

Severe congenital factor V deficiency presenting as intracranial hemorrhage in early infancy

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ABSTRACT

Congenital factor V deficiency is a rare autosomal recessive bleeding disorder with heterogeneous clinical manifestations. Intracranial hemorrhage is an uncommon but life-threatening presentation in infancy. We report a 3-month-old male infant who presented with vomiting and refusal to feed and was subsequently diagnosed with a massive right temporal intraparenchymal hemorrhage with intraventricular extension secondary to severe congenital factor V deficiency. Importantly, the infant had earlier warning signs of an underlying bleeding disorder, including severe neonatal anemia with markedly prolonged prothrombin time (PT) and international normalized ratio and a hematoma at a vaccination site despite Vitamin K administration. Coagulation studies showed markedly prolonged PT and activated partial thromboplastin time, with factor V activity <1%; mixing studies corrected the clotting times, and other measured coagulation factors were not reduced. Genetic testing confirmed a homozygous pathogenic frameshift variant in the *F5* gene (c.2862del; p.Ser955AlafsTer4). The child was managed with repeated fresh frozen plasma transfusions and intensive care support. This case emphasizes the importance of recognizing early bleeding clues and considering severe factor V deficiency in infants with intracranial hemorrhage despite Vitamin K prophylaxis.

Key words: Factor V deficiency, Genetic mutation, Infant, Intracranial hemorrhage, Rare bleeding disorder

Congenital factor V deficiency, also known as parahemophilia, is an extremely rare inherited coagulation disorder, with an estimated prevalence of approximately 1 in 1,000,000 individuals [1]. It results from pathogenic variants in the *F5* gene, leading to reduced or absent activity of coagulation factor V, a critical cofactor in the prothrombinase complex responsible for thrombin generation. Clinical manifestations vary widely, ranging from mild mucocutaneous bleeding to severe hemorrhagic complications. Severe disease is generally associated with factor V activity below 1% [2]. Intracranial hemorrhage is rare but represents one of the most severe complications, particularly in neonates and young infants [3].

We report a case of severe congenital factor V deficiency presenting with massive intracranial hemorrhage in the early infancy, with diagnosis supported by coagulation factor assays, mixing studies, and molecular genetic testing. The case is particularly notable for the presence of earlier bleeding clues in the neonatal period and after vaccination, followed by catastrophic intracranial hemorrhage requiring neurosurgical intervention.

CASE REPORT

A male infant aged 3 months and 7 days, born on December 18, 2024, presented with poor feeding and recurrent vomiting for 2 days. He was the second child of a non-consanguineous marriage. The infant was delivered by lower-segment cesarean section at term gestation, with a birth weight of 2.3 kg, length of 49 cm, and head circumference of 34 cm. The liquor was meconium-stained. APGAR scores were 5 at 1 min and 7 at 5 min. The infant cried at birth and did not require resuscitation. Intramuscular Vitamin K was administered at birth. Soon after birth, the neonate developed respiratory distress and was admitted to the neonatal intensive care unit.

Initial laboratory investigations revealed severe anemia (hemoglobin, 4 g/dL) with markedly prolonged prothrombin time (PT) (69.7 s) and international normalized ratio (INR) (5.8), while the platelet count was normal. Chest radiography and cranial ultrasonography were normal. Echocardiography demonstrated a large patent ductus arteriosus with a bidirectional shunt and a patent foramen ovale, with otherwise normal cardiac function. The neonate received packed red blood cell transfusions (10 mL/kg) on days 1 and 3 of life and fresh frozen plasma (FFP) transfusions (10 mL/kg)

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on days 2 and 4. The infant improved clinically and was discharged after 10 days of hospitalization with a diagnosis of a low-birth-weight infant with anemia, possibly secondary to fetomaternal hemorrhage. At 1.5 months of age, the infant developed a hematoma at the vaccination site, for which Vitamin K was administered. This episode represented an additional early clue to an underlying bleeding disorder.

At 3 months and 5 days of age, the infant attended a family celebration, where he was lifted playfully into the air. The following day, he developed vomiting and refusal to feed, which persisted for 2 days. On admission, the infant was lethargic, irritable, and pale, with a tense anterior fontanelle. Vital signs showed a heart rate of 182/min, respiratory rate of 32/min, and oxygen saturation of 90% on room air. Neurological examination revealed increased tone with preserved reflexes and anisocoria. During hospitalization, the infant developed focal seizures involving the right upper and lower limbs.

