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Severe factor V deficiency in infants

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Introduction

Hemostasis is a set of physiological processes that ensure the inhibition of bleeding after breaking the continuity of the blood vessel wall, the tightness of the vascular bed, and the fluidity of the circulating blood [1]. The interaction of platelets and plasma coagulation factors with vascular endothelial cells and subendothelial tissues plays an important role in hemostasis.

Most plasma bleeding disorders, apart from hemophilia and von Willebrand disease (platelet-plasma diathesis), can be classified as orphan diseases, i.e. as occurring with a frequency of less than 5/10,000 people in the general population [2]. Rare bleeding disorders are inherited in an autosomal recessive manner and they do not cause any clinically significant bleeding symptoms in heterozygotes [3–5].

Congenital factor V (FV) deficiency is a very rare bleeding disorder, occurring with a frequency of 1:1,000,000 in the general population, and is inherited in an autosomal recessive manner [3, 4].

Methods and results

Case history

Parents brought their 4-month-old daughter to the hospital because of her reluctance to eat, which had lasted for several days, vomiting after each feeding, and increasing apathy.

The child was of Polish descent, born GV PIII on time, spontaneous delivery, Apgar 10, with a body weight of 4,040 g, and normal postnatal development. The family history revealed the death of the patient's brother on the fourth day of life; the autopsy examination showed a subcapsular hematoma of the left lobe of the liver, and kidney bleeds; the mother had had two spontaneous miscarriages.

Results

Cranial ultrasound (CrUSS) and computed tomography (CT) of the head showed a focal lesion in the form of an intracerebral hematoma with a mass effect in the right frontal lobe.

Basic coagulation parameters were urgently determined, showing platelet count 257.0 K/μL (N), activated partial thromboplastin time (APTT) 449.6 s (reference values: 27.2–53.3 s), prothrombin time (PT) 60.7 s (reference values: 9.1–12.1 s), prothrombin index 18.2% (reference values: 88–120%), international normalized ratio (INR) 5.71 (reference values: 0.9–1.39), and bleeding time 8 s (reference values: 4–8 s). Other laboratory test results were normal. The child had blood group 0 Rh (+).

After a fresh frozen plasma (FFP) transfusion, the girl was urgently operated on; a right frontal craniotomy with the removal of the hematoma was performed. The diagnostics of coagulation disorders was extended to include the activity of coagulation factors. The first measurement was performed 48 hours after the FFP transfusion. Significantly decreased factor V (FV) activity (5.4%; reference values: 62–139%) and decreased ristocetin cofactor (vWFR:Co) activity (34.4%; reference values: 53–148%) were found.

The next measurement was performed 72 hours after the FFP transfusion; the test confirmed severe FV deficiency (0.9%), reduced vWFR:Co activity (37.4%), mild von Willebrand factor (vWF) deficiency (44.7%; reference values: 53–148%), and mild factor VIII (FVIII) deficiency (42.5%; reference values 50–150%). The activity of the above-

mentioned coagulation factors, checked many times during the follow-up period which lasted for several months, showed a tendency to normalize vWF:Co, vWF, and FVIII, and persistent, extremely low, FV activity (<1%).

Genetic testing performed by next-generation sequencing (NGS) using a custom-made panel [6] revealed two heterozygous missense changes in the *F5* gene (NM_000130.4): a known pathogenic variant c.5419G>A, resulting in an alanine-to-threonine substitution at position 1,807, and a novel, likely pathogenic, change c.6136A>C, resulting in a threonine-to-proline substitution at position 2,046. In order to verify the biallelic nature of the revealed changes, we performed Sanger sequencing of the parents. The results confirmed that the c.5419G>A change was inherited from the father, and the c.6136>C change was inherited from the mother. Coagulation indices and FV activity of the girl's parents and older sister were normal.

The treatment included FFP transfusion from a male donor, initially every other day, then every three days, vasoconstrictors, and tranexamic acid.

The patient underwent control CrUSS several times and magnetic resonance imaging (MRI) of the head twice, which showed the correct evolution of post-hemorrhagic changes, with the formation of malacic cavitation (Figure 1). The image of the abdominal organs in the ultrasound examination was normal.

