Case Report

Von Willebrand disease type 2N in a neonate: A case report

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ABSTRACT

The occurrence of von Willebrand disease (VWD) is relatively uncommon. Type 1 is more prevalent than the other types. The disease prevalence is about only 1%, in which type 1 includes 60–80% of the cases, type 2 includes 20–30% of cases, and type 3 accounts for < 5% of the cases. It mainly arises due to homozygous or composite heterozygous mutations in the von Willebrand factor gene (12p13.3) leading to synthesis of a truncated protein or allele silencing. We report a case of newborn 34-week gestation who presented with abdominal distension with melena and seizures. The child's plasma was studied and it revealed VWD.

Key words: Activated partial thromboplastin time, Consanguinity, Factor VIII, Melena, Platelet count, Von Willebrand disease

Von Willebrand disease (VWD) is the most common human inherited bleeding disorder. Its incidence is approximately 1% [1]. Originally described by the Finish physician Erik von Willebrand in 1926, VWD occurs due to quantitative deficiencies and/or qualitative defects in von Willebrand factor (VWF), a complex plasma protein with multiple functions, overall contributing to the formation of a platelet thrombus at the site of injury preventing blood loss [2]. VWF accomplishes the major hemostasis function by anchoring platelets to the sites of vascular injury (primary hemostasis function), binding to factor VIII (FVIII), thus protecting FVIII from degradation, and delivering it to the sites of vascular injury (thereby facilitating secondary hemostasis). VWF binds to platelets through several receptors, most notably glycoprotein Ib (GPIb), but also GPIIb/IIIa. VWF also binds to subendothelial matrix components, most notably collagen and thus, facilitates anchoring of platelets to damaged endothelium by forming an adhesive bridge.

The peculiar structure of VWF, in size and formation of multimers, is relevant, as the larger VWF molecules facilitate better anchoring of platelets and thus thrombus formation and prevention of bleeding. This is a heterogeneous quantitative or qualitative deficiency in the VWF, also associated with a concomitant decrease in FVIII, since VWF serves as the carrier protein for FVIII [3]. The deficiency of VWF results in bleeding disorder variable in severity according to the degree of deficiency and the specific characteristics of the molecule, having features of both primary and secondary hemostatic defects. Clinical expression of VWD is usually mild in type 1, moderately severe with type 2, and most severe with type 3. The severity of bleeding correlates with the degree of the reduction of FVIII. Mucocutaneous bleeding is a typical, prominent manifestation of the disease and may affect the quality of life. However, the rate of spontaneous bleeding is low even in patients with severe VWF deficiency [4]. We report the case of a neonate with melena which on further investigations revealed Type 2NVWD.

Access this article online	
Received - 18 June 2020 Initial Review - 04 July 2020 Accepted - 18 August 2020	Quick Response code
DOI: 10.32677/IJCH.2020.v07.i08.006	

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The patient was born at 34 weeks gestation and was delivered by lower segment cesarean section in view of fetal distress. She was the first child of 3rd degree consanguineous parents and in previous two generations as well. The age of the mother was 23 years and father 30 years. The antenatal period was uneventful. The child weighed 1960 g at birth and was appropriate for gestational age.

Initial clinical examination of the neonate was normal. Later, the newborn had jitteriness on the 1st day of life, and investigations were carried out. The initial hemoglobin was 13.6, packed cell volume was 42.8%, and platelet count (PC) was 30,700/mm^3. Later, the patient developed intolerance to feed and subsequently on day 6th of life she developed seizures. In due course of time, she developed melena on day 12th of life for which a number of laboratory investigations were carried out. Ultrasonography cranium was normal, PC was 8000/mm^3, and activated partial thromboplastin time (aPTT) was more than 1 min but deranged. The melena was persistent for which baby received platelet and fresh frozen plasma transfusion on the very same day and packed red blood cells transfusion on day 13th of life.