Cranial ultrasonography revealed dilated ventricles with hyperechoic intraventricular echoes suggestive of grade IV intraventricular hemorrhage, along with a 27 × 27 mm heterogeneous echogenic lesion in the right temporal region. Non-contrast computed tomography of the brain demonstrated a large right temporal intraparenchymal hemorrhage with intraventricular extension and significant mass effect, consistent with severe intracranial hemorrhage and raised intracranial pressure (Fig. 1). The child was referred to a tertiary care center for further management.

At the referral center, the infant was admitted to the pediatric intensive care unit with raised intracranial pressure and coagulopathy. He required mechanical ventilation, osmotherapy with hypertonic saline and mannitol, and antiepileptic therapy. Laboratory investigations revealed severe anemia (hemoglobin, 5.4 g/dL) and an INR of 7.0. The child received four transfusions of FFP and packed red blood cells until the coagulation parameters normalized. Due to progressive neurological deterioration, the infant underwent right frontotemporoparietal decompressive craniectomy with duroplasty and insertion of a left frontal Ommaya reservoir on March 26, 2025. Electroencephalography initially showed attenuated background activity over the right hemisphere, suggestive of severe structural injury. Repeat electroencephalogram demonstrated frequent left hemispheric seizures progressing to status epilepticus, which responded to phenobarbitone, midazolam infusion, and lacosamide. Serial neuroimaging revealed cerebral edema, cortical laminar necrosis, diffuse cerebral atrophy, and organized subdural hemorrhage.

The coagulation profile revealed a PT of 82 s (control, 14.5 s), an activated partial thromboplastin time (aPTT) of 56 s (control, 32 s), and an INR of 7. Factor assays showed factor V activity <1%, factor VIII 73.23%, factor IX 64.6%, factor II 145%, factor VII >150%, and factor X >150%. Mixing studies demonstrated correction of the prolonged clotting times, supporting a coagulation

factor deficiency rather than an acquired inhibitor. The combination of markedly prolonged PT and aPTT, factor V activity <1%, normal measured levels of factors II, VII, VIII, IX, and X, and correction on mixing study supported isolated severe factor V deficiency. Enhanced whole-exome sequencing identified a homozygous frameshift pathogenic variant in exon 13 of the *F5* gene: c.2862del (p.Ser955AlafsTer4). This deletion leads to premature truncation of the factor V protein, confirming autosomal recessive congenital factor V deficiency (OMIM #227400).

The child remained hospitalized for 20 days during the index admission and gradually stabilized following four FFP transfusions (10 mL/kg) administered on 4 consecutive days, after which the coagulation parameters normalized, along with intensive care support. At discharge, the infant was seizure-free and tolerating feeds, although developmental concerns were noted, including absence of a social smile and poor eye contact, suggestive of neurological sequelae. The family was advised regarding bleeding precautions and prompt medical evaluation during bleeding episodes, with FFP (15 mL/kg) recommended for acute bleeding. The patient was readmitted on May 28, 2025, for elective cranioplasty. He underwent right frontotemporoparietal autologous cranioplasty at the site of the previous right frontotemporoparietal craniectomy, with duroplasty and left frontal Ommaya reservoir insertion performed on March 26, 2025. The post-operative course was uneventful, and the child was discharged after 4 days of hospitalization. At follow-up, he remained seizure-free, although neurodevelopmental concerns persisted (Fig. 2).

DISCUSSION

Congenital factor V deficiency is a rare inherited bleeding disorder caused by pathogenic variants in the *F5* gene and follows an autosomal recessive inheritance pattern [4]. Severe disease is generally associated with factor V activity below 1%, although bleeding severity does not always correlate closely with plasma factor V levels [5]. In our patient, several early clues of an underlying bleeding disorder were present: Severe neonatal anemia with markedly prolonged PT and INR, followed by a hematoma at the vaccination site. Despite these warning signs, the diagnosis was established only after the occurrence of massive intracranial hemorrhage. The combination of severe factor V deficiency, a homozygous frameshift variant, intracranial hemorrhage with intraventricular extension, and the need for decompressive craniectomy makes this case clinically distinctive. Management of congenital factor V deficiency relies primarily on FFP because a licensed factor V-specific concentrate is not routinely available [6].

