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CASE REPORT – OPEN ACCESS



# Type 2B Von Willebrand Disease Mimicking Autoimmune Thrombocytopenia in the Neonatal Period

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ABSTRACT

**Background:** Type 2B von Willebrand disease (VWD) is a hereditary bleeding disorder caused by changes in the von Willebrand factor (VWF), which increases the binding of VWF to platelets. Type 2B VWD may present with thrombocytopenia.

**Case Report:** A four-day-old newborn was brought to the neonatal intensive care unit presenting with bleeding and severe thrombocytopenia. The platelet level was 10,000/mm$^3$, and coagulation tests were normal. There were no clinical evidence of sepsis; therefore, alloimmune or autoimmune thrombocytopenia was suspected. When we found out that her mother and relatives had intermittent thrombocytopenia, advanced tests were performed. Ristocetin cofactor activity was low; type 2 VWD was considered. Using low-dose ristocetin, we increased platelet aggregation. Heterozygous c.3946G > A (p.Val-1316Met) mutation was detected, and type 2B VWD was diagnosed.

**Conclusion:** Type 2B VWD may cause a diagnostic problem in the differential diagnosis of neonatal thrombocytopenia including neonatal autoimmune thrombocytopenia.

**Keywords:** von Willebrand disease type 2B, von Willebrand factor, thrombocytopenia

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## INTRODUCTION

Von Willebrand disease (VWD) is an inherited bleeding disease related with deficiency, dysfunction, or both of von Willebrand factor (VWF) (1–3). There are three basic types of VWD. While type 2 is due to a qualitative defect, types 1 and 3 are quantitative defects of VWF (1–3). In type 2B VWD, patients tend to have a bleeding tendency related to loss of high molecular weight VWF multimers and labile thrombocytopenia (1–3). Neonatal alloimmune thrombocytopenia (NAIT) and maternal immune thrombocytopenia should be considered in an infant presenting with severe thrombocytopenia without infection (2, 4). Herein, we present a case showing diagnostic difficulties and mimicking autoimmune thrombocytopenia.

## CASE REPORT

A four-day-old female newborn was admitted to the pediatric department with jaundice and blood in the stool. Due to hyperbilirubinemia and severe thrombocytopenia, she was transferred to the neonatal intensive care unit. Total bilirubin was 17.9 mg/dL and phototherapy was started immediately. As the platelet (Plt) count was 10,000/mm$^3$, a consultation from the pediatric hematology department was sought. Head ultrasound was negative for intracranial hemorrhage. Physical examination revealed an icteric appearance, small bruises, and petechial rashes on the body. The liver and spleen edge were palpated 1 cm under the rib and thought to be physiological for the newborn. Plt concentrate was immediately transfused.

Laboratory tests found white blood cell: 13,000/mm$^3$, hemoglobin: 14.8 g/dL, Plt: 10,000/mm$^3$, mean corpuscular volume: 97 fL, mean platelet volume: 8.1 fL. Prothrombin time, activated partial thromboplastin time, and fibrinogen results were within normal limits. Blood chemistry showed that only total bilirubin was 17.9 mg/dL and indirect bilirubin was 17.2 mg/dL. Bilirubin levels decreased with phototherapy.

The patient had no e no clinical findings of sepsis. The mother's Plt count during pregnancy was about 50,000/mm$^3$. Neonatal autoimmune thrombocytopenia could be the differential diagnosis. However, when we questioned her family history, her mother, grandfather, aunt, and uncle had a history of intermittent thrombocytopenia. Advanced coagulation tests were performed considering genetic bleeding disorder (Table 1). Factor VIII (FVIII):C: 53%, VWfAg: 50.3 IU/dL, VWfAC (Ricof): 5.1%, VWfAC (Ricof)/VWfAg: 0.1, FVIII:C/VWfAg: 0.8. When ristocetin cofactor activity was low, type 2 VWD was considered. Ristocetin-induced Plt aggregation (RIPA) test was performed. In the RIPA test, although Plt aggregation is low in healthy people at low ristocetin levels, the RIPA test showed increased aggregation in our patient. Symptoms of gastrointestinal bleeding

