P1659 UNIQUE GENOTYPE-PHENOTYPE RELATIONSHIP IN VON WILLEBRAND DISEASE: A SINGLE CENTRE EXPERIENCE

Topic: 33. Bleeding disorders (congenital and acquired)

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Background:

von Willebrand Disease (VWD) is the most common hereditary coagulation disorder. Generally, coagulation disorders are more prevalent in communities with high rate of consanguinity. Due to segregation of multiple alleles, combinations of abnormal variants causing unique clinical presentations can occur.

Aims: We aim to present our single centre experience of VWD in pediatrics.

Methods: Retrospective data analysis of all pediatric patients diagnosed with (VWD) throughout a period of 10 years, dating from January 2012 till December 2021. In addition, molecular testing using next generation sequencing (NGS) of a family, with a spectrum of bleeding phenotypes was done.

Results:

Out of 455 cases with hereditary coagulation disorders, 219 (48%) were diagnosed with VWD throughout the study period (141 girls and 78 boys), with an age of presentation ranging from 18 months to 14 years. Significant bleeding episodes were encountered in 42/219 patients (19%). History of consanguinity was documented in 175 cases (80%).

The most common presenting feature was mucocutaneous bleeding, followed by menorrhagia and then post-traumatic/post-surgical hemorrhage. Factor replacement therapy was used in 34 cases and desmopressin (DDAVP) in 22 cases. Hormonal therapy was offered to 18 girls presenting with menorrhagia. However, only 7 of them were compliant.

The index case is a 4-year-old girl, presented with profuse post-adenotonsillectomy hemorrhage. Her past history was negative for any significant bleeding, but no previous surgical challenges. Parents are cousins, and family history was irrelevant. Routine preoperative investigations didn’t reveal any abnormalities apart from raised mean platelet volume (14 fl), and a platelet count of 180 x 10^9/L. Bleeding didn’t respond optimally to FFP, but controlled with multiple platelet transfusions and recombinant activated factor VII.

Molecular studies using NGS revealed two different heterozygous variants in the CD36 gene. The first heterozygous variant was NM_001001547.2:c.338_339del (p.Ser113Phefs*20), a frameshift variant which results in loss of function of the protein product of CD36 gene. The second was deletion of exons 2 and 3 (NM_001001547.2:c.1_120del), which results in loss of a significant portion of the coding region of CD36 gene. To our knowledge, both novel variants have not been reported in the literature. Biallelic mutations in CD36 are associated with platelet glycoprotein IV deficiency (PG4D), characterized by macrothrombocytopenia with variable bleeding phenotype (PubMed: 7533783; OMIM: 173510). In addition, A heterozygous variant in the VWF gene, NM_000552.4:c.3692A>G (p.Asn1231Ser), was identified.

This heterozygous variant was reported in a case with von Willebrand disease type 1 (PubMed: 28971901). The distinctive combination of these three variants explains the severe bleeding phenotype. NGS identified the same heterozygous frameshift variant of CD36 in the mother, while the father carries both the deletional variant of CD36 and the missense variant of VWF gene. Two sisters (ages: 8 & 15 years) harbor the heterozygous VWF gene variant.
On further enquiries, the eldest was found to have mild to moderate menorrhagia, that didn’t require any medical advice. Family pedigree is shown in figure 1.

**Summary/Conclusion:** Genotype-phenotype correlation is mandatory in coagulation disorders, presenting with significant bleeding episodes.