Factor V is synthesized predominantly by hepatocytes, with a proportion stored in platelet α -granules after

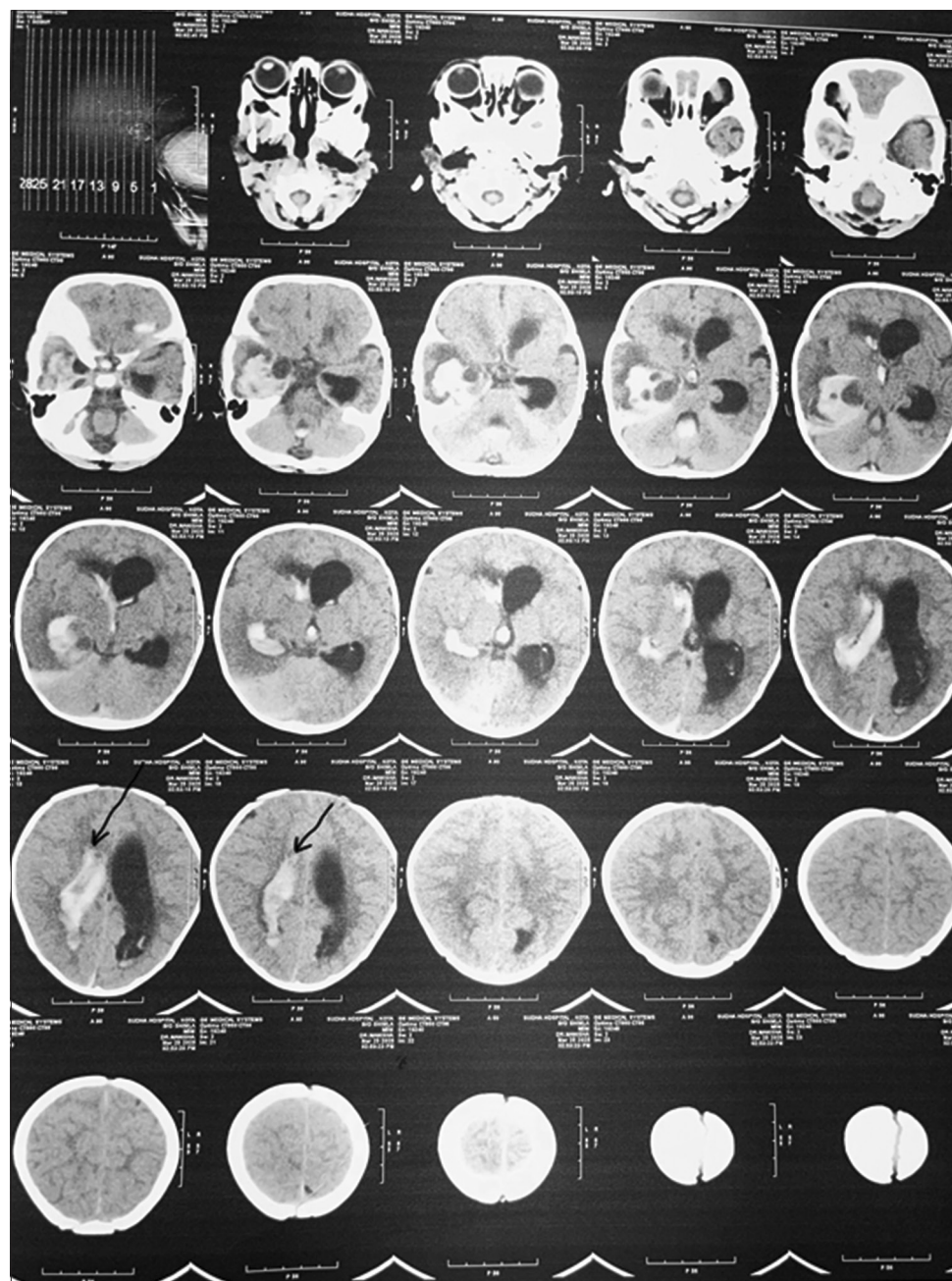


Figure 1: Non-contrast computed tomography of the brain showing a large right temporal intraparenchymal hemorrhage with intraventricular extension into the bilateral lateral ventricles, third, and fourth ventricles, resulting in ventriculomegaly. Black arrows indicate the intraparenchymal hemorrhage and intraventricular blood. There is significant mass effect with effacement of adjacent sulci and cisternal spaces, compression of the ipsilateral temporal horn, and features suggestive of uncal herniation

uptake from plasma, and functions as a critical cofactor in the prothrombinase complex, accelerating the conversion of prothrombin to thrombin. Consequently, factor V deficiency prolongs both PT and aPTT, while thrombin time is generally normal [5]. The severity of bleeding does not always correlate with plasma factor V levels because platelet-derived factor V contributes to local hemostasis, helping to explain the variable clinical phenotype [5,7]. Spontaneous intracranial hemorrhage is an uncommon but devastating complication and has been described in neonates and young infants with severe factor V deficiency [3,8].

