Case Report

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A Case of Protein C Deficiency Complicated by Asymptomatic Neonatal Cerebral Infarction

Huang Chunling, Chang Yanmei*, Xin Yang and Tong Xiaomei

Department of Pediatrics, Peking University Third Hospital, China

***Corresponding author:** Chang Yanmei, Department of Pediatrics, Peking University Third Hospital, Peking 100191, China

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ABSTRACT

Case Abstract: A male infant, who was delivered at 36+5 weeks gestational age, was admitted to the hospital at 7 days of life due to jaundice of 3 days duration. During the hospitalization, a conventional cranial ultrasound revealed an infarct in the left basal ganglia. Laboratory testing and genetic screening in the infant and the parents indicated hereditary protein C deficiency.

Symptoms and Signs: The infant had no apparent clinical manifestations or signs.

Diagnostic Method: An infarct in the left basal ganglia was diagnosed based on the cranial ultrasound and head MRI. Further examinations revealed reduced C protein activity (14%). Genetic testing for protein C mutations in the infant and parents indicated a heterozygous mutation in the PROC gene of the infant and mother [c.970G>A (guanine>adenosine)]. This mutation is a known pathogenic mutation leading to the p.G324S variant (glycine>serine) of protein C deficiency.

Treatment Method: No specific treatment was given.

Clinical Outcome: The infant was discharged from the hospital 1 week later without receiving specific treatment. The infant is now 24 months of age and has achieved normal growth and development for his age.

Related Medical Departments: Pediatrics and Neurology.

Introduction

Neonatal cerebral infarction can cause brain damage due to local occlusion of the cerebral artery or vein between 20 weeks gestation and 28 days of life [1]. Neonatal cerebral infarction can result in nervous system sequelae, such as intellectual and motor development disorders, epilepsy, and visual and hearing impairment [2]. The affected infants may have neurobehavioral abnormalities, such as attention and executive function deficits [3]; however, the etiology of neonatal cerebral infarction is not clear. It has been reported that hereditary protein C deficiency is an important risk factor for neonatal cerebral infarction [4]. Cases of neonatal cerebral infarction are rarely reported in China. Herein we present a case of hereditary protein C deficiency complicated by asymptomatic neonatal cerebral infarction to elucidate the clinical diagnosis and treatment of the similar conditions.

Clinical Data

General Information

A male infant, who was delivered at 36+5 weeks gestational age, was admitted to the hospital at 7 days of life due to jaundice of 3 days duration involving the face and torso. The symptoms

worsened with time. The bilirubin level was 16.5 mg/dl on day 5 and 18.6 mg/dl on days 6 and 7 of life. The infant was diagnosed with neonatal hyperbilirubinemia and admitted to the hospital. The infant had no nervous system anomalies, such as fever, drowsiness, convulsions, or slow reactions. The breastfeeding routine was well-established, and the infant had normal urination and defecation. The mother was a primigravida and there was no ante- or intra-partum fetal distress. The infant was born vaginally and had no postnatal asphyxia. The Apgar scores were 10 at 1 min, 5 min, and 10 min of life. There were no abnormalities involving the amniotic fluid, placenta, or umbilical cord. A normal breastfeeding routine was established. The infant urinated and defecated within 24 h after birth, and the stool was yellow. The mother had gestational diabetes during pregnancy and achieved effective control of blood glucose through dietary approaches. There was a rupture of the fetal membranes 10 h before the onset of labor. The mother had no fevers or abnormal hemogram values. There was no history of hereditary disorders of the cardiovascular, cerebrovascular, and nervous systems. The physical examination at the time of admission was significant for the following: the infant's spirit and reaction were good with stable vital signs; there was moderate jaundice on the face, torso, and extremities (x 4); the bregma was flat and soft; and the heart, lungs, abdomen, and nervous system did not reveal any abnormalities.

