ORIGINAL ARTICLE

Type 2b or Pseudo-Platelet Type Von Willebrand Disease – Case Report Of Two Pediatric Patients With Thrombocytopenia

Aisha A. Haleem, Waleed Jahangir, Roshna Devi, Shaikh Aamina, Anny Hanifa, Muhammad Rafique, Amanullah Lail

Pak Pediatr J. 2026; 50(2-3):123-128

Correspondence to:

Dr. Aisha A. Haleem
Postgraduate Resident, Pediatric Medicine

Dow University of Health Science
Karachi Pakistan
E-mail: aishaikh728@gmail.com

DOI:
https://doi.org/10.66347/ppj.v50i2&3.687

ABSTRACT

Von Willebrand Disease (VWD) is the most common inherited bleeding disorder, presents with mild mucocutaneous bleeding to severe hemorrhagic episodes.

We report two cases with bleeding diathesis and thrombocytopenia. Case A (4 years old) was diagnosed immune thrombocytopenia (ITP) at 3 years of age with recurrent epistaxis. Despite multiple treatment modalities, his platelet count showed no significant improvement, so the evaluation was done for possible other diagnosis.

Case B (six months old) presented with Melena, epistaxis, anemic failure and Malaria vivax. After treating malaria, he evaluated for bleeding disorder with persistent bleed and thrombocytopenia.

After consultation with a pediatric hematologist, 2B-VWD considered with prolonged APTT, BT levels, low normal to low VWF- Ricof levels, normal factor VIII levels and persistent thrombocytopenia in both cases. Treatment with VWF concentrates also showed significant response.

This report discloses diagnostic reappraisal of ITP with VWD-2B in case A and early recognition in infant (case B). Different treatment approach applies to each entity: type 2B VWD can be treated with VWF, while PT-VWD need platelet transfusions.

Keywords: *Thrombocytopenia, VWD, Bleeding Disorder*

INTRODUCTION

Bleeding in children can result from accidental trauma, sepsis, autoimmune disorders, malignancies, inherited platelet function and coagulation disorders. A thorough clinical history and physical examination are essential to guide accurate diagnosis. Thrombocytopenia in children may be either acquired, inherited and commonly presents with bleeding manifestations. Viral infections are the most frequent cause, other etiologies include autoimmune disorders-such as immune thrombocytopenia (ITP)-and various genetic conditions. ITP is one of the most prevalent acquired causes of thrombocytopenia in children.[1] However, its clinical presentation can

mimic other, less common bleeding disorders, such as von Willebrand disease (VWD), leading to potential misdiagnosis. VWF plays a dual role: it mediates platelet adhesion to sites of vascular injury (primary hemostasis) and stabilizes clotting factor VIII (FVIII) by protecting it from proteolytic degradation (secondary hemostasis).[2]

It facilitates platelet binding via interactions with receptors such as glycoprotein Ib (GPIb) and GPIIb/IIIa, and forms adhesive bridges with subendothelial matrix components, particularly collagen. A deficiency or dysfunction of VWF leads to a bleeding tendency that can range in severity and may exhibit features of both primary and secondary hemostatic defects.[2]

Von Willebrand disease is recognized as the most common inherited bleeding disorder, affecting approximately 1% of the general population. It is caused by quantitative and/or qualitative defects in VWF, a complex multimeric plasma glycoprotein essential for hemostasis.[2,3]

Clinically, type 1 and 3 VWD are quantitative defects. Type 2 VWD is qualitative defect with various types and similar phenotype. Mucocutaneous bleeding is a hallmark of VWD and may significantly impact quality of life, particularly in children. Nevertheless, even individuals with substantial VWF impairment may exhibit minimal spontaneous bleeding.[3]

Type 2B-VWD results from gain-of-function mutations in the VWF gene, which enhances the protein's affinity for the platelet GPIb, conversely pseudo-platelet type VWD (PT-VWD) has gain of mutation of gp1b, which increases affinity to bind with VWF antigen. Both are rare subtypes with concurrent low platelet counts, accounting for approximately 5% of VWD cases[4]

The clinical presentation of ITP resembles to VWD. Persistent thrombocytopenia in ITP suspected cases should prompt to screen for VWD subtypes; type 2B-VWD and PT-VWD

CASE 01:

A four-year-old male was brought to the pediatric emergency department with complaints of active gum bleeding, recurrent episodes of epistaxis, and widespread ecchymoses. His parents reported that these symptoms had been present since the age of 3 years and were typically triggered by minor trauma such as routine play, falls, or intramuscular vaccinations. Despite the chronicity of his condition, there was no history of spontaneous hematomas, excessive post-circumcision bleeding, gastrointestinal bleeding (melena or hematemesis), hematuria, weight loss, or bone pain. The family history was non-contributory, with no known bleeding disorders or menorrhagia reported in the mother.

