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CASE REPORT

Neonatal Onset Type 2B von Willebrand Disease due to p.Arg1306Trp Variant: a Case Report and a Literature Review

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SUMMARY

Background: **Type 2B von Willebrand disease (VWD) is a less common subtype and is difficult to diagnose. This case report and literature review highlights a rare neonatal onset of type 2B VWD initially misdiagnosed as neonatal alloimmune thrombocytopenia (NAIT).**
Methods: **The neonate presented with severe thrombocytopenia and was unresponsive to NAIT treatments. Genetic testing was conducted because of the unclear family history of thrombocytopenia.**
Results: **Next-generation sequencing revealed a p.Arg1306Trp von Willebrand factor variant, confirming type 2B VWD.**
Conclusions: **This study underscores the critical role of genetic testing in diagnosing challenging cases of neonatal thrombocytopenia, irrespective of family history, and aims to elucidate the clinical manifestations and course of neonatal onset type 2B VWD.**
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KEYWORDS

type 2B von Willebrand disease, thrombocytopenia, neonate, next-generation sequencing

LIST OF ABBREVIATIONS

IV - intravenous
PO - per os
MPD - methylprednisolone
PC - platelet concentrate
IVIG - intravenous immunoglobulin
NGS - next-generation sequencing

INTRODUCTION

Von Willebrand disease (VWD) is the most commonly inherited bleeding disorder, with a prevalence of approximately 1% - 2% in the general population [1]. VWD mainly has three sequential classification systems: types 1, 2, and 3. Types 1 and 3 VWD are quantitative disorders, whereas type 2 VWD is characterized

by qualitative defects resulting from gain-of-function mutations [1].

Type 2B VWD is a less common subtype, with an incidence of approximately 5% of all VWD cases, and is difficult to diagnose [2]. Herein, we report a case of severe thrombocytopenia diagnosed as type 2B VWD caused by the p.Arg1306Trp pathogenic variant. This case demonstrates the difficulty in diagnosing type 2B VWD, while also highlighting the uncommon occurrence of symptom manifestations of this disease during the neonatal period.

CASE REPORT

A male neonate, born at 37 + 5 weeks via Cesarean section with a birth weight of 3,040 g, was admitted on his second day for petechiae and ecchymoses evaluation. His family members, including the mother, father, and older sister, had no relevant medical history. The mother was a 34-year-old woman who had previously delivered a full-term infant without any notable abnormalities. Throughout pregnancy, no significant events occurred, and prenatal examinations did not reveal any problems.

Initial laboratory evaluation revealed a hemoglobin level of 14.3 g/dL, a normal white blood cell count of 10.85 × 10^3/μL, a decreased platelet count of 8 × 10^3/μL, and mean platelet volume of 9.6 fL with large platelets observed. No signs or laboratory results supported a diagnosis of sepsis or disseminated intravascular coagulation. He was initially treated with platelet concentration (PC) transfusion and intravenous immunoglobulin (IVIG) for 3 days to clinically diagnose neonatal alloimmune thrombocytopenia (NAIT).

Although the platelet count increased to 39 × 10^3/μL two days after the treatment, it decreased to 19 × 10^3/μL on the next day. Despite receiving PC transfusion nine times, IVIG infusion three times, two cycles of intravenous methylprednisolone infusion, and two cycles of oral prednisolone over a month, he demonstrated a transient response, and the platelet count remained < 30 × 10^3/μL within seven days after the treatment. Negative blood tests on the mother excluded NAIT-inducing antibodies.

