by a regional hospital.

He came to our emergency department when he was 2 months old, presented with icteric looking, fever, and decreased activity and appetite. Physical examination showed icteric skin and sclera, hepatomegaly (4 cm below the right costal margin), and splenomegaly (3 cm below the left costal margin), but no obvious facial dysmorphism or micropenis. His weight and height were at the third to 15th percentile for chronological age. Initial laboratory data revealed microcytic anemia (hemoglobin, 7.3

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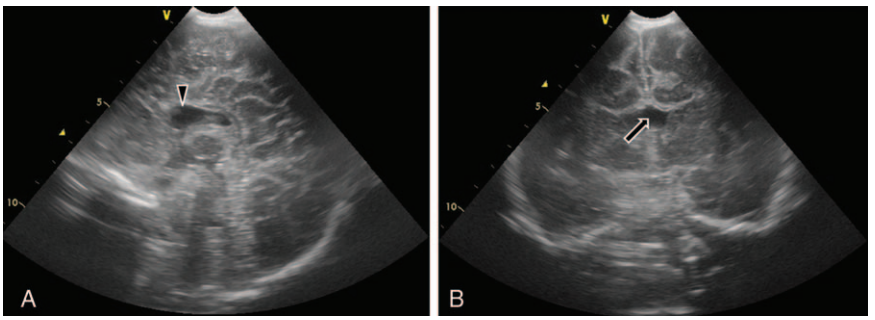

Figure 1. (A and B) Sagittal and coronal section of brain sonography showed agenesis of genu and rostrum of the corpus callosum (arrowhead) and absence of septum pellucidum (arrow).

g/dL; mean cell volume, 67 fL; hematocrit, 22%). The blood biochemistry results were as follows: total bilirubin, 8.4 mg/dL (normal <1.2 mg/dL); direct bilirubin, 4 mg/dL (normal <0.5 mg/dL); alanine aminotransferase, 30 U/L (normal 8–34 U/L); aspartate aminotransferase, 67 U/L (normal 23–68 U/L); and γ-glutamyl transpeptidase, 192 IU/L (normal 7–80 IU/L). The blood glucose levels were in the normal range. Besides, several episodes of clay-colored stools were found after admission. Series workup for cholestatic jaundice including blood and urinary culture showed no bacterial growth. Abdominal sonography, magnetic resonance cholangiopancreatography, and cholescintigraphy showed normal liver and gallbladder anatomy and patent hepatobiliary tract, all of which excluded the possibility of biliary atresia.

Later, serologic test for CMV revealed elevated CMV immunoglobulin M (Ig M) and immunoglobulin G (Ig G) (IgM, 5.450 cutoff index; IgG, 23.17 IU/mL). Urine and blood polymerase chain reaction (PCR) for CMV were also positive (urine and blood PCR for CMV was 290 and 622 copies/mL, respectively). Active CMV infection was suspected, and we arranged further ophthalmological examination and brain sonography to evaluate CMV-associated complications. Ophthalmological examination showed bilateral CMV retinitis. Brain sonography demonstrated lobar type of holoprosencephaly (Fig. 1). Brain magnetic resonance imaging (MRI) showed agenesis of genu and rostrum of the corpus callosum, and ectopic posterior lobe of the pituitary gland in the hypothalamus (Fig. 2). Based on the MRI findings, lobar holoprosencephaly and SOD were diagnosed. Visual-evoked potential study suggested bilateral visual–cortical pathway dysfunction. Pituitary hormone studies revealed secondary adrenal insufficiency, cortisol < 1 ug/dL (normal 4.75–23.27 ug/dL), adrenocorticotropic hormone, 32.96 pg/mL (normal 10–70 pg/mL); secondary hypothyroidism, free T4, 0.87 ng/dL (normal 0.89–1.79 ng/dL), thyroid-stimulating hormone, 4.67 μIU/mL (normal 0.25–4.00 μIU/mL), and growth hormone deficiency, insulin-like growth factor-1, 13.5 ng/mL (normal 50–143 ng/mL). These lab data findings were consistent with panhypopituitarism. Genetic testing for *HESX1* gene detected no pathologic sequence variants. In order to identify whether the CMV infection was congenital or acquired infection, we used the newborn screening sample of dried blood spots (DBS) on filter paper (Guthrie card) collected at birth for demonstration of CMV deoxyribonucleic acid (DNA) by PCR. However, CMV on DBS was negative.