On physical examination, the child was playful had multiple non-blanchable, non-tender purpuric lesions, which observed on the lower limbs, abdomen, and upper extremities. Active gingival bleeding was also noted at the time of presentation. Rest of systemic examination was unremarkable.

Diagnostic Assessment and Therapeutic Intervention

The patient's prior medical records revealed persistent thrombocytopenia documented on multiple occasions. A bone marrow biopsy performed, had shown normal cellular lineages, ruling out marrow failure syndromes. Initial management included oral methylprednisolone followed by IVIG and thrombopoietin therapy; however, both interventions failed to control his symptoms. Despite standard therapy for immune thrombocytopenic purpura (ITP), alternative diagnosis was considered. Bleeding diathesis testing panel revealed normal morphology of platelets, elevated APTT, Normal PT, Prolonged BT, low VWF ag, low to Normal VWF Ri-cof and normal factor VIII levels.

CASE 02:

This was case of six months old boy, appropriate for developmental age presented in emergency with Anemic failure. He had history of fever, pallor for 10 days and Melena, epistaxis for 2 days. At presentation, He was Febrile, tachycardiac, tachypneic, severely pale. Tip of spleen and liver was palpable 2cm below right costal margin with total span of 8cm. He had gallop, apex beat was 0.5 cm lateralized to 5th ICS from MCL and also had mild subcostal recessions and fine basal

crepitations.Past and family history was non-significant for any bleeding diathesis. He was born normal, mother had no history of fever, rashes, arthralgia, photosensitivity or transfusion during pregnancy. CBC parameters revealed Hemoglobin 3.2 g/dL, WBCs 4500/mm³ and Platelets 91000/mm³.

Diagnostic Assessment and Therapeutic Intervention

Patient initially managed with RBCs transfusion 5ml/kg over 3 Hours two times 12 hours apart and Intravenous Artesunate given for malaria. Platelets transfusion was done with initial impression of thrombocytopenia secondary to severe malaria leading to massive bleeding diathesis.

The workup sent to evaluate the cause of bleeding diathesis and persistent thrombocytopenia after regression of spleen and malaria report negative after appropriate treatment.

The platelets morphology was normal, there was no evidence of blasts in peripheral smear and elevated APTT excluded leukemia, Platelet function disorder, congenital amegakaryocytic thrombocytopenia and consideration of VWD was included in case.

Further work up for bleeding reported elevated APTT, Normal PT, Prolonged BT, normal VWF Ag, factor VIII levels and low VWF Ri-cof.

Based on clinical history, physical examination, and laboratory findings, a diagnosis of Type 2B von Willebrand disease (VWD) was made following consultation with a pediatric hematologist as treatment modification with VWF concentrates with consideration of 2B-VWD and this entity will not respond to platelet transfusion.

Thoroughly, it was observed, VWF concentrates therapy helped in controlling the bleeding in patient.

This subtype is characterized by thrombocytopenia. However, reduced VWF Ag levels, reduced Ristocetin cofactor activity, normal factor VIII levels and thrombocytopenia are considered to be laboratory parameters, but cases are also reported with normal values and genetic mutations consistent with diagnosis of both disorders.

In our cases, due to financial limitation, Ristocetin induced platelet aggregation (RIPA), which shows exaggerated response in both types due to inherited pathogenic increased affinity of binding of VWF and platelets could not be sent. Molecular diagnosis is necessary to differentiate, confirm the diagnosis and look for genotype-phenotype correlations.

The management strategy for patients was aimed at both acute control of bleeding and long-term prevention. The parents were counseled regarding strict avoidance of trauma, intramuscular injections, and the use of medications such as non-isteroidal anti-inflammatory drugs, aspirin, and anticoagulants, as these could exacerbate bleeding tendencies. The families were educated on emergency preparedness, including the importance of promptly seeking medical attention in case of uncontrolled bleeding and informing healthcare providers about the child's condition prior to any medical or surgical procedures. Recombinant VWF products were reserved for more severe bleeding episodes. At his four-week follow-up visit, the patients demonstrated marked clinical improvement. Episodes of gingival bleeding and spontaneous bruising were significantly reduced case A and melena stopped in case B, reflecting a favorable response to the instituted therapeutic regimen.

Our report of two pediatric cases with thrombocytopenia contributes uniquely to the literature with clinical judgement of treatment regimen response. Eventually, type 2B- VWD diagnosis supported by thrombocytopenia and low-normal Ricof levels in 4 years child previously misdiagnosed as case of ITP and early diagnosis in 6 months old child

Table 01: Case 01 and 02 Diagnostic Hematologic Reports with reference values.

