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Case Report

Fetal hydrocephalus and neonatal stroke as the first presentation of protein C deficiency

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Abstract

Severe protein C-deficiency is a rare heritable thrombophilia of the newborn. Infants with biallelic *PROC* mutations present purpura fulminans and intracranial thromboembolism, while the prenatal onset of mutated heterozygotes remains unclear. We herewith present the first case of fetal ventriculomegaly and neonatal stroke associated with heterozygous *PROC* mutation. The infant was born to a healthy mother at 38 gestational weeks. The fetal growth had been normal, but the routine ultrasound screening had indicated mild hydrocephalus at 28 weeks of gestation. He developed convulsions two days after birth. Computed tomography of the brain revealed multiple hemorrhagic infarctions and ventriculomegaly. Dissociated levels of the plasma activity between protein C (21%) and protein S (42%) reached to determine the heterozygote of *PROC* c.574_576delAAG, a common thrombophilic predisposition in Asian ancestries. PC-mutant heterozygotes may have a limited high risk of cerebral thromboembolism during the perinatal course.

Keywords: Ventriculomegaly; Heritable thrombophilia; Perinatal stroke

1. Introduction

Hydrocephalus, or ventriculomegaly, occurs in association with anomaly, infection, tumor, and hemorrhagic complication. It begins at any age with an incidence of 0.48–0.81 per 1000 live births [1]. Fetal ventriculomegaly arises from loss of cerebral tissue, excessive production of cerebrospinal fluid (CSF) or obstruction to CSF pathways. Thromboembolic and hemorrhagic events result in hydrocephalus involving both cerebral atrophy and decreased CSF reabsorption.

Protein C (PC), protein S (PS) and antithrombin (AT) deficiencies are the most potent thrombophilias

Abbreviations: AT, antithrombin; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; PC, protein C; PS, protein S

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beyond the ethnicity. Heterozygotes with the gene mutation of PC (*PROC*), PS (*PROS1*) or AT (*SERPINC1*) are at the established high risk of venous thromboembolism in adolescents and young adults [2]. Pediatric thrombosis occurs at the highest incidence in the newborns. The neonatal onset of the natural anticoagulant factor defects is exclusively PC-deficiency [3]. Purpura fulminans and intracranial thromboembolism are the first presentation of severe PC-deficiency. Congenital hydrocephalus was reported in patients with homozygous or compound heterozygous *PROC* mutations of parental origin [3,4]. However, there is no information about the prenatal onset of heterozygous carriers.

We report the first case of fetal hydrocephalus secondary to cerebral thromboembolism associated with a heterozygous *PROC* mutation registered in adult patients with thrombosis [5]. The perinatal course indicated a critical role of PC-deficient hypercoagulability.

2. Case report

A 2-day-old infant was transferred to our hospital because of seizures. He was born at 38 gestational weeks, weighing 2750 g, by vaginal delivery to a healthy mother. Fetal growth was normal. Ultrasound and magnetic resonance imagings (MRI) suggested slight enlargement of the left lateral ventricle with ischemic atrophy at 28 and 34 weeks of gestation, respectively. Family history was unremarkable. He had normal umbilical cord and placenta with full Apgar scores at birth.

On admission, the infant was intubated for generalized convulsions. He was afebrile showing no anomaly, anemia, skin eruption or abnormal jaundice. There was no bulging fontanelle. Electro-/echo-cardiographies revealed no cardiovascular diseases. Computed tomography (CT) scanning of the brain (Fig. 1a) showed obsolete hemorrhagic lesions in bilateral ventricles and subarachnoid cavities and low intensity area in the right frontal lobe. Peripheral blood counts showed leukocytes 17.2×10^9/L (reference range [rr]: $3.30–8.60 \times 10^9$), hemoglobin 16.7 g/dL (rr: 13.7–16.8) and a platelet count of 259×10^9/L (rr: $158–348 \times 10^9$). Coagulation studies revealed normal prothrombin time 16.2 s (rr: 10.0–13.5) and prolonged activated thromboplastin time 144.1 s (rr: 26.0–41.0) because of vitamin K deficient state. Fibrinogen concentration was 88 mg/dL (rr: 200–400) with increased levels of fibrinogen degradation products 8.4 μg/mL and D-dimer 4.7 μg/mL (rr: <1.0). AT activity (43%) was normal for age. Blood chemistry was unremarkable. C-reactive protein was 0.10 mg/dL (rr: <0.14). On day 1 after admission, he was extubated

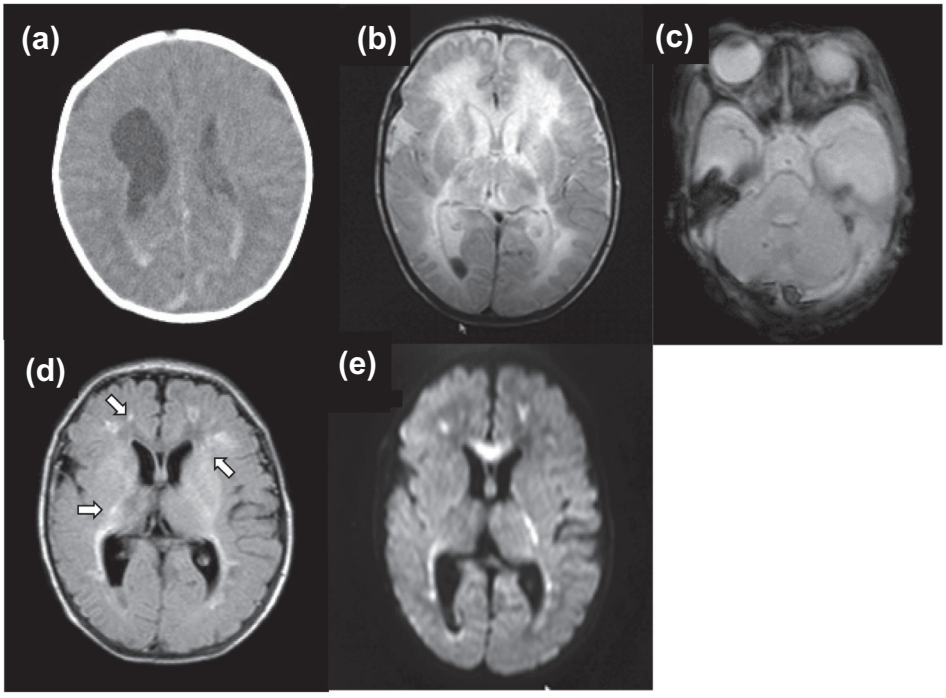

Fig. 1. Computed tomography (CT) of the brain on admission (a) indicates obsolete hemorrhagic lesions in bilateral ventricles and subarachnoid cavities and low intensity area in the right frontal lobe. Magnetic resonance imaging (MRI) of the brain on day 8 after birth (b–e) indicates multiple infarctions including obsolete (d, *arrows*) and acute lesions, along with bilateral ventriculomegaly. T2-weighted image (b) shows multiple low intensity areas in the left frontal lobe, the left frontal horn of lateral ventricle and bilateral cerebellar hemisphere. T2 star-weighted image (c) shows low intensity area in cerebellar hemisphere. Fluid attenuation inversion recovery (d) and diffusion weighted images (e) show multiple high intensity areas in different distribution.