At that time, we noticed that patient had a family history of unexplained thrombocytopenia on the paternal side. A next-generation sequencing (NGS) panel test (59 genes) for platelet disorders was conducted to identify a heterozygous c.3916C>T (p.Arg1306Trp) variant in the von Willebrand factor (VWF) gene (NM_000552.5). Further tests including the factor VIII assay, VWF ristocetin cofactor activity (VWF:RCo), and VWF antigen (VWF: Ag) were performed, and the results were 84% (reference range: 60% - 140%), 32.0% (reference range: 56% - 187%), and 83.2% (reference range: 47% - 197%), respectively. The RCo:antigen ratio was approximately 0.38, confirming a diagnosis of type 2B VWD. This variant has not been reported in general population databases, such as gnomAD v2.1.1. and v3.1.2, and KOVA (https://www.kobic.re.kr/kova/), and has been predicted to be damaging by multiple in silico meta-prediction tools (BayesDel noAF 0.35, MetaRNN 0.92, REVEL 0.769). Situated in the VWFA1 domain essential for platelet glycoprotein binding, the p.Arg1306Trp variant in VWF, as per prior in vitro studies, markedly enhances VWF binding to platelets and sensitivity to shear stress [3,4]. Furthermore, previous studies have reported multiple types of 2B VWD in patients/families [5-7]. Hence, classified as pathogenic, it aligns with the American College of Medical Genetics/Association for Molecular Pathology guidelines [8] and ClinGen recommendations (https://clinicalgenome.org/), supported by evidence codes PM2_Supporting, PP3_Moderate, PS3_Moderate, PP1_Strong, and PP4_Supporting.

Despite recurrent severe thrombocytopenia, the petechiae and ecchymoses improved and no other severe organ hemorrhages were detected. After 58 days of hospitalization, the patient, requiring only two PC transfusions, was discharged with a platelet count of 126 × 10^3/μL at the last follow-up. The clinical course is shown in Figure 1.

DISCUSSION

This report highlights the rarity of neonatal VWD, where symptoms immediately appear after birth, posing a diagnostic challenge due to the limited instances in neonates. The primary aim is to underscore the significance of genetic testing in recurrent neonatal thrombocytopenia and to enhance our understanding of neonatal onset type 2B VWD through a review of case reports.

In the reported case, the recurrence of severe thrombocytopenia despite NAIT treatment, absence of alloantibodies in the maternal serum, and transient response to treatment led to a reconsideration of the initial diagnosis. A family history of thrombocytopenia indicated a possible genetic disorder, subsequently confirmed by NGS to be VWD. Traditional approaches for genetic causes of thrombocytopenia, especially related to potential VWD, involve initiating VWF-related biochemical assays [1,2]. However, the absence of a clear family history posed a challenge, making NGS the initial diagnostic step. This approach, distinct from conventional diagnostics, becomes invaluable in situations where recurrent thrombocytopenia's etiology remains elusive, and standard interventions yield no response. The significance of NGS as a crucial diagnostic tool has become apparent in complex clinical scenarios.

Type 2B VWD in neonates is infrequently documented, displaying variable onset, severity, and symptom presentation, often leading to delayed diagnosis, especially without a family history. We reviewed the data from nine neonates with type 2B VWD to enhance our understanding of this condition during the neonatal period (Table S1). Most cases exhibited general petechiae shortly after birth, whereas others presented with severe

