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CASE REPORT

Septo-optic dysplasia as a cause of neonatal cholestasis

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Abstract

Septo-optic dysplasia (De Morsier Syndrome) is defined by the presence of 2 out of 3 characteristics: mid line defects, optic nerve hypoplasia and hypopituitarism. Although it is a rare disease, its diagnostic must be fast, preferably in the neonatal period, in order to avoid future morbidity. In this report we present a case of neonatal cholestasis, a common condition in pediatrics, as one of the initial signs of the syndrome.

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INTRODUCTION

Septo-optic dysplasia (De Morsier syndrome) is a condition characterized by two out of three of the following criteria: midline defect, optic nerve hypoplasia, and hypopituitarism[1-4].

Although this disease is rare, it can manifest early in the neonatal period by the observation of common signs in pediatric practice, including jaundice and hypoglycemia, and the delay in diagnosis may increase the morbidity of these patients. In this study, we present a case of neonatal cholestasis as an early manifestation of the syndrome.

CASE REPORT

S.M.L.P. is a female patient, born premature (gestation period of 36 weeks and 3 days) by C-section, with rupture of the amniotic membranes during labor, and proper weight for gestational age. The mother presented pre-eclampsia during pregnancy, and the serological tests were negative for HIV and syphilis upon admission to the maternity hospital. There were no complications during childbirth, and the patient was born in good health without the need for resuscitation. The patient's father and two-year brother are healthy.

The patient presented symptoms of vomiting and hypoglycemia in the early neonatal period and received total parenteral nutrition (TPN) composed of 4 mg/kg of amino acids, 1 mg/kg of lipids, and 9 mg/kg/min of glucose. Nasogastric tube insertion was difficult, and early enteral nutrition was limited because of vomiting.

In the second week of life, a physical examination indicated the presence of hepatomegaly and cholesteric jaundice, which was initially associated with TPN. The maximum level of bilirubin was 20 mg/dL (direct bilirubin of 13 mg/dL) at the age of 17 days. On the same day, an abdominal ultrasound (USG) was performed and confirmed the presence of hepatomegaly, and transfontanellar ultrasound revealed a moderate dilation of the lateral ventricles and absence of septum pellucidum. The serological tests for toxoplasmosis, rubella, cytomegalovirus, HIV, and syphilis were negative.

At the age of 1 month and 7 days, the patient was transferred to a general hospital with suspected gastric band. The patient presented with cholestatic jaundice, with 11.2 mg/dL of total bilirubin (direct bilirubin of 7 mg/dL), as well as increased transaminase levels (AST of 129 IU/L, reference value of up to 45 IU/L; and ALT of 129 45 IU/L, reference value of up to 40 IU/L), increased alkaline phosphatase levels (159 IU/L, reference range is 38-126 IU/L), and increased gamma-glutamyltransferase levels (457 IU/L, reference range is 5-27 IU/L).

A physical examination revealed hepatosplenomegaly and bilateral horizontal nystagmus. The main diagnostic hypotheses were neonatal hepatitis and biliary atresia. The diagnosis was elucidated with a liver biopsy, which revealed neonatal cholesteric hepatitis without ductal proliferation. The tests for inborn errors of metabolism and dosage of alpha 1-antitrypsin were negative.

At the age of three months, the patient underwent a new transfontanellar USG, which revealed hypogenesis of the corpus callosum, and agenesis of the septum pellucidum; this diagnosis suggested the presence of septo-optic dysplasia. A funduscopic examination was performed at the age of 3 months and 11 days and revealed hypoplastic optic disc in both eyes, confirming the presence of septo-optic dysplasia.The hormone levels were determined because of hypoglycemia, and the results indicated reduced levels of growth hormone (GH), cortisol, and prepubertal gonadotropic hormones (LH and FSH), although lower levels of pubertal hormones were expected for this age (Table 1). Therefore, glucocorticoid hormone replacement was initiated and led to a complete resolution of the episodes of hypoglycemia.

Table 1. Laboratory tests performed because of hypoglycemia.

Test	Results	Reference value/ range
Cortisol	0.35 mcg/dL	> 18 mcg/dL*
Insulin	< 0.2 mcIU/mL	2.6-24.9 mcIU/mL
GH	3.21 ng/mL	> 5 ng/mL*
Free thyroxin (T4l)	1.07 ng/mL	0.92-1.99 ng/mL
Thyroid-stimulating hormone (TSH)	5.54 mcUI/mL	0.50-8.35 mcIU/mL
Estradiol (E2)	116.6 pg/mL	12.5-498.0 pg/mL
LH	0.1 mIU/mL	1.0-95.6 mIU/mL
FSH	0.22 mIU/mL	1.7-21.5 mIU/mL

* Expected value for hypoglycemia.

Magnetic resonance imaging (MRI) was performed in the skull and sella turcica, and the results revealed hypoplasia of the optical channels, absence of the septum pellucidum, volumetric reduction of white matter in the cerebral hemispheres associated with diffuse tapering of the corpus callosum, ectasia of the lateral ventricles, and mega cisterna magna. The pituitary gland was within the range of normality, and homogeneous impregnation was revealed by the contrast dye, and the pituitary stalk was thin.

The patient was discharged 6 months and 25 days later and was transferred to a specialized care facility. At discharge, the patient did not present hepatosplenomegaly but presented with nystagmus, and her levels of liver damage markers and bilirubin were normal. At the age of eight months, new tests revealed the presence of central hypothyroidism, and levothyroxine replacement was initiated.

