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Letter to the Editors-in-Chief

A novel F7 mutation (p.Gly217Arg) associated with infantile intracranial hemorrhage successfully managed with rFVIIa

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To The Editor

Congenital factor VII (FVII) deficiency is a rare autosomal recessive bleeding disorder, with an estimated incidence of approximately 1 in 500,000 individuals worldwide [1]. The clinical spectrum is remarkably heterogeneous, ranging from asymptomatic laboratory abnormalities to severe and life-threatening hemorrhages, such as intracranial hemorrhage (ICH) [2]. Herein, we report an infant with a novel F7 gene mutation who presented with subdural hemorrhage and was successfully managed with recombinant activated factor VII (rFVIIa).

A 2-month-old female infant, born to consanguineous parents, was admitted with seizures and irritability. Cranial imaging revealed a subdural hemorrhage. Laboratory evaluation demonstrated markedly prolonged prothrombin time (PT) of 76 s and INR of 6.83, with reduced FVII activity of 5.4 %. Additional parameters included a normal activated partial thromboplastin time (aPTT), hemoglobin 11.2 g/dL, platelet count 312 $\times$ 10^9/L, and normal fibrinogen level (280 mg/dL). Liver function tests (AST, ALT, total bilirubin) were within reference ranges, excluding secondary coagulopathy.

Genetic analysis identified a homozygous missense variant in exon 7 of the F7 gene, c.649G > A (p.Gly217Arg). This variant is absent from major population and disease databases (ClinVar, EAHAD, gnomAD). While another nucleotide substitution at the same codon (c.649G > C, p.Gly217Arg) has previously been classified as likely pathogenic, the present substitution (c.649G > A) has not been reported, suggesting a novel likely pathogenic variant.

The p.Gly217Arg substitution is located within the catalytic domain of FVII. In silico analyses (PolyPhen-2 and MutationTaster) predict a deleterious effect. The replacement of a small nonpolar glycine by a positively charged arginine may disturb local folding and impair catalytic function.

The patient received rFVIIa at a dose of 30 μg/kg every 6 h during the acute phase, which resulted in rapid correction of coagulation parameters and clinical stabilization. No further bleeding episodes were observed. Neurological evaluation at discharge revealed normal tone, reflexes, and age-appropriate motor development. EEG did not show epileptiform activity, and neurodevelopmental assessment at 3 months confirmed intact cognitive and motor milestones. She remained clinically stable at follow-up.

Intracranial hemorrhage is a major cause of morbidity and mortality in congenital FVII deficiency, particularly in early infancy. In a retrospective study of neonates with severe Factor VII deficiency, most intracranial bleeding events occurred within the first week of life, with high rates of death or severe neurological sequelae [3]. Our case emphasizes the need for early recognition, genetic confirmation, and timely administration of rFVIIa. From a genetic perspective, this variant fulfills ACMG criteria for likely pathogenic (PS1: same amino acid change as a previously established likely pathogenic variant; PM2: absent from controls; PP4: phenotype highly specific for FVII deficiency). The identification of this novel F7 mutation further expands the mutational spectrum of congenital FVII deficiency.

In conclusion, clinicians should maintain a high index of suspicion for FVII deficiency in infants presenting with unexplained ICH and markedly prolonged PT/INR. Comprehensive laboratory evaluation and genetic testing not only confirm the diagnosis and support counseling but also contribute to genotype–phenotype correlation. A multidisciplinary approach involving hematologists, neurologists, and geneticists is essential for optimizing outcomes in such rare and severe presentations.

Ethical declarations

Availability of data and materials: All data generated or analyzed during this study are included in this published article (and its supplementary information files).

CRediT authorship contribution statement

Mustafa Ozay: Writing – original draft. **Ugur Gumus:** Data curation, Formal analysis. **Ekrem Ünal:** Project administration, Writing – review & editing.

Informed consent

The family of the patient signed the free and informed consent form. In addition, appropriate permissions have been obtained for reproduced images.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

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Author contributions

All authors certify that she/he has participated sufficiently in the intellectual content and the analysis of data. All the authors took part in the follow-up and care of the patient. Each author has reviewed the final version of the manuscript and approved it for publication.

Declaration of competing interest

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