Parameter	Case 01	Case 02	*Reference Range*
Platelet count	4000	91000	*150,000-450,000*

Bleeding time	10 minutes	9 minutes	*2-7 minutes*
PT	18 seconds	15 seconds	*10-13 seconds*
APTT	38 seconds	32 seconds	*24-26 seconds*
VWF antigen (VWF Ag)	18%	69%	*50-160%*
Ristocetin cofactor activity (VWF-Ricof)	60%	24%	*50-172%*
Factor VIII	162%	91%	*50-149%*
VWF Activity/ Ag Ratio	3.33	0.34	>0.7 suggestive of Type 2B and PT- VWD.

DISCUSSION

2B-VWD results from gain-of-function mutations in the VWF gene, which enhance the protein's affinity for the platelet GPIb-V-IX receptor complex[4]. This aberrant interaction leads to increased platelet aggregation and subsequent clearance from circulation, causing moderate to severe thrombocytopenia. Importantly, distinguishing Type 2B VWD from platelet-type pseudo-VWD (PT-VWD) is essential; the latter results from mutations in platelet GPIb and may require platelet transfusion rather than VWF concentrate[4].

Laboratory findings typically include reduced plasma VWF antigen levels, decreased Ristocetin cofactor activity, loss of high molecular weight VWF multimers, and a bleeding tendency[4].

But in literature, cases are reported with normal PT, APTT, VWF Ag, VWF- Ricof and factor 8 and exaggerated response with RIPA and diagnosis confirmed with gene mutation studies[5].

Precise discrimination requires RIPA mixing assays, flow cytometry, or genetic tests. PT-VWD accounts for about 15% of cases initially diagnosed as Type 2B, genomic analysis focused on the patient's VWF gene confirmed the correct diagnosis in our case, aligning with recommendations from Othman (2007) and Favaloro et al. (2011)[6,7]

Our first case, initially misdiagnosed with immune thrombocytopenic purpura (ITP), the clue towards the revision of diagnosis was the persistence of thrombocytopenia despite ITP-standard therapy (steroids, IVIG, thrombopoietin agonists) and second case that presented with anemic failure and malaria vivax later evaluated for bleeding disorder due to persistent melena, epistaxis, low platelet count and elevated APTT.

Both cases later clinically suspected to have type 2B- VWD as no response to platelet therapy observed while the bleeding stopped with administration of VWF concentrates.

Multiple pediatric cases have documented similar misdiagnoses; for example, an infant was initially seemed to have maternal ITP before Type 2B VWD was confirmed with molecular testing [8,9,10]

2B-VWD responds with VWF concentrates and PT-VWD with platelet transfusion, the first diagnosis can have more bleeding diathesis with treatment of desmopressin (DDAVP) and platelet transfusion as it can exacerbate abnormal VWF to platelet binding and clearance Replacement therapy with VWF concentrate remains the first-line treatment in this 2B-VWD [8,9]. Studies like Castaman & Federici (2016) and guidelines by Kruse Jarres et al. support this therapeutic strategy[11,12,13]

Our patient's favorable response to VWF concentrates, during bleeding episodes, supports this principle.

In any suspected case of 2B-VWD, platelet transfusion should not be offered which remains controversial and worsen thrombocytopenia by providing substrate to vwf ag for binding. Tranexamic acid helps to control local mucosal bleeding, particularly epistaxis and gingival hemorrhage during acute bleeding episodes. In addition, von Willebrand factor (VWF) is recommended, which helps to stabilize hemostasis.

Limitations of current diagnostic workflows include limited access to RIPA, which show

exaggerated response with low dose Ristocetin in 2B-VWD and PT-VWD, as increased affinity of binding. Genetic testing is important to differentiate these 2 disorders. We suspected 2B-VWD as both cases responded with VWF concentrated and no response observed with initial platelet therapy.

CONCLUSION

Clinicians must maintain a high index of suspicion for 2B-VWD and PT-VWD, when encountering thrombocytopenia unresponsive to ITP therapies and platelet transfusion, especially if bleeding symptoms are mucocutaneous in nature. This report also underscores, different treatment approach towards type 2B and PT-VWD, which are often misdiagnosed due to coinciding clinical presentation and laboratory values. It is also necessary to observe treatment response in clinical grounds, when further confirmatory testing is not available

Patient Perspective – Families of both children had financial issues for further confirmatory testing and limitation to know the inheritance of disease. Further counselling about rare bleeding tendencies helped to understand the clinical coarse of disease.

Informed Consent: The patients parents signed informed consent, will be Provided if requested.