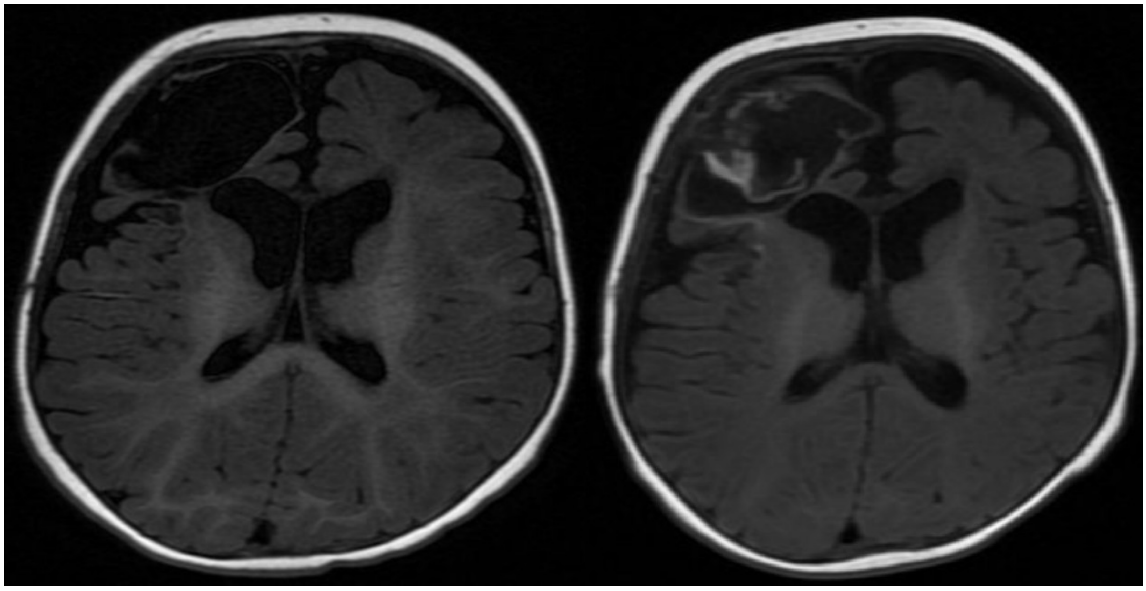

Figure 1. Brain magnetic resonance imaging (MRI): correct evolution of post-hemorrhagic changes

Currently, the 2-year-old patient remains in a good condition, is developing normally, and shows no abnormalities in neurological examination. She remains under constant hematological care and receives a transfusion of fresh frozen plasma once a week. Hemostasis parameters controlled before transfusion are still several times above the norm, and FFP transfusion only partially corrects the hemostasis.

Discussion

Several different factors are involved in the plasma coagulation cascade, including plasma proteins, tissue factor (TF) contained in cell membranes, cell membrane phospholipids, and calcium ions [5].

Factor V (FV, proaccelerin), one of the plasma coagulation factors, is a glycoprotein discovered in 1943 by Paul Owren while examining women with hemophilia-like bleeding symptoms [3]. The factor V gene (*F5* gene) is located on the long arm of chromosome 1 at position 23 [4, 7]. It is synthesized by hepatocytes. About 80% of the factor in blood plasma is in an inactive form, and 20% is contained in the granules of the platelets. It has both a procoagulant effect i.e. after being activated by thrombin Va it is a cofactor in the reaction of prothrombin activation by factor Xa which is crucial for clot formation, and an anticoagulant effect i.e. it stimulates the inactivation of factor VIIIa by activated protein C [3, 5, 7].

Congenital factor V deficiency, also known as Owren's Disease or parahemophilia, is a very rare bleeding disorder with a frequency of 1:1,000,000 in the general population, and is inherited in an autosomal recessive manner [3, 4]. The disease is diagnosed most frequently in Iranians (approx. 1:100,000), which may result from a tendency towards consanguineous marriages in this population [3]. Two types of the disease are distinguished: type I, characterized by a very low or undetectable FV antigen and factor activity deficiency, which is the form occurring in the majority of patients; and type II, characterized by reduced factor activity with its normal or slightly reduced levels [3–10]. Based on FV activity, the disease can be classified as mild (≥10% activity), moderate (<10–≥1%), or severe (<1%) [7]. Only a few cases of infants with severe factor V deficiency have been reported in the literature (Table I) [4, 11–15].

Table I. Characteristics of infants with severe factor V (FV) deficiency (FV <1%) and bleeding into central nervous system

No.	**Gender**	**Age**	**Clinical manifestation**	**Imaging studies of brain***	**Homozygous/ heterozygous**	**Family history**	**Ref.**
1	F	4 months	Nausea, vomiting, apathy	Intracerebral hematoma in frontal brain lobe	Heterozygous	Positive, brother died due to generalized bleeding	
2	F	2 months	Vomiting, twitching left canthus, poor movement	Fronto-temporal-parietal hemorrhage, subdural hematoma	Heterozygous	Negative	[4]
3	M	Infant	Asymmetric head, tense fontanelle	Subdural hematoma on right side	No data	No data	[13]
4	M	5 weeks	Apathy, pallor, reduced feeding	Hematoma on right hemisphere	Homozygous	Negative	[14]
5	M	3 months	No data	Subdural and intraparenchymal hemorrhage	No data	No data	[11]
6	M	4 months	Vomiting, epileptic attack, reduced feeding	Subdural hematoma and extradural hematoma in frontal area	Heterozygous	Yes	[15]
7	M	2 months	Apathy, reduced feeding	Intraparenchymal hemorrhage	Compound heterozygous	No data	[12]