Examinations

Because of the preterm birth, a cranial ultrasound was performed that revealed an infarct in the left basal ganglia. A subsequent MRI confirmed acute cerebral infarction and bilateral changes in the globi pallidi (Figure 1). To determine the cause of the neonatal cerebral infarction, we performed the following laboratory tests and examinations. An MRA of the head showed no apparent abnormalities. An echocardiography showed two ventricular septal defects (1.5 and 2 mm) with a patent foramen ovale. No abnormalities were demonstrated by electroencephalography. The NBNA score was 38 (normal). The coagulation parameters and coagulation factors (II, V, VII, VIII, and IX) were normal. Protein C and S activities were 14% and 55%, respectively. The PC-to-PS activity ratio was 0.25. The reduced protein C activity indicated a high probability of protein C deficiency. The infant and his parents underwent additional genetic screening for protein C mutations, which indicated a heterozygous mutation in the PROC gene of the infant [c.970G>A (guanine>adenosine)]. This mutation is a known pathogenic mutation leading to p.G324S variant (glycine>serine). The same mutation was detected in the PROC gene from the mother, but not from the father (Figure 2).

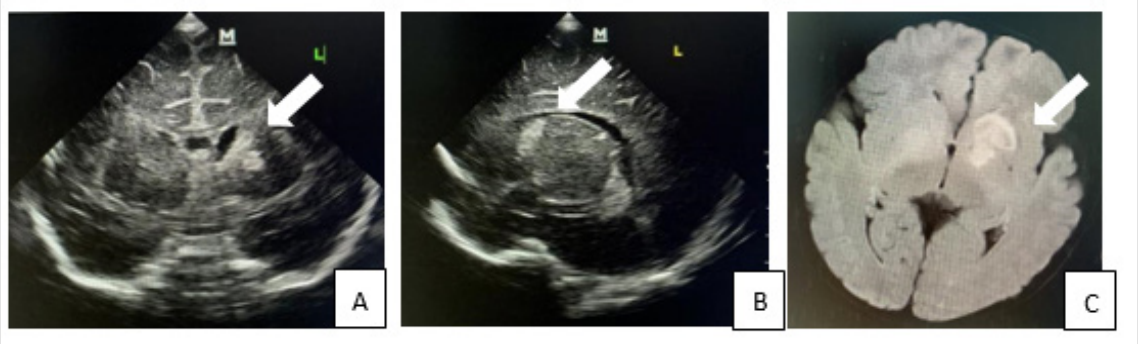

Figure 1: Radiologic manifestations of infarct in the left basal ganglia.

A. A hyperechoic wedge-shaped infarct in the left basal ganglia on the coronal plane of cranial ultrasound.

B. A hyperechoic wedge-shaped infarct in the left basal ganglia on the sagittal plane of cranial ultrasound

C. Hyperintensities in the left basal ganglia upon T2-weighted head MRI. The arrowhead indicates an infarct in the left basal ganglia.

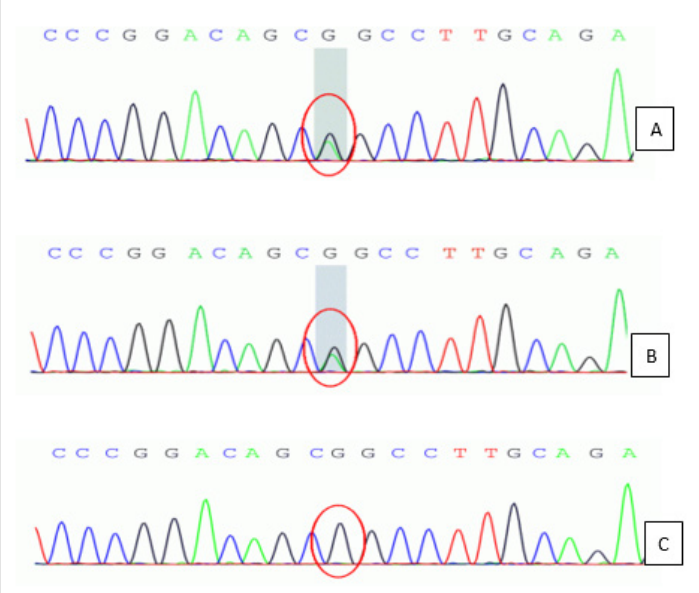

Figure 2: Genetic testing for the PROC gene mutation in the infant and parents.