**Table 1.** Laboratory tests of the patient and her relatives

| | Platelets (x10³/mm) | VWF:Rco (UI/dL) | VWF:Ag (U/dL) | VWF:Rco/ VWF:Ag ratio | FVIII:C % | FVIII/VWF: Ag ratio | RIPA % 0.6 mg/mL | Genetic analysis |
|---|---|---|---|---|---|---|---|---|
| Child | 10 | 5.1 | 50.3 | 0.1 | 58 | 0.8 | 65 | c.3946G>A (p.Val1316Met) heterozygous |
| Mother | 80 | 32.2 | 78.5 | 0.41 | 59.1 | 1.46 | 72 | c.3946G>A (p.Val1316Met) heterozygous |
| Uncle | 46 | 7 | 56.8 | 0.3 | 78 | 1.6 | ND | c.3946G>A (p.Val1316Met) heterozygous |
| Aunt | 96 | 11.5 | 50.2 | 0.2 | 76.4 | 1.52 | 68 | c.3946G>A (p.Val1316Met) heterozygous |
| Grand father | 110 | 21.6 | 57.8 | 0.37 | 85 | 1.47 | ND | c.3946G>A (p.Val1316Met) heterozygous |

VWF: Von Willebrand factor; Rco: Ristocetin cofactor; Ag: Antigen; FVIII: Factor VIII; C: clotting; RIPA: Ristocetin-induced Plt aggregation

improved after Plt transfusion without the need for FVIII/VWF concentrate. Genetic testing of the VWF gene from the whole family revealed a heterozygous c.3946G>A (p.Val1316Met) mutation in our patient and other symptomatic family members. Our patient is now nine months years old without any complaint of severe bleeding.

## DISCUSSION

VWD is an inherited hereditary hemorrhagic disorder especially related with mucocutaneous hemorrhage. VWD is caused by a deficiency (type 1 and 3) or qualitative abnormality (type 2) of VWF (1–3, 5–8). VWF also prolongs the half-life of factor VIII (FVIII) and concentrates it at the site of the damaged endothelium (5–7). Type 2B VWD is a rare subtype with autosomal dominant inheritance (1–3, 9). In this subtype, varying degrees of thrombocytopenia may develop due to the increased affinity of VWF to the glycoprotein 1b (GP1b) receptor on the Plt surface (1–3).

In neonatal thrombocytopenia, a number of causes are considered for the differential diagnosis. NAIT is the most common case of thrombocytopenia in healthy infants. NAIT is the cause of early resistant thrombocytopenia in about one third of newborns with the disease (1–3, 9). Other common causes such as infections, disseminated intravascular coagulation, or autoimmune thrombocytopenia should be investigated. Neonatal autoimmune thrombocytopenia occurs by transferring antibodies against maternal Plt to the fetus. A positive history of thrombocytopenia in the mother during and before pregnancy suggests autoimmune thrombocytopenia in the newborn. However, type 2B VWD rarely can mimic neonatal autoimmune thrombocytopenia.

Mucosal bleeding and superficial hemorrhages such as ecchymosis and petechial are the most common symptoms in VWD. Joint and intramuscular hemorrhages are frequently seen in type 3 VWD, characterized by severe FVIII and VWF deficiency (1, 10–11).

Algorithmic approaches are recommended for the diagnosis of VWD. The diagnosis of all subtypes of VWDs is confirmed in a specialized laboratory where multimeric structure, gene analysis, or tests such as RIPA and collagen binding are performed. Given that VWF has a high affinity for Plt in type 2B VWD, it is diagnosed by Plt aggregation at low ristocetin levels in the RIPA test (1–3, 9–12).

Thrombocytopenia is aggravated by the use of desmopressin which releases abnormal VWF from endothelial stores. Therefore, it is not recommended for treatment. Factor VIII/VWF replacement therapy is often preferred. Nevertheless, replacement therapy may not always provide bleeding control and platelet transfusion is needed in these cases (1–3). This case emphasized that type 2B VWD may rarely present in addition to NAIT and neonatal autoimmune thrombocytopenia which are common in resistant neonatal thrombocytopenia.

**Informed Consent:** Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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