RESEARCH ARTICLE

Congenital coagulation factor V deficiency with intracranial hemorrhage

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Abstract

Background: Congenital coagulation factor V (FV) deficiency is a very rare hemorrhagic disease with an incidence of approximately one in a million. The common clinical manifestations of FV deficiency include ecchymosis and mucosal bleeding. Life-threatening intracranial bleeding is rare. It has been reported in several cases. However, the molecular basis has been established in only a few cases.

Methods: We reported a 2-month-old girl with congenital FV deficiency and intracranial hemorrhage. Coagulation screening combined with clinical manifestations was performed to diagnose congenital FV deficiency. Genetic testing was performed to identify the pathogenic genes. A literature review was included to emphasize the clinical manifestation, diagnosis, and treatment for congenital FV deficiency with intracranial bleeding.

Results: The coagulation tests revealed a significantly prolonged prothrombin time (PT) of 51 s and an activated partial thromboplastin time (APTT) of 73.7 s. The patient had a plasma FV activity of 0.9%. Genetic testing showed compound heterozygous mutations of the patient’s FV gene. A literature review showed that patients with homozygous or compound heterozygous variants of the FV gene were often associated with a severe bleeding phenotype.

Conclusion: Our study provides a direction for the rapid and accurate diagnosis and treatment for FV deficiency to avoid life-threatening bleeding. Infants with spontaneous cranial hematoma and intracranial hemorrhage should be investigated for underlying hemostatic defects. Congenital coagulation factor deficiency should be considered. Once congenital FV deficiency is diagnosed, fresh frozen plasma (FFP) should be given on a regular basis. Liver transplantation may be performed in severe cases.

KEYWORDS
coagulation factor V deficiency, intracranial hemorrhage, molecular basis
Coagulation factor V (FV) is a large glycoprotein synthesized in the liver and circulates in plasma as an inactive precursor with a half-life of 12–36 h. FV is a single-chain glycoprotein that consists of 2196 amino acids. The FV gene maps to human chromosome 1q21-25. The coding sequence consists of 25 exons and 24 introns. Factor V is activated to its active form (FVa) by thrombin or FXa. Once activated, FVa acts as a nonenzymatic cofactor within the prothrombinase complex that greatly accelerates the ability of FXa to rapidly convert prothrombin to thrombin. Approximately 20% of the total FV in blood is stored in the α-granules of platelets. Platelet FV is not synthesized but originates from the plasma through the endocytosis of plasma FV by megakaryocytes. Platelet FV is partially activated and more resistant to inactivation by activated protein C (APC). Following platelet activation, platelet FV can reach a local concentration that exceeds the FV plasma concentration by more than 100-fold at the site of injury.

Congenital FV deficiency is a rare autosomal recessive bleeding disorder with an incidence of approximately one in a million. Patients with FV deficiency and significant bleeding symptoms show very low plasma FV levels and are usually homozygous or compound heterozygous for mutations located in the FV gene. More than 100 mutations have been reported to be responsible for FV deficiency. Nearly half of these are missense mutations, while the rest include deletions, insertions, nonsense mutations, and splice site mutations. The common manifestations of FV deficiency are accompanied by a variety of bleeding features, including ecchymoses, epistaxis, gingival bleeding, hemorrhage following minor trauma, and menorrhagia. Life-threatening bleeding, including central nervous system bleeding, gastrointestinal bleeding, and hemarthrosis, are rarely reported in patients with FV deficiency. Intracranial bleeding is the most feared complication. FV deficiency with intracranial bleeding has been reported in several cases, but the molecular basis has been established in only a few cases.

Here, we present an FV-deficient patient with intracranial bleeding and review the literature on the clinical characteristics and treatment responses of this condition.

CASE HISTORY

A 2-month-old girl was admitted to the hospital because of a one-day history of frequent ejective vomiting without an obvious cause. After a few hours, she developed twitching in her left canthus and corner of her mouth after vomiting. Physical examination revealed dull eyes and poor movement. The anterior fontanelle tension was high. Her pupils were unequal bilaterally, the diameter of the right pupil was approximately 4 mm, and the light reflection disappeared. The diameter of the left pupil was approximately 2.5 mm, and the light reflection was dull. The mouth angle was skewed to the right when the patient cried. The left nasolabial fold became shallow, and the left limb movement was poor.

Her parents are not consanguineous. Her family history was unremarkable.