A. Heterozygous mutation in the PROC gene in the infant.

B. Heterozygous mutation in the PROC gene from the mother.

C. No mutation in the PROC gene from the father.

Diagnosis and Differential Diagnosis

The cranial ultrasound and head MRI confirmed the diagnosis of a neonatal cerebral infarction in the left basal ganglia. The infant was diagnosed with hereditary protein C deficiency by laboratory and genetic testing.

Treatments

The infant was treated with mannitol (0.25g/kg q12h x 5 days) after detecting the neonatal cerebral infarction by cranial ultrasound. The infant had no convulsions, drowsiness, sleep apnea, poor reactions, or dystonia. A repeat cranial ultrasound confirmed that no infarct expansion had occurred. No antithrombotic or anticoagulant therapy was prescribed.

Treatment Results, Follow-Up, and Outcome

The infant was discharged 7 days after admission. The infant had a follow-up evaluation at the Children's Health Clinic in our hospital 23 months after birth. He had normal growth and development for his age.

Discussion

Neonatal cerebral infarction is a severe neurologic disorder. It has been reported that the incidence of ischemic cerebral infarction in full- and near-term newborns is between 6 and 17 per 100,000 [4]. The Peking University First Hospital and the Peking University Third Hospital estimated constituent ratios of diseases, with neonatal cerebral infarction accounting for 0.7% [5]. Apparently, neonatal cerebral infarction is not a rare disease. Neonatal cerebral infarction has no specific clinical manifestations in most situations. Greater than one-half of affected newborns present with convulsions [5-7]. Approximately one-third of newborns present with changes in the level of consciousness, tone anomalies, focal neurologic deficits, apnea, dyspnea, or feeding difficulties for unknown reasons [8]. The infant described in the present study exhibited none of the convulsions or symptoms described above. The infant was diagnosed with an asymptomatic cerebral infarction. There is a wide range of causes for neonatal cerebral infarction. Indeed, protein C deficiency is an independent high-risk factor for neonatal cerebral infarction [9-11].

Human protein C is a vitamin K-dependent plasma serine protease synthesized in the liver. The protein C system, consisting of protein C, protein S, and thrombomodulin, plays an important role in maintaining normal hemostatic balance. Protein C deficiency can increase the risk of developing blood clots, resulting in a hypercoagulable state and a higher likelihood of cerebral thrombosis [12]. The incidence of protein C deficiency is 1/40,000-250,000 in the general population [13] and 1/500,000-750,000 in newborns [14]. The incidence of asymptomatic protein C deficiency is 1/200-500, and incidence of symptomatic protein C deficiency 1/20,000 [15,16]. Deficiencies in protein C, protein S, and antithrombin are

the primary cause of inherited hypercoagulable states in Asian populations [17]. The incidence of protein C deficiency in Asians is considerably higher than the global population as a whole. A screening study among 3129 people in South Korea reported an incidence of protein C deficiency of 0.35% [18]. Among healthy Chinese populations, the incidence of protein C deficiency is about 0.29% [19]. As shown above, protein C deficiency is not a rare disease and can also be asymptomatic. The severity of the protein C deficiency symptoms is related to the mode of inheritance and time of onset.