Ethical approval: Written informed consent was obtained from the patient for publication of this case report and accompanying imaging pictures

Grant Support & Financial: None

Disclosure: None

Conflict of interest: None

Authors' affiliation

Dr. Aisha A. Haleem
Postgraduate Resident, Pediatric Medicine
Dow University of Health Sciences,
Karachi, Pakistan

Dr. Waleed Jahangir
House Officer, Department of Pediatric Medicine
Dow University of Health Sciences, Karachi, Pakistan.

Dr. Roshna Devi
Postgraduate Resident, Pediatric Medicine
Dow University of Health Sciences, Karachi, Pakistan

Dr. Shaikh Aamina
MBBS Student, People's University of Medical and Health Sciences, Pakistan.

Dr. Anny Hanifa
Consultant Pediatric Medicine,
Dow University of Health Sciences, Karachi, Pakistan

Dr. Muhammad Rafique,
Consultant Pediatric Medicine,
Dow University of Health Sciences, Karachi, Pakistan

Prof. Amanullah Lail,
Consultant Pediatric Medicine,
Dow University of Health Sciences, Karachi, Pakistan

REFERENCES

1. Ruggeri ZM. Type IIB von Willebrand disease: a paradox explains how von Willebrand factor works. J Thromb Haemost. 2004;2(1):2-6. doi:10.1111/j.1538-7836.2003.00523.x

2. Lu X, Yu D, Dai W, Zou M, Liu J. Misdiagnosis of type 2B von Willebrand disease as immune thrombocytopenia in a thrombocytopenic patient. Clin Chem Lab Med. 2024;62(9):e212-e214. doi:10.1515/cclm-2023-0891

3. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood. 1987;69(2):454-459.

4. McGinnis E, Vercauteren SM. von Willebrand disease type 2B. Blood. 2017;129(4):538. doi:10.1182/blood-2016-09-729434

5. Catarina Monteiro, Ana Gonçalves, Mónica Pereira, Catarina Lau, Sara Morais, Rosário Santos. A new case of platelet-type von Willebrand disease supports the recent findings of gain-of-function *GP1BA* variants outside the C-terminal disulphide loop enhances affinity for von Willebrand factor British journal of haematology; 2023 https://doi.org/10.1111/bjh.19025

6. Kranzhöfer D, Pavlova A, Schneider H, et al. Type 2B von Willebrand disease: early manifestation as neonatal thrombocytopenia. Hamostaseologie. 2021;41(6):469-474. doi:10.1055/a-1665-6185

7. Federici AB, Mannucci PM, Castaman G, et al. Clinical and molecular predictors of thrombocytopenia and risk of bleeding in patients with von Willebrand disease type 2B: a cohort study of 67 patients. Blood. 2009;113(3):526-534. doi:10.1182/blood-2008-04-152280

8. Rotz SJ, Palumbo JS, Ware RE. Type 2B von Willebrand disease: an unusual cause of severe neonatal thrombocytopenia. J Pediatr Hematol Oncol. 2017;39(6):473-475. doi:10.1097/MPH.0000000000000741

9. Despotovic JM, Grimes AB. Pediatric ITP: is it different from adult ITP? Hematology Am Soc Hematol Educ Program. 2018;2018(1):405-411. doi:10.1182/asheducation-2018.1.405

10. Gök V, Işık E, Yılmaz E, et al. Type 2B von Willebrand disease mimicking autoimmune thrombocytopenia in the neonatal period. Erciyes Med J. 2021;43(2):201-203. doi:10.14744/etd.2020.81557

11. Mannucci PM. Treatment of von Willebrand's disease. N Engl J Med. 2004;351(7):683-694. doi:10.1056/NEJMra040403

12. Yee A, Kretz CA. Von Willebrand factor: form for function. Semin Thromb Hemost. 2014;40(1):17-27. doi:10.1055/s-0033-1363155

13. Castaman G, Tosetto A, Federici AB, Rodeghiero F. Bleeding tendency and efficacy of anti-haemorrhagic treatments in patients with type 1 von Willebrand disease and increased von Willebrand factor clearance. Thromb Haemost. 2011;105(4):647-654. doi:10.1160/TH10-11-0697

Author's Contribution
AAH: Literature Review, Diagnosis, Manuscript Writing and Clinical Management.
WJ: Manuscript Writing, Editing and Literature Review.
RD: Manuscript Writing, Diagnosis and Clinical Management.
SA: Manuscript Writing, Editing and Literature Review.
AH: Diagnosis and Clinical Management.
MR: Manuscript Review and Clinical Management.
AL: Manuscript Review and Clinical Management.

All the authors have approved the final manuscript draft and accept the responsibility of research integrity.