The hemoglobin level was 67 g/L, the red cell count was 2.33 × 10^{12}/L, the white cell count was 18.89 × 10^{9}/L (neutrophils 78.9%), and the platelet count was 650 × 10^{9}/L. A computerized tomography (CT) scan showed right frontotemporal parietal hemorrhage (Figure 1) and high-density shadows in the right occipital lobe and longitudinal fissure cistern, considering the subarachnoid space and subdural hematoma (Figures 2 and 3).

The coagulation examinations revealed a markedly prolonged prothrombin time (PT) of 51.0 s (normal range 8.8–13.6 s), an international normalized ratio (INR) of 4.71 (normal range 0.8–1.6), and an activated partial thromboplastin time (APTT) of 73.7 s (26–40 s). The patient’s fibrinogen and thrombin time were normal. Her liver function tests were normal. After an infusion of 50 ml of fresh frozen plasma (FFP), 1 U of cryoprecipitate and 1 U of suspended red blood cells, her anemia, and coagulation were significantly improved (hemoglobin 117 g/L, red cell count 3.87 × 10^{12}/L, PT 15.9 s, INR 1.45 and APTT 40.6 s). Then, the evacuation of her intracranial hematoma was performed without excessive bleeding. After the operation, the anterior fontanelle tension was significantly reduced. Ceftriaxone was used to prevent perioperative infections, dexamethasone was used to relieve brain edema, valproic acid was used for antiepileptic treatment, and FFP was continued to improve her coagulation function.

Three days after the discontinuation of FFP and cryoprecipitate transfusion, both PT (33.0 s) and APTT (101.9 s) were markedly prolonged. Decreased activity or deficiency of coagulation factors was suspected. Further coagulation factor activity tests showed a FII level of 84.6%, a FV level of 0.9%, a FVII level of 67.7%, a FVIII level of 70.5%, a FIX level of 56.7%, a FX level of 105.5%, and a FXI level of 80.1%. To exclude evidence of inhibitors, we performed a mixed plasma correction experiment. Both the prolonged PT and APTT were corrected with normal mixed plasma. The neonatal FV levels in developmental hemostasis are similar to those in adults. Congenital
FV deficiency was suspected based on the relevant coagulation tests and clinical manifestations. Furthermore, full-exome high-throughput sequencing of the FV gene of the patient and her parents was performed to confirm the diagnosis of congenital FV deficiency (Table 1). The father was heterozygous for the c.4317_4318del mutation on exon 13. Nevertheless, the mother was heterozygous for the c.1063del mutation on exon 5. The patient was compound heterozygous and harbored both mutations of the FV gene, which she inherited from her parents. The c.4317_4318del and c.1063del mutations of the FV gene both caused changes in the open reading frame of the FV gene, leading to changes in protein function. The c.4317_4318del and c.1063del mutation sites constitute compound heterozygous mutations. The disease corresponding to the mutation is consistent with the phenotype of this case. These results suggest that the c.4317_4318del and c.1063del mutations of the FV gene are pathogenic mutations. This is a case of congenital FV deficiency due to compound heterozygous mutation.

The parents rejected the suggestion of a liver transplant. After anti-infection treatment, intracranial pressure reduction, nutritional nerve, antiepileptic, vitamin K1 supplements, FFP infusions, and other symptomatic support therapy, the patient’s condition improved gradually, and she was discharged after 21 days in the hospital.

Thirteen days after discharge, the patient returned to the hospital for evaluation of her coagulation function and for a prophylactic infusion of coagulation factors to prevent potential recurrence of serious bleeding. Coagulation function examination showed a PT of 42.4 s, INR of 3.91, and APTT>200 s. The level of plasma FV activity was 0.4%. FFP infusion was given to supplement coagulation factors. She was discharged after 3 days of hospitalization.

Nearly a month after the second discharge, the patient was admitted to the hospital at the age of four and a half months due to intermittent vomiting for 1 h. An emergency head CT scan revealed a new left subdural hemorrhage (Figure 4). After admission, hemostasis, nerve nutritional medications, and an infusion of FFP were given. The left subdural hematoma decreased. The patient was discharged automatically after 6 days of treatment.