Protein C deficiency is inherited in an autosomal dominant or recessive manner. Protein C deficiency inherited in an autosomal dominant manner is usually associated with heterozygous mutation in the PROC gene. The patients suffer from repeated thrombosis, with an average age at onset being 30-40 years. The patients are rarely symptomatic before 20 years of age [20]. The autosomal recessive inheritance of protein C deficiency is usually caused by homozygous or compound heterozygous mutations. This condition occurs in 1/500,000-750,000 of live births. The autosomal recessive inheritance is usually associated with purpura fulminans, which occurs several hours or days after birth. The onset is rarely delayed until childhood or adolescence [21]. This condition is mostly related to a heterozygous mutation. Compared with the general population, heterozygous protein C deficiency can cause a 10-fold increase in thromboembolic events [22]. Li et al. [23] reported one newborn with purpura fulminans and renal thrombosis 4 h after birth. This newborn died 2 months after birth despite active treatment. The molecular detection indicated a compound heterozygote mutation in the PROC gene. We performed a literature review of another five newborns with inherited protein C deficiency reported in China in the past 40 years. Three of the newbords did not undergo genetic testing, while the remaining two were shown to have a compound heterozygote mutation in the PROC gene. The time of onset was 4-43 h after birth in the aforementioned 6 neonates. All of the neonates presented with purpura fulminans and intracranial thrombosis.

Two of the neonates had eye trauma, two had intracranial hemorrhages, and two had renal thromboses; all of the neonates died. In general, the newborns affected by protein C deficiency have a poor prognosis and higher mortality than adults. In the present case, the mother harbored the heterozygous mutation in the PROC gene and had not developed a thromboembolism; however, it is unknown if the mother will have associated symptoms in the future. The infant did not present with purpura fulminans or other symptoms. Therefore, autosomal recessive inheritance was suspected in this neonate, although the possibility of autosomal dominant inheritance could not be entirely ruled out. Both the infant and mother require ongoing follow-up to observe signs of thromboembolism. In other reports, protein C deficiency is divided into early- and late-onset types by the time of onset. Purpura fulminans, intracranial thrombosis, and a protein C level<10% usually occur within 24 h after birth in infants with early-onset protein C deficiency. The symptoms of late-onset protein C deficiency do not appear until approximately 15 years of age, with a protein C level>10%. The patients generally present with deep venous thrombosis [24]. Thus far, the child remains asymptomatic with a protein C level>10%. Late-onset protein C deficiency is suspected, and there is a possibility of thromboembolic events in the future. In addition, perinatal factors may also increase the susceptibility or aggravate the symptoms of heterozygous individuals. For example, fetal distress and infection may increase the susceptibility of heterozygous individuals to neonatal or childhood thrombosis [25-27]. Our reported case was not combined with unfavorable perinatal factors, such as fetal distress or infection, which explained the absence of neonatal thrombosis.

The treatment measures adopted for infants with inherited protein C deficiency are determined based on the hypercoagulable status with or without a thrombosis. For severely or critically ill patients with a thrombosis, protein C replacement therapy is the primary treatment, or fresh frozen plasma can be administered. The American College of Chest Physicians (ACCP) Antithrombotic Therapy and Prevention of Thrombosis guidelines recommend the administration of fresh frozen plasma at a dose of 10-20 ml/kg every 12 h. Another recommended treatment is 20-60 IU/kg protein C concentrate until the lesions disappear [22]. There are no specific treatments for neonatal cerebral infarction, and symptomatic treatment is the main therapeutic option. The present case was asymptomatic except for the cerebral infarction and only received the treatment to alleviate hydrocephalus at the acute stage. This patient was admitted to the hospital due to neonatal hyperbilirubinemia. Inherited protein C deficiency and an infarct in the left basal ganglia were suspected during the hospitalization. Inherited protein C deficiency can cause thrombosis in several organs, including the brain. This condition was speculated to cause the infarct in the left basal ganglia in the case presented herein. The infant had normal physical growth and nervous system development at 23 months of age; however, this infant requires long-term follow-up to observe for signs of thromboembolism. Molecular detection in the infant and the mother with protein C deficiency will lay the basis for next-generation prenatal and postnatal disease prevention and diagnosis.

Conflict of Interest Statement

All authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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