The initial differential diagnosis for prolonged PT and severe anemia in infancy included vitamin K deficiency

bleeding, disseminated intravascular coagulation, liver disease, and an acquired coagulation inhibitor. Vitamin K deficiency was considered less likely because intramuscular Vitamin K prophylaxis had been given at birth and Vitamin K was again administered after the vaccination-site hematoma, while the later presentation showed persistent marked coagulation abnormality with factor V activity <1%. A consumptive coagulopathy was less likely in the setting of a normal platelet count at the neonatal presentation. An acquired inhibitor was considered unlikely because the mixing study corrected the prolonged clotting times. The measured levels of factors II, VII, VIII, IX, and X were not reduced, supporting an isolated factor V defect rather than a broad reduction in multiple

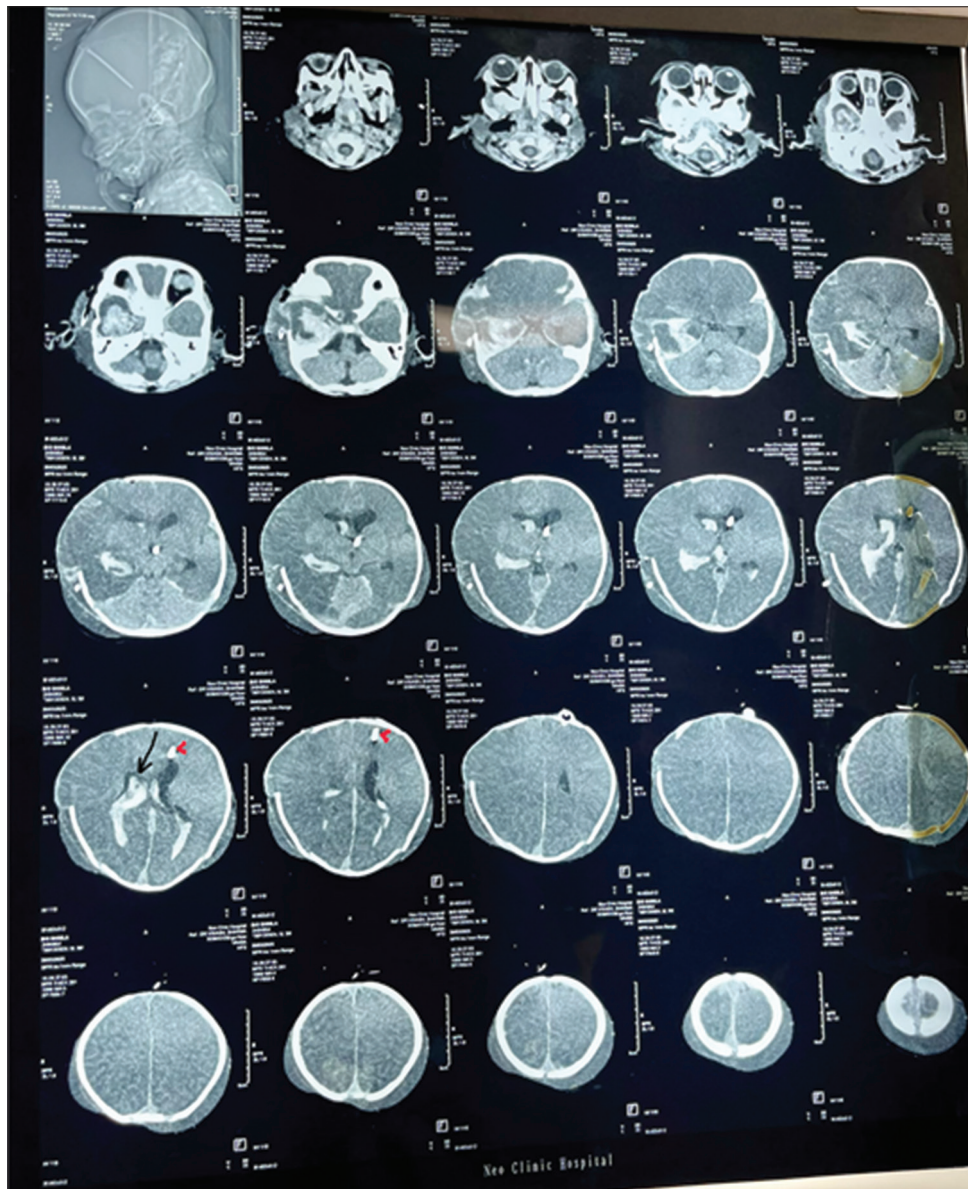


Figure 2: Follow-up non-contrast computed tomography brain demonstrating a right fronto-temporo-parietal craniectomy defect with drain in situ. Diffuse cerebral hypodensity with loss of gray-white matter differentiation, predominantly in the parieto-occipital regions, suggestive of cerebral edema/infarction, is noted. A residual intraparenchymal hemorrhage is present in the right basal temporal lobe (black arrow). An Ommaya reservoir (red arrowhead) is seen within the left lateral ventricle with the catheter tip extending into the third ventricle, with associated cerebral edema and herniation of brain parenchyma through the craniectomy defect

coagulation factors. Molecular analysis subsequently identified a homozygous pathogenic F5 frameshift variant, confirming the inherited diagnosis [5,9,10].

FFP remains the mainstay of treatment for acute bleeding and perioperative replacement in congenital factor V deficiency because specific factor V replacement is generally unavailable [6,11]. Published reports describe initial FFP doses of approximately 15–20 mL/kg, with subsequent dosing individualized according to clinical bleeding and coagulation parameters [12,13]. In the present case, the child received four FFP transfusions (10 mL/kg) on 4 consecutive days, after which the coagulation parameters normalized, together with intensive care and neurosurgical management. Platelet transfusion may have a role in selected severe or refractory bleeding because platelet α -granules contain factor V [5,11].

