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Case Report

Novel gene mutation causing type 3 Von Willebrand disease: a case report and review of literature

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ABSTRACT

Von Willebrand disease (VWD) Type 3 is an uncommon bleeding disorder, resulting from the near absence of Von Willebrand factor (VWF) and extremely low factor-VIII levels. It is a close differential diagnosis of hemophilia. A wide heterogeneity of VWD mutations are reported in the literature. We report a 16-year-old girl with hemarthrosis, finally diagnosed with Type 3 VWD. Clinical exome sequencing confirmed the diagnosis, revealing a homozygous mutation c.4387G>T (p. Glu1463Ter) in exon 28 of the VWF gene, a unique mutation not yet reported in the literature.

Keywords: Hemophilia, Factor-viii, VWF, VWD, Hemarthrosis

INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder. The estimated prevalence ranges from 7 per million children with type 1 VWD to 1-2 per million children with type 2 and type 3 Von Willebrand disease.[1] It is caused due to a functional or a quantitative deficiency of the VW. VWF is a large multimeric glycoprotein crucial for coagulation and hemostasis primarily involved in the activation of platelets and platelet aggregation. It is also a major carrier protein for factor VIII and is essential for its normal recovery, stability and survival. Impaired function or decreased quantity of VWF accelerates the degradation of factor VIII, causing major bleeds.[2]

Three types of VWD are described. Type 1 and 3 are due to quantitative deficiency of VWF and type 2 is due to qualitative defects in VWF.[3] Type 3 is a rare form, resulting in the near absence of VWF and extremely low factor VIII levels, manifesting as severe bleeding with major deficiencies in primary and secondary hemostasis and can be mistaken for severe hemophilia.[4] VWD predominantly shows an autosomal dominant inheritance with the exception of type 2N and type 3 VWD having an autosomal recessive inheritance. We are reporting an adolescent girl with type 3 VWD, with a unique homozygous mutation.

CASE REPORT

A 16-year-old female, born out of second-degree consanguineous marriage, presented to us with spontaneous swelling of the right elbow for three months without any significant trauma. The antenatal and postnatal periods were uneventful. Her past history was significant for recurrent prolonged epistaxis, prolonged bleeding following tooth shedding, easy bruising and swelling of the ankle and knee joints following minimal trauma. A history of heavy menstrual bleeding for the

past six months was also present. No significant episodes of bleeding were reported in her family members. Investigations done elsewhere revealed prolonged activated partial thromboplastin time (90 sec). The parents did not pursue further evaluation and management due to social constraints.

A clinical examination at our centre revealed pallor and ecchymosis at the phlebotomy site. Musculoskeletal examination revealed a tender swelling of the right elbow, with restricted active and passive range of motion. Multiple ecchymoses of varying sizes and ages were noted on the trunk and limbs. Other joint examinations did not reveal significant findings.

Complete blood count (Table 1) revealed low hemoglobin with normal platelet count. The coagulation profile (Table 2) showed normal levels of prothrombin time and thrombin level. Activated partial thromboplastin time (aPTT) was prolonged, which was corrected on mixing with normal plasma as part of a mixing study. Lupus anticoagulant was absent. Factor assays showed extremely low levels of factor VIII. Other coagulation factors were within the normal range. Ristocetin-induced platelet aggregation was decreased, even at higher concentrations of ristocetin, which raised a concern for Von Willebrand factor deficiency. VWFr activity assay revealed extremely low levels of VWF, suggestive of type 3 Von Willebrand disease. Clinical exome sequencing confirmed the diagnosis, detecting a homozygous mutation: c.4387G>T (p. Glu1463Ter) in exon 28, a unique mutation not yet reported in the literature.

Her hemarthrosis was managed with rest, ice compressions, compression bandage, limb elevation, antifibrinolytics, factor-VIII concentrates (1:1 Factor-VIII: VWF) and physiotherapy.

Table 1: Complete blood count and differential count.

Test	Results	Normal range
Hb (g/dL)	8.9	12-15
RBC (million/mm^3)	3.73	3.8-4.8
HCT (%)	29.3	36-46
WBC (cells/mm^3)	6190	4000-11000
Platelets (lakhs/mm^3)	4.06	1.50-4.50
MCV (FL)	78.6	83-101
MCH (Pico gram)	25.2	27-33
MCHC (g/dL)	32	31.4-34.5

Hb: hemoglobin; RBC-red blood cell count; HCT: hematocrit; WBC-white blood cell count; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width.

Table 2: Blood coagulation findings.

