

Case Report

A case of a new mutation of PROC causing neonatal purpura fulminans

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Received April 18, 2016; Accepted November 15, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: Purpura fulminans in the neonatal period due to congenital protein C deficiency is a rare autosomal recessive disorder, we describe a newborn who presented with purpura fulminans and disseminated intravascular coagulopathy (DIC). Subsequent blood genetic analysis demonstrated a c.1015G>A transversion in a homozygous state of protein C gene which confirmed the diagnosis of congenital protein C deficiency. Her mutation site c.1015G>A transversion has not been previously reported.

Keywords: Newborn, purpura fulminans, PROC, protein C deficiency

Introduction

Purpura fulminans in the neonatal period due to severe congenital protein C deficiency is a rare autosomal recessive disorder with an incidence of 1 per 500000. In normal neonates, the physiological level of protein C is very low and measurement of levels or activity of protein C have not been validated. With the advance in molecular diagnosis techniques during recent years, the diagnosis of hereditary protein C deficiency in neonates can be confirmed by genetic testing.

Case report

A 2-day-old female baby was admitted to hospital for skin purpura and jaundice. She was born to a 27-year-old, healthy, G2P1 mother at 38 weeks and 4 days of gestation by elective repeat cesarean section, her birth weight was 2800 g. The mother received complete antenatal care with normal serology screening and no complications during pregnancy. Membranes were ruptured at delivery with clear amniotic fluid. The umbilical cord and the placenta were normal. No resuscitation required. On newborn exam there was a skin rash over the hips of the baby. Initially the rash looked light blue and small, but spread rapidly over the next 2 days with patch-like purpuric lesions. Jaundice was noticed at day 1. The family history was negative.

On admission skin purpura was seen on the back, the abdomen, the hips and the perineal region. Two blisters, 3 cm diameter of 3 cm appeared on the back. No deformities were seen. Physical exam was otherwise normal.

The baby was admitted to NICU. Coagulation studies showed a significantly prolonged PT, APTT, with low fibrinogen level and platelet counts, and elevated D-dimer. Baby was treated with fresh frozen plasma at a dose of 10 ml/kg twice a day. Cryoprecipitate was administered to supplement fibrinogen to maintain the level of fibrinogen above 1 g/L. In addition, low molecular weight heparin (LMWH) injected twice a day at a dose of 75 IU/kg/day subcutaneously to inhibit thrombosis. Red blood cell concentrated was infused to correct anemia. Laboratory parameters improved and, with clinical improvement of the skin purpura and resolution of one of the blisters. See **Figure 1**.

The plasma protein C level was 14%, which was significant lower than normal. The activity of protein S was 67.5% and the activity of a2-plasminogen inhibitor was 80%, both in the normal range. The baby and her parents had genetic testing for hereditary protein C deficiency.

The genetic tests confirmed the baby had hereditary protein C deficiency: She had homozygous mutations in protein C gene (PROC), in coding region 1015 the base of G mutated to A

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Figure 1. Skin purpura reduced after treatment. A. Skin purpura on the day of admission. B. The skin color changed from black to red, especially the lesion on the back and the blister on the hip had resolved completely.

Table 1. Baby and her parents' gene test results

	Gene	Chromosomal	Nucleic acid	Amino acid	Homogenous/Heterozygous
Baby	PROC	Chr2: 128186151	c.1015G>A (E9)	p.339V>M	Homogenous
Father	PROC	Chr2: 128186151	c.1015G>A (E9)	p.339V>M	Heterozygous
Mother	PROC		c.1015G wild type		

at chr2: 128186151. This mutation site of PROC has not been previously reported. The father is a heterozygous protein C deficiency patient at the same coding region. The mothers genetic testing was normal see **Table 1**.

Discussion

Homogenous hereditary protein C deficiency, which is a common cause of neonatal purpura fulminans, is clinically manifested by acute disseminated intravascular coagulation and hemorrhagic necrosis of skin. In clinical practice, plasma protein C activity level as a percentage of age matched controls is usually used to assess protein C level. For healthy adults, the upper limit of protein C level is 124%-165% and the lower limit is 65%-75% [1]. The normal range of protein C level during the fetal period and the neonatal period is 7%-18% and 24%-54% respectively [2]. Protein C is a vitamin K-dependent plasma serine protease zymogen, if deficient, may lead to insufficient inactivation of thrombin and hypercoagulation [3].

The protein C gene, PROC, OMIM # 176860, is located in the chromosome 2q 13-14 region, and a total of 151 PROC gene mutations have been identified to date [4]. Genetic testing of

parents should also be performed to determine the origin of the pathogenic mutation and provide prenatal genetic advice to parents for future pregnancies. In this case the molecular analysis showed a c.1015G>A transversion in a homozygous state of protein C gene which has not been reported yet.

The principle of treatment for purpura fulminans caused by homozygous hereditary protein C deficiency is to control DIC, inhibit thrombosis and replace protein C. An effective way to control DIC is infusion of fresh frozen plasma (FFP) and to maintain the platelet count at acceptable levels. FFP is the only source of protein C other than protein C concentrate [5].

Human plasma-derived protein C concentrate is produced by filtration and column chromatography purification with mouse monoclonal antibody and gel column. Ceprotrin™ is the first drug approved by U.S. Food and Drug Administration (FDA) to treat hereditary protein C deficiency. Protexel™ produced by French Blood Products Labs is another one [6].

In 1988, it was reported that liver transplantation was successful in treating pediatric homozygous hereditary protein C deficiency [7].

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When protein C concentrate is not available, liver transplantation may be a treatment option.

After FFP or protein C concentrate is administered, anti-coagulation therapy may be initiated with heparin or low molecular weight heparin. In recent years, subcutaneous injection of protein C concentrate has also been proved to be effective in treatment of hereditary protein C deficiency. This reduces dependence on intravenous access for long-term replacement. However, the efficacy and dose of subcutaneous treatment in the long term require further investigation [8].

Neonatal purpurafulminans caused by congenital protein C deficiency is a life threatening condition. Early recognition of the clinical symptoms is important. FFP replacement with heparin treatment is effective in China, where the protein C replacement is not yet. Genetic test of the patient and their parents is critical for diagnosis, so that the family can receive genetic counselling for future pregnancies.

Disclosure of conflict of interest

None.

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