This case highlights the importance of recognizing rare coagulation factor deficiencies in infants presenting with intracranial hemorrhage despite Vitamin K prophylaxis. The combination of unexplained neonatal anemia, markedly prolonged PT/INR, a hematoma after vaccination, and later catastrophic intracranial bleeding should prompt early comprehensive coagulation testing. Early diagnosis allows timely plasma replacement, appropriate genetic counseling, bleeding precautions, and planning for future invasive procedures. The literature also demonstrates that severe factor V deficiency can present with intracranial hemorrhage in early life and may require repeated plasma replacement, underscoring the need for early recognition and individualized management [12,13]. Comparison of the present case with published reports is shown in Table 1.

Table 1: Brief comparison of the present case with published reports of severe congenital FV deficiency presenting with intracranial hemorrhage. The comparison emphasizes age at presentation, severity of FV deficiency, molecular findings, and the need for plasma replacement

Report	Age/Presentation	FV/Genetics	Management/Outcome
Current case	3 months; massive right temporal ICH with IVH and mass effect	FV <1%; homozygous F5 frameshift c. 2862del (p.Ser955AlafsTer4)	Repeated FFP; decompressive craniectomy and Ommaya reservoir; survived with persistent neurodevelopmental concerns
Neonatal case report (2007)[12]	5 weeks; intracerebral bleed after neonatal bleeding clues	FV <0.01 IU/mL; severe congenital deficiency	FFP 20 mL/kg 4 times weekly; no further bleeds reported through 21 months; neurodevelopment normal
Congenital FV deficiency with ICH (2022)[13]	2 months; intracranial hemorrhage	FV 0.9%; compound heterozygous F5 variants	FFP-based management; emphasizes early coagulation testing and genetic diagnosis

ICH: Intracerebral hemorrhage, IVH: Intraventricular hemorrhage, FV: Factor V, FFP: Fresh frozen plasma

CONCLUSION

Severe congenital factor V deficiency is a rare but life-threatening cause of intracranial hemorrhage in infancy. Early recognition of warning signs such as unexplained neonatal anemia, persistent prolongation of PT and aPTT, and bleeding after minor procedures can facilitate diagnosis before catastrophic hemorrhage occurs. Coagulation factor assays, mixing studies, and molecular testing establish the diagnosis and guide counseling and long-term management. In severe bleeding, prompt FFP replacement, intensive care, and timely neurosurgical intervention may be lifesaving.

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