The patient was started on hormone replacement with cortisone acetate (20 mg/m^2/d) and levothyroxine (10 μg/kg/d). Because of the presence of systemic CMV infection complicated with CMV retinitis in the patient, intravenous ganciclovir (5 mg/kg/dose every 12 hours) was also administered. Significant improvement of cholestasis was seen in our patient after ganciclovir treatment and hormone replacement therapy. His jaundice subsided, and his stool became fully pigmented. Since CMV DNA was negative after 2 weeks of intravenous ganciclovir treatment, we changed the therapeutic strategy to valganciclovir tablets (16 mg/kg/dose every 12 hours). After 14 weeks of continuous valganciclovir therapy, total resolution of retinal lesions was noted on ophthalmological examination, and we discontinued valganciclovir. He remained clinically stable, and he was discharged from the hospital at the age of 3 months.

Outpatient department follow-up at 7 months of age showed that he was growing well, and his growth parameters were at the 25th to 50th percentile for weight and 75th to 85th percentile for height. Repeated tests of CMV DNA remained negative. He is currently receiving cortisone and thyroxine supplement at outpatient department without any side effects. A lifelong hormone replacement treatment with monitoring of serum hormone levels and symptoms of hormone deficiency are needed for this patient.

3. Discussion

We report a case of cholestatic jaundice caused by panhypopituitarism and acquired CMV infection in a 2-month-old male infant. Cholestasis in infants due to acquired CMV infection[1–4] had been reported widely in the previous literature. However, panhypopituitarism, a consequence of SOD, is a rare cause of cholestasis in infants. In addition, it is usually prone to neglect and misdiagnosis in infant with cholestasis. This case emphasizes the importance of endocrine disorders as one of the etiologies of prolonged jaundice in infants.

Cholestatic hyperbilirubinemia is defined as serum conjugated bilirubin greater than 1.0 mg/dL (if the total bilirubin is <5.0 mg/dL) or greater than 20% of the total serum bilirubin (if the total serum bilirubin is >5.0 mg/dL).[5] The most common causes of infantile cholestasis are biliary atresia (25.89%) and idiopathic neonatal hepatitis (26%). CMV is the most common infection identified (31.51%). However, endocrine disorders such as hypopituitarism or hypothyroidism are rare (2%) in the causes of infantile cholestasis.[6] The overall mortality rate of neonatal cholestasis is 25%, and biliary atresia is the most common underlying cause of mortality (67.6%).[7] The mechanisms of the development of cholestasis in pituitary hormone insufficiency/deficiency are unclear, but it is known that thyroid hormone, growth hormone, and cortisol are involved in the mechanisms.