Ten days after the third discharge, she was admitted to the hospital due to two convulsions half a day prior, which manifested as double upper limb lifting, leg flexion, and a cluster attack, and the longest duration was approximately 10 min. Coagulation function examination showed PT 53.1 s, INR 4.68, and APTT 114 s. The level of FV activity was 0.5%. She was given an infusion of FFP, nutritional

| Gene | Mutation position | Gene subregion | HGVS | Mutation type | heterozygosity |
|------|-------------------|----------------|------|---------------|----------------|
| FV   | chr1:169510010–169510011 | exon13 | NM_000130.5: c.4317_4318del: p.P1440Rfs*4 | Frameshift deletion | Patient: Heterozygous |
|      |                    |       |      |               | Father: Heterozygous |
|      |                    |       |      |               | Mother: Wild type |
| FV   | chr1:169524475–169524475 | exon7 | NM_000130.5: c.1063del: p.A355Lfs*12 | Frameshift deletion | Patient: Heterozygous |
|      |                    |       |      |               | Father: Wild type |
|      |                    |       |      |               | Mother: Heterozygous |

Abbreviation: HGVS, human genome variation society.
nerve medications, hemostasis, and valproic acid antiepileptic treatment. Three days later, the patient was discharged and continued oral valproic acid antiepileptic treatment.

At 6 months, the patient was admitted to the hospital with a 2-day swelling of the left buttock. Ultrasound showed an uneven subcutaneous echo mass in the left buttock (considering a hematoma). Her hemoglobin level was 48 g/L, and her white cell count was 17.95 × 10^9/L. Coagulation function examination showed PT 55.0 s, INR 4.88, and APTT > 200 s. Through anti-infection, hemostasis, anemia correction, FFP infusion, and other treatments, her hip swelling was reduced, her coagulation function and anemia improved, and she was discharged 6 days later. The patient received regular infusions of FFP, and thus far, no spontaneous bleeding has occurred.

3 | DISCUSSION

Hereditary FV deficiency, also known as parahemophilia or Owren's disease, is an autosomal recessive hemorrhagic disorder that was first described by Owren in 1947 in Norway. It is a very rare hemorrhagic disease, accounting for 7.2% of the cases of rare hereditary hemorrhagic diseases. Heterozygotes are usually asymptomatic. The plasma FV activity in heterozygotes ranges between 25 and 60 percent of normal. Study findings indicated that FV activity levels greater than 25 percent of normal were sufficient to stop bleeding or prophylaxis for surgery. The common clinical manifestations of FV deficiency include ecchymosis, mucosal bleeding, hemorrhage following minor lacerations, menorrhagia, and a high risk of excessive bleeding after trauma, dental extractions or surgery. Bleeding from other sites is less common. Life-threatening gastrointestinal and intracranial bleeding are rare.

In this study, we report a phenotype of severe intracranial hemorrhage in early childhood. The unusually severe bleeding phenotype prompted us to review the literature for intracranial hemorrhage symptoms in FV deficiency. We summarized the clinical features of the reported congenital FV deficiency with intracranial hemorrhage-related cases (Table 2). The first was reported in 1984 in a small girl with periventricular hemorrhage at 28–30 weeks' gestation and postnatal periventricular hemorrhage. She had a very low FV concentration of 2%, but the molecular basis for FV deficiency had not been established. Her parents were probably heterozygous with variable penetrance (maternal FV concentration 52%, paternal 78%), while her brother was apparently normal with a FV value of 100%. She was treated with FFP. To date, 22 cases of congenital FV deficiency with intracranial hemorrhage have been reported. Among these cases, two patients had post-traumatic intracranial hemorrhages. The rest had spontaneous intracranial hemorrhage. The gender distribution was similar (nine females, and 13 males). Among the previous spontaneous intracranial hemorrhages in the congenital FV deficiency cases, most spontaneous intracranial hemorrhages occurred in infancy (13 of 20). All of the patients had FV activity less than 5% of normal. Twelve of the 22 patients had FV activity less than 1%. Unlike hemophilia A and B, the severity of bleeding symptoms of FV deficiency was only partially related to the level of FV activity in plasma. However, low clotting factor levels are associated with an increased risk of bleeding in general.