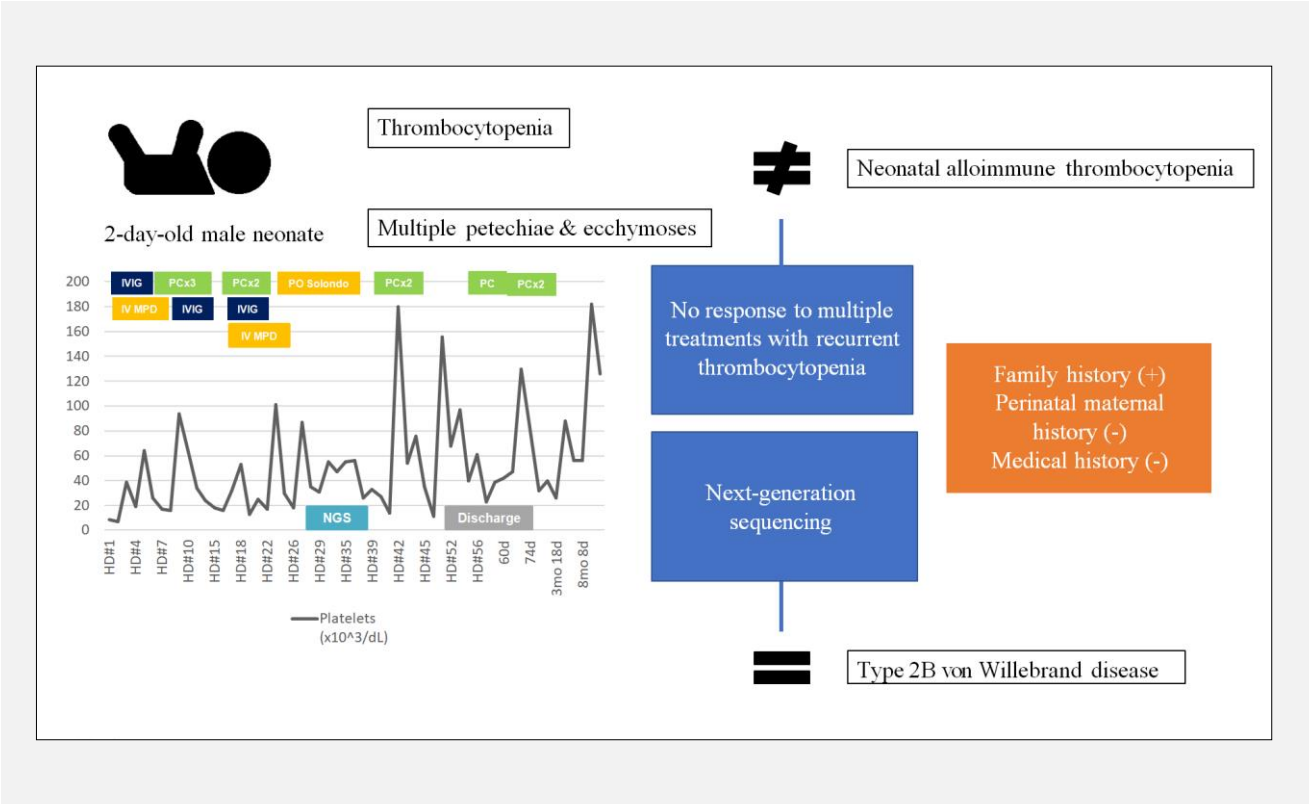

Figure 1. The clinical and laboratory course of the patient, from the initial manifestation of symptoms to the diagnosis.

bleeding symptoms, such as multiple hematomas, gastrointestinal bleeding, or intracranial hemorrhage. Three patients had documented family histories of type 2B VWD, two had family histories of unexplained thrombocytopenia, and one had maternal immune thrombocytopenia purpura. Most reviewed cases had VWF profiles oriented toward type 2B VWD. Only one case report indicated a normal VWF profile, except for high-molecular-weight VWF multimers, emphasizing the clinical importance of genetic testing. Furthermore, because severe thrombocytopenia and a small sample volume in neonates can limit platelet function analysis, genotyping can guide the diagnosis of VWD or allow confirmation of the VWD subtype.

Based on individual case reports, severe bleeding or surgery may warrant a combination of factor VIII (FVIII)/VWF and PC transfusion. However, in less severe cases such as ours, treatment mainly involves PC transfusion and close observation. In most neonatal cases, including our own, where thrombocytopenia was observed, initial suspicions typically revolved around NAIT or immune thrombocytopenia, except for instances with a significant family history of type 2B VWD and a case where bleeding symptoms were present, antifibrinolytic agents along with FVIII/VWF concentrates were applied. Consequently, common practices involve PC transfusion, IVIG, and steroid preparations. In most cases, regardless of the initial treatment, patients demonstrated spontaneous resolution of clinical symptoms and platelet counts as they grew, indicating a favorable recovery.

CONCLUSION

We report a case of severe neonatal thrombocytopenia diagnosed as type 2B VWD that was initially suspected to be related to NAIT. The persistence of severe thrombocytopenia, absence of antibodies in the maternal serum, and lack of treatment efficacy raised doubts on the initial diagnosis. The family history was later reported in our case. A diagnosis of type 2B VWD should be considered in neonates with severe thrombocytopenia and poor treatment response, even without a family history. Conducting genetic tests in the early stage allows pediatricians to efficiently confirm VWD and its subtypes, enabling timely and appropriate treatment of bleeding events.

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Declaration of Interest:
The authors declare no competing financial interests.

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