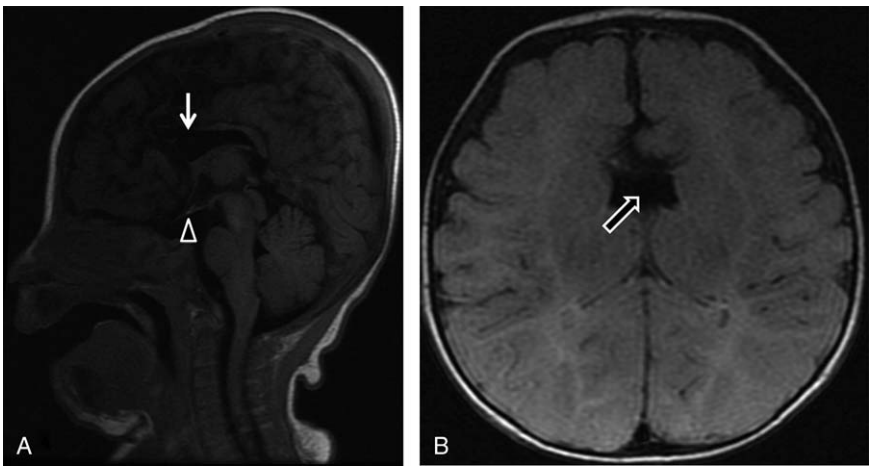

Figure 2. (A and B) Sagittal and axial section of brain magnetic resonance imaging showed lobar holoprosencephaly, agenesis of genu, and rostrum of the corpus callosum (arrow in white), absence of septum pellucidum (arrow in black), and ectopic posterior lobe of the pituitary gland in the hypothalamus or floor of the third ventricle (arrowhead, a small high signal intensity spot in the hypothalamus).

All 3 hormones are important independently in bile acid formation and excretion. Thyroid hormone and cortisol can influence the bile acid-independent bile flow and bile formation. Growth hormone can also modulate the biosynthesis and secretion of bile acids. Deficiency of growth hormone may affect liver function through decreased bile acid synthesis and structural abnormalities of the bile acid canaliculi. The infants with hypopituitarism usually present with elevation of both direct and total bilirubin.[5,8–11]

Our case was consistent with the diagnosis of SOD that the patient presented with panhypopituitarism (included secondary adrenal insufficiency, secondary hypothyroidism, and growth hormone deficiency), agenesis of the corpus callosum, and absence of septum pellucidum. SOD is a rare congenital heterogeneous malformation affecting 1 in 10,000 live births.[12] Although it is known that cholestasis is more common in Asian infants, previous study reported that South Asian ethnicity is associated with a lower prevalence of SOD.[13] It is characterized by the presence of 2 or more of the followings: optic nerve hypoplasia (unilateral or bilateral), hypothalamic–pituitary dysfunction involving 1 or more of the hypothalamic–pituitary hormones, and midline brain abnormalities such as agenesis or hypoplasia of septum pellucidum and/or corpus callosum.[14–16] Hypopituitarism in patients with SOD is usually permanent and requires lifelong treatment. Growth hormone deficiency is the most common endocrine abnormality of SOD, followed by deficiencies of TSH and ACTH.[17] Other associated features include developmental delay, hypoglycemia, seizures, and visual impairment.[12]

Otherwise, CMV infection was another cause of cholestasis in our case. It was lack of powerful evidence to prove whether his CMV infection was congenital or acquired infection, although the latter was more preferred based on his clinical presentations. For this, we used DBS test to confirm it. DBS is effective to identify whether ascertained CMV infection is congenital or postnatal infection.[18,19] In our case, the DBS result was negative, so acquired infection was confirmed. As opposed to congenital infection, acquired CMV infection is rarely associated with harmful or long-term disability and usually does not contain any neurological sequelae in term infants. It may be due to contact with CMV-infected genital secretions during vaginal delivery, postpartum transmission through breastfeeding, or from blood transfusions.[20] Patients with acquired CMV infection may present with symptoms include fever, pneumonitis, hepatosplenomegaly, lymphadenopathy, hepatitis, hyperbilirubinemia, and abnormalities of blood counts and liver function tests. However, most infected term infants are asymptomatic because the infants have maternal-transmitted CMV IgG antibody.[21,22]

In conclusion, the causes of infantile cholestasis are varied and complex. Some of the causes can result in substantial morbidity or mortality if treatment is delayed. Early detection of cholestatic jaundice and accurate diagnosis are important for successful treatment and an optimal prognosis. Although an endocrine disorder such as panhypopituitarism is rare in the causes of infantile cholestasis, we must keep this reason in mind. The early diagnosis and treatment of aggravated endocrine and neurologic functions may consequently reduce morbidity and mortality. We believe this case can remind clinicians the importance of evaluating pituitary and neurological function in infantile cholestasis if the patient also has any specific phenotype consistent with hypopituitarism.

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