At present, the patient is being monitored by a multidisciplinary team that includes pediatricians, pediatric endocrinologists, physical therapists, ophthalmologists, pediatric neurologists, and pediatric gastroenterologists. The patient is under hormone replacement therapy with prednisolone at 2 mg/m^2/day and levothyroxine at 50 mcg/day and presents good neuropsychomotor development.

DISCUSSION

Neonatal cholestasis can be identified using a wide range of diagnostic strategies. Diagnosis is urgent because of the possibility of occurrence of biliary atresia.

In this case, the patient should immediately undergo laparoscopic Kasai portoenterostomy. This diagnosis can be made via liver biopsy. Differential diagnosis includes bile duct cyst, idiopathic neonatal hepatitis, neonatal sclerosing cholangitis, prolonged use of parenteral nutrition, congenital infections, inborn errors of metabolism, alpha-1-antitrypsin deficiency, and pituitary hormone deficiencies (hypothyroidism, adrenal insufficiency, or panhypopituitarism)[3]. In the present case, we identified a rare case of neonatal cholestasis associated with septo-optic dysplasia and hypopituitarism.

Septo-optic dysplasia or De Morsier syndrome is a rare and heterogeneous genetic condition, and its incidence is estimated at 1.73 cases per 10,000 children[2]. It is defined by two out of three of the following criteria: midline defects, optic nerve hypoplasia, and hypopituitarism. Only 30% of cases are presented with the full syndrome[1-6].

Midline defects comprise a wide spectrum of changes, and the most common are agenesis of the corpus callosum and absence of septum pellucidum, which occur in 50% of cases. These changes have a strong positive correlation with pituitary deficiencies[1,2].

In the case reported here, the patient had agenesis of the septum pellucidum and hypoplasia of the corpus callosum, and these changes were not initially addressed in the context of jaundice; however, these changes are strongly associated with hormone deficiencies, which can cause jaundice. Other possible changes include cerebellar hypoplasia, cervical aplasia, and schizencephaly[7].

Some patients may also present cortical malformations, and these cases are designated septo-optic dysplasia plus and are primarily associated with agenesis of the septum pellucidum[8]. These malformations are usually accompanied by motor deficits and delay in psychomotor development[9].

Our patient did not present cortical defects and had a slight delay in development. The ectopic neurohypophysis found in the MRI of the skull is a strong predictor of hypopituitarism whereas the identification of anomalies in hemispheric migration is indicative of neuropsychomotor delay[10].

Hypothalamus-pituitary insufficiency is found in 62%-80% of the cases[5] and can range from isolated deficiency to pan hypopituitarism. The most common form is GH deficiency[3-6], followed by a deficiency in the adrenocorticotropic hormone (ACTH) and TSH.

In the case reported here, the initial manifestation was GH and ACTH deficiency. It is important to note that the thyroid hormone deficiency occurred some months after the initial diagnosis and, therefore, these patients required a strict follow-up because other pituitary hormone deficiencies could manifest at different periods. Diabetes insipidus is the rarest form of the manifestation[7] but was not observed in the case described above. Children can also present pubertal disorders, particularly central precocious puberty.

It is believed that this manifestation is due to the reduced presence of inhibitory factors of hypothalamic neurons, which produce gonadotropin-releasing hormone (GnRH)[2].

Optic nerve hypoplasia can be either one-sided or, more often, bilateral (70% of cases), and can manifest as coloboma, strabismus, nystagmus, and visual impairment[5]. Studies show that patients with bilateral impairment have a higher risk of developing endocrine dysfunctions (as in the case reported here) and psychomotor delay[8]. Patients rarely present microphthalmia and anophthalmia[8]. The diagnosis of pale optical disk during ophthalmoscopic examination of the eye is a negative predictive factor for vision[9].

This syndrome has the same incidence in both sexes, and most cases are sporadic. Its cause is unknown; however, it has been associated with several factors, including vascular insult at the sixth to the seventh week of embryogenesis, bleeding in the first trimester of pregnancy, alcoholism or maternal drug use, viral infections during pregnancy, and exposure to teratogens[5,9].

Primiparity, prematurity, young age of the mother, and gestational diabetes are also considered risk factors[10]. Mutations in the HESX1, SOX2, and SOX3 genes have been identified in family cases, but they represent only 1% of the cases, suggesting that the origin of the syndrome is multifactorial[1,5]. In the case described here, this syndrome was not observed in other family members; therefore, the only risk factor was prematurity.

The most common neonatal manifestations of the syndrome are nystagmus and signs of hypopituitarism, particularly hypoglycemia and micropenis with cryptorchidism (in boys). There may be a distinctive phenotype characterized by a broad and prominent forehead, depressed nasal bridge, and cranium-facial disproportion.

Our patient did not present this phenotype but presented neonatal hypoglycemia and nystagmus. The affected patients may also present neurological symptoms such as focal engines, cognitive deficits, and seizures. Neonatal cholestasis is an unusual manifestation and can lead to cirrhosis if left untreated[3].

It is believed that corticosteroid deficiency may reduce bile flow and that GH deficiency interferes in the biosynthesis and secretion of bile acids. Hormone replacement therapy usually leads to a complete reduction of hyperbilirubinemia and increase the levels of transaminases, as it was the case reported here, because treatment started before the establishment of cirrhosis[4].

Therefore, it is important to consider the diagnosis of septo-optic dysplasia when dealing with cases of neonatal cholestasis with the view to choose the most appropriate therapeutic methods at the early stage and prevent complications.

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