Test	Results	Reference range
PT (Sec)	10.5	11.0-13.4
PTT (clot based) (Sec)	65.8	20.6-30.6
PTT mix (Sec)	30.6	
Factor 8 (clot based) (%)	3.4	70-150
Factor 9 (clot based) (%)	88.1	70-120
VWF (immunoturbidimetry) (%)	7.6	47.8-173.2
Platelet aggregometry with ristocetin 1.2 mg/ml concentration (%)	0.8	72-95
Platelet aggregometry with ristocetin 2.0 mg/ml concentration (%)	2	76-95
Factor 5 (clot based) (%)	135.2	70-120
Factor 2 (clot based) (%)	110.7	70-120
Factor 10 (clot based) (%)	134.5	70-120
Factor 11 (clot based) (%)	74.6	70-120
Factor 12 (clot based) (%)	27.5	70-120
Fibrinogen (mg/dL)	249.9	250-520
Thrombin test (clot based) (Sec)	16.5	16.4-18.8
Lupus anticoagulant (dRVVT method)	Absent	Absent/ Present

PT: prothrombin time; INR: international normalised ratio; PTT: partial thromboplastin time; VWF: von Willebrand factor.

DISCUSSION

Type 3 VWD is a rare variant. Its inheritance is usually autosomal recessive. More recently, even compound heterozygous inheritance has been identified.[5] Epidemiological data predominantly from western literature estimates a prevalence of 0.1-5 per million.[6] Trasi et al. postulated that type 3 patients are more numerous in India owing to a high rate of consanguineous marriages in certain communities and an underdiagnosis of milder variants.[7]

Tosetto et al in their international and collaborative cross-sectional study, described a clinical phenotype of type 3 VWD patients enrolled by 3WINTERS-IPS and MCMDM-1 VWD studies, with particular emphasis on bleeding symptoms and comparison with type 1 VWD patients.[8] 223 unrelated type 3 VWD patients were enrolled in the study. Hemarthroses, deep hematomas, intracranial bleeding, menorrhagia and bleeding in the oral cavity were reported to be five-fold more frequent in type 3 VWD patients compared to VWD type 1. Bleeding phenotypes were more severe when the VWF antigen level was less than 20 IU/dL at diagnosis of type 3 VWD. An apparent clustering of hemarthroses with gastrointestinal bleeding and epistaxis was noted in this study in type 3 VWD, a finding which was present in our patient. Post-surgical bleeding or post-extraction bleeding was similar to that reported for type 1 VWD.[8]

A recent cohort study by Kasatkar et al enumerated the molecular pathology in a large series of unrelated type 3 VWD families in India.[9] This study enrolled 85 unrelated type VWD patients. Mutations were identified in 77 cases combining several techniques (PCR-RFLP, MLPA, and direct DNA sequencing). Fifty-nine different mutations were identified including nonsense (34%), missense (22%), splice site (6.8%), gene conversions (10.2%), insertions (3.4%), duplication (1.7%), small deletions (17%) and large deletions (5.1%), of which 34 were novel mutations. This study shed light on the extreme heterogeneity in genetic mutations causing type 3 VWD, with arginine hotspot mutations being the most common. Nineteen patients in this study were discovered to have a wide spectrum of mutations at exon 28. Missense mutations and gene conversions were the most common abnormalities reported at this exon. None of the listed mutations was identified in our patient.

Though mutations in exon 28 are listed, our patient is unique, as this is the first reported pathogenic homozygous mutation identified at exon 28 with a c.4387G>T (p.Glu1463Ter) defect leading to type 3 VWD. A homozygous nonsense variation in exon 28 of the VWF gene (chr12: g.6019031C>A; Depth: 142x) that results in a stop codon and premature truncation of the protein at codon 1463 (p.Glu1463Ter; ENST00000261405.10) was detected as a variant description.

The development of inhibitors to VWF is a rare phenomenon.[10] Alloantibodies against VWF are reported in 7-14% of type 3 VWD patients who have received multiple transfusions. Existing literature points to large deletions being associated with alloantibodies. Our patient is theoretically at risk of developing antibodies as well as life-threatening bleeding and needs close monitoring.

CONCLUSION

This case is a unique mutation in type 3 VWD and is not reported in any of the known VWD mutation databases. Genetic mutations causing type 3 VWD demonstrate wide variation. Data from India is limited, and further research is essential to enumerate and understand genetic and phenotypic characteristics. Additional testing of unaffected and affected family members will yield more information in curating appropriate protocols for testing and provide a better understanding of the genetic profile of type 3 VWD.

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