Genetic testing is of great value in identifying pathogenic genes and determining the gene-phenotypic relationships as well as in predicting other clinical features, such as inhibitor production. Patients with homozygous or compound heterozygous variants of the FV gene usually have plasma FV levels less than 10% of normal, while carriers of heterozygous variants usually maintain plasma FV levels of approximately 50%. Only nine patients were genetically tested for FV: of which seven had homozygous mutations and two had compound heterozygous mutations. For the patient in our case, whole-exon high-throughput gene sequencing of the FV gene was performed, and the result showed compound heterozygosity causing a frameshift deletion. The first mutation (c.4317_4318del) within exon 13 caused changes in the gene's open reading frame, resulting in changes in protein function. The second mutation (c.1063del) within exon 7 also caused changes in the open reading frame of the gene, resulting in changes in protein function. Neither of these mutations have been reported.

The treatment for congenital FV deficiency focuses on increasing the plasma FV concentration. As there is no FV concentrate available, the primary treatment for FV deficiency is infusion of FFP. Antifibrinolytic drugs such as tranexamic acid may be used for patients with mild bleeding or minor surgery. Patients with severe bleeding or major surgery need FFP. Approximately twenty percent of FV is stored in platelet alpha-granules. Transfusion of platelets can be performed when severe bleeding in FV deficiency patients does not respond well to conventional treatment. Recombinant activated FVII may also be used to treat acute severe bleeding by increasing thrombin production at the site of injury. For patients with severe FV deficiency, regular
TABLE 2 Summary of the clinical features of cases with congenital V factor deficiency with intracranial hemorrhage

| Study            | Gender | Age⁹  | Clinical presentation                                      | Bleeding history | Parental consanguinity | Family history⁶ | Cranial Trauma                  | Imaging results⁵ | FV | Mutation         |
|------------------|--------|-------|-----------------------------------------------------------|------------------|------------------------|----------------|-------------------------------|-----------------|----|-----------------|
| Whitelaw A, et al.¹ | Female | 32 weeks’ gestation | Acceleration in the biparietal diameter                   | No               | No                     | No             | Right ventricular dilatation   | 2%              | No data | Homozygous       |
| Yoon SG et al.¹² | Male   | 53 years | Deep drowsy mental status                                 | No               | No data                | No             | Intracranial hemorrhage in left thalamus and intraventricular hemorrhage in occipital hom of left lateral ventricle | <1%             | No data |                |
| Ehrenforth S, et al.¹³ | Female | 7 days | Mydriasis, anisocoria and hyperexcitability               | No               | No                     | No             | A subdural hematoma covering the entire left hemisphere | <5%             | No data |                |
| Yoneoka Y, et al.¹⁴ | Female | 62 years | Left hemiparesis, gradually getting comatose              | No               | No data                | No             | Hematoma in the right putamen | <5%             | No data |                |
| Totan M, et al.¹⁵ | Male   | 3 months | Vomiting, epistaxis, pallor and epileptic seizure         | No data          | Yes                    | No data        | A parenchymal hemorrhage and mild edema in the parietal region | 2.1%            | No data |                |
| Salooja N et al.¹⁶ | Male infant | A large asymmetric head, a full tense fontanelle, widely split skull sutures | Yes             | No data                | No             | A large right sided subdural hematoma with considerable midline shift and obstructive hydrocephalus | <1%             | No data |                |
| Lee WS, et al.¹⁷ | Female | 18 days | Excessive crying, irritability, and hematemesis. Umbilical bleeding, anterior fontanelle tensed | No               | Yes                    | No             | A right, large, intracerebral bleed with intraventricular extension and hydrocephalus | 3%              | No data |                |
| Bossone A, et al.¹⁸ | Male    | 52 years | Post-traumatic intracranial bleeding                      | No               | No data                | Na data        | No data                       | 5%              | Homozygous |                |
| Fu QH, et al.¹⁹ | Male    | 37 years | Severe headache and vomiting                              | Yes              | Yes                    | Yes            | Haematom in frontal lobe of the cerebrum | 1.6%            | Homozygous |                |
| Liu LG, et al.²⁰ | Male    | 37 years | Headache, nausea                                          | Yes              | Yes                    | Yes            | Left frontal hematoma          | 1.6%            | Homozygous |                |
| Chingale A, et al.²¹ | Male    | 5 weeks | Pallor, irritability, lethargy and reduced feeding        | Yes              | Yes                    | No             | A right, large, intracerebral bleed causing a shift of the midline to the left | <1%             | Homozygous |                |
| Ellestad SC, et al.²² | Male fetus | No data | Echogenic debris, distortion of the parenchyma and a midline shift consistent with intracranial hemorrhage. | No data          | No                     | No             | Echogenic debris, distortion of the parenchyma and a midline shift consistent with intracranial hemorrhage. | 2.5%            | No data |                |
| Lungi B, et al.²³ | Male    | 11 years | No data                                                   | Yes              | No data                | No data        | No data                       | <1%             | Homozygous |                |
| Wang Q, et al.²⁴ | Female  | infant | Enlarged head mass, poor response, extensive petechiae, edema in right hip and outer thigh | No data          | No                     | No             | Subarachnoid hemorrhage, right temporal top scalp hematoma | 4.0%            | No data |                |
| Page S, et al.²⁵ | Male    | 3 months | No data                                                   | Yes              | No data                | No data        | Unilateral subdural and intraparenchymal hemorrhage with herniation and obstructive hydrocephalus | <1%             | No data |                |
| Castoldi E, et al.²⁶ | Male    | 31 years | A sudden headache and blurred vision in the left eye      | Yes              | No                     | No             | Subdural frontal intracranial hemorrhage | <0.5%           | Homozygous |                |