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Table 1: Laboratory investigations at different time periods

Investigation	2nd day of life	5th day of life	7th day of life	10th day of life	17th day of life	18th day of life	23rd day of life
Hb	13.6	12.1	10.3	14.5	8.4	7.7	9.5
PCV	42.8%	37.1%	31.9%	45.2%	25.6%	23.7%	28.1%
PC	307,000	60,000	4000	4000	8000	100,000	110,000
PT		25 s		24 s			19.9 s
INR		2.04		1.95			1.07
aPTT		>1 min		>1 min			>1 min

Hb: Hemoglobin, PCV: Packed cell volume, PC: Platelet count, PT: Prothrombin time, INR: International normalized ratio

Again, she developed melena on 23rd day of life, so a panel of tests was done, and in mixing studies the PC was 110,000/mm^3, PT was 19.9 s, international normalized ratio-1.07, and aPTT was 104.4 s [Table 1]. In mixing study with adsorbed plasma, aPTT got corrected, so factor deficiency was suspected. Then, the factor assay was done and FVIII level was <1% of normal. The neonate received cryoprecipitate transfusion and she showed improvement. Further VWF:Ag test was done which was normal, clearly suggesting binding defect of FVIII with VWF (Type 2NVWD).

DISCUSSION

Type 2NVWD is a rare recessively inherited bleeding disorder, comprising 1–2% of all VWD patients [5]. The gene coding for VWF is located at the chromosome 12p13.2. It is a large gene consisting of 178 kilobases and containing 52 exons. VWD is a complex genetic disorder in which three subtypes have been described. Type 1 account for 70% of cases, is the mildest form of the disease and caused by a partial deficiency of VWF. Type 2 cases are more difficult to diagnose due to the qualitative nature of the defect. These defects range from absence of certain protein multimers for binding during hemostasis to improper binding and decreased affinity. This Type 2 sub-group accounts for approximately 20–30% of cases. Qualitative VWD type 2 is further divided into four variants: 2A, 2B, 2N, and 2M, based on the characteristics of the dysfunctional VWF. The type of mutation affecting the VWF locus forms the basis for classification of most type 2 VWD variants.

In our study, FVIII level was <1% of normal and VWF:Ag was normal, clearly suggesting binding defect of FVIII with VWF (Type 2NVWD). Type 2N is a VWD variant characterized by a defect in the FVIII binding function of VWF, with reduced FVIII but normal VWF levels [6]. It may be misdiagnosed as hemophilia A [7]. In type 2N, the VWF is not able to function as the carrier and protector of FVIII. The level of FVIII in the body is low as it does not have the VWF to protect it from being broken down. With low levels of FVIII, the body cannot make a fibrin clot. A person with type 2NVWD can appear to have mild hemophilia with similar symptoms. Although it is not hemophilia, as the problem is with the VWF and not the FVIII. Another name for type 2N is type 2 Normandy as it was first described in the patient from the Normandy region in France.

In our study, there was third degree consanguinity and history of menorrhagia in maternal grandmother. In a study by Al-Rahal, menorrhagia was the most common manifestation in adolescent and adult females with type 3 VWD [8]. In a case report by Dukka *et al*., the patient improved after administration of recombinant FVIII with no evidence of bleeding present later similar to our case report [5]. In a case report by Echahdi *et al*., the main stay of treatment of VWD was FVIII concentrate and similar to our study after giving cryoprecipitate the baby improved with no further bleeding manifestations [3].

CONCLUSION

VWD is a rare entity often misdiagnosed with hemophilia A. Type 2 NVWD is a qualitative defect characterized by abnormal binding of FVIII with VWF. Parents should be educated about the disease to prevent the complications. The risk of increased bleeding associated with elective and medical procedures should always be considered. Parents should also be explained about the possible treatment options with recombinant FVIII for the disease.

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Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Trivedi P, Tiwari A, Singh N, Kishore K, Thakur NS, Chandramohan GM. Von Willebrand disease tyoe 2N in a neonate: A case report. Indian J Child Health. 2020; 7(8):344-345.