8	F	1 month	Hemiparesis, worse psychomotor development	Subdural hemorrhage on left hemisphere	No data	No	[15]

*Imaging studies: brain magnetic resonance (MRI), brain computed tomography (CT), or brain ultrasonography

Patients with FV deficiency can present with various clinical symptoms, ranging from asymptomatic or oligosymptomatic in mild or moderate deficiency, to life-threatening bleeding in cases of severe deficiency [2, 7–9]. The most common clinical manifestations are mucosal bleeding, excessive menstrual bleeding, a tendency to postoperative and postpartum bleeding, and, less often, spontaneous hematomas, bleeding from the gastrointestinal tract, and recurrent miscarriages. In patients with severe FV deficiency, bleeding occurs in the neonatal period or early childhood as bleeding from the umbilical cord stump, intracranial bleeding, or post-traumatic joint bleeding. According to the literature, only a few infants with severe FV deficiency and spontaneous bleeding into the central nervous system have been described [4, 11–15]. The presented patient is another such case.

In our patient, the symptoms appeared in the first six months of life and resembled life-threatening intracranial bleeding. In addition, the family history of the patient's brother's death aged four days (abdominal bleeding in autopsy, coagulation disorders not diagnosed) and her mother's two miscarriages could indicate the presence of a rare, severe bleeding disorder in the family.

Patients with factor V deficiency have prolonged APTT and PT, and the degree of abnormalities correlates with the activity of factor V determined by the coagulation method [3, 9, 10]. Our patient showed significant deviations in coagulation indices on the day of admission to hospital: APTT increased by almost 10 times, PT increased by five times, and INR increased by four times. Multiple measurements of FV activity (<0.9%) were the basis for the diagnosis of hemorrhagic diathesis with severe factor V deficiency.

The genetic test results confirmed the genetic basis of factor V deficiency. So far, over 150 mutations in the *F5* gene have been identified [3, 7]. In the presented girl, two heterozygous missense mutations were found, including one pathogenic and one likely

pathogenic but not yet described in the literature. She inherited these abnormalities from her parents.

Due to the lack of concentrates containing only FV, the treatment of patients with a deficiency of this factor is based on the transfusion of fresh-frozen plasma [3, 4, 7, 9]. The recommended doses, and the frequency of transfusions, depend on the activity of the factor in the patient and the clinical situation. In cases of minor bleeding, topical treatment and antifibrinolytic drugs may be sufficient [2]. In other cases, it is recommended to increase the factor activity to about 10% with prophylactic transfusions, and >15–20% before surgery or in the case of severe bleeding [7]. The half-life of FV is 36 hours, which should be taken into account when planning the frequency of transfusions.

Repeated administration of FFP may cause transfusion-dependent complications, i.e. the risk of viral infections, which is currently reduced to a minimum, plus other challenges such as inhibitor formation, circulatory system overload, and lung damage. Due to the presence of FV in platelet granules, transfusion of platelet concentrate is suggested as an alternative therapy. Platelet FV in thrombocytes is delivered in an inactive form directly to the bleeding site where it is activated, which increases its local effectiveness, and makes it protected against the inhibitor circulating in the blood [7–9].

Liver transplantation should be considered in patients with severe FV deficiency and coexisting life-threatening bleeding. However, this is a method of treatment which carries the possibility of significant complications [11, 12].

In vitro studies on plasma-derived factor V concentrate are in progress. The results so far indicate a beneficial effect on the correction of PT and APTT, so there is the prospect in the future of targeted supplementation treatment in patients with severe factor V deficiency [3, 7].

The described patient is receiving FFP once a week and so far we have not observed post-transfusion complications; since the introduction of substitution treatment, no spontaneous bleeding has been observed in the child.

Conclusions

1. Severe congenital FV deficiency is a very rare bleeding disorder that can present with life-threatening intracranial bleeding in infancy.

2. Patients with severe FV deficiency and their families require hematological, genetic and molecular diagnostics, and genetic counseling.
3. The presentation of very rare cases is necessary to improve the diagnostic process and future treatment of patients with severe FV deficiency.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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