(Continues)
| Study               | Gender | Agea | Clinical presentation                                      | Bleeding history | Parental consanguinity | Family historyb | Cranial Trauma | Imaging resultsc | FV | Mutation                  |
|---------------------|--------|------|----------------------------------------------------------|------------------|------------------------|-----------------|---------------|------------------|----|--------------------------|
| Ozkaya H, et al.6    | Female | 12 years | Unconscious                                              | Yes              | Yes                    | No              | Yes           | A large subdural hematoma | 1% | No data                  |
| Frotscher B, et al.25 | Male   | 4 months | Reduced feeding, vomiting and diarrhea, a partial epileptic attack | Yes              | No                     | Yes             | No            | An acute left subdural hematoma associated with a frontal extradural hematoma | <1% | Compound heterozygous   |
| Wang DM, et al.24    | Female | 5 years | Headache, nausea, vomiting                               | Yes              | No data                | No data         | No            | Bilateral frontotemporal epidural hematoma | 1% | No data                  |
| Nuzzo, et al.8       | Female | newborn | Multiple intracranial hemorrhages in the neonatal period  | Yes              | Yes                    | No data         | No            | No data          | <0.5% | Homozygous               |
| DesPain AW, et al.31 | Male   | 2 months | Altered mental status, poor oral intake, and lethargy.    | Yes              | No data                | No data         | No            | Intraparenchymal, hemorrhagic stroke in the left middle cerebral artery territory with midline shift | <1% | Compound heterozygous   |
| Hino-Fukuyo N, et al.27 | Female | 1 month | Right hemiparesis, delayed psychomotor development       | Yes              | No data                | No              | No            | Subarachnoid and subdural hemorrhaging of the left hemisphere | <1% | No data                  |

aAge at first intracranial hemorrhage.
bFamily history of hematological disease.
cImaging included CT, ultrasound or magnetic resonance imaging.
infusion of FFP can effectively prevent life-threatening bleeding, such as intracranial hemorrhage and gastrointestinal hemorrhage. FFP infusions carry risks associated with transfusion-related infections, circulating load, acute lung injury, and the development of factor inhibitors. Studies have reported that liver transplantation might be a good option for patients with severe FV deficiency. Liver transplantation should be considered in the early stages of severe FV deficiency or during the first life-threatening bleeding event. Liver transplantation is the most effective radical cure available at present, but its risks and costs are also not affordable for ordinary people.

In this study, we investigated an infant with spontaneous intracranial hemorrhage due to congenital FV deficiency and identified two heterozygous mutations of the F5 gene associated with FV deficiency. Two new mutations (c.4317_4318del within exon 13 and c.1063del within exon 7) in the F5 gene were identified that have never been previously reported worldwide. Our study provides a direction for clinicians to rapidly and accurately diagnose and treat FV deficiency to avoid life-threatening bleeding and neurological complications. In conclusion, infants with spontaneous cranial hematoma and intracranial hemorrhage should be investigated for underlying hemostatic defects. Congenital coagulation factor deficiency should be kept in mind, especially when the level of factor activity is very low. Once a patient is diagnosed as having congenital FV deficiency, the patient should be given FFP on a regular basis. Liver transplantation may be performed in severe cases.

**DATA AVAILABILITY STATEMENT**

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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