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Case Report

Bernard soulier syndrome; A rare bleeding disorder

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ABSTRACT

Bleeding syndromes in the newborn are rare, but they may be life-threatening and demand immediate attention. Congenital bleeding disorders especially pose a diagnostic challenge to the clinician because of their rarity and the need to be differentiated from the other common causes of bleeding in children. We present a case of an infant presenting with bleeding symptoms early in his life (since 5 months of age) which was initially thought to be immune thrombocytopenic purpura (ITP) with low platelet count. No response to steroids and further evaluation by platelet aggregometry and flowcytometry led to the correct diagnosis – Bernard soulier syndrome(BSS). Though, there is no specific treatment available for this rare bleeding disorder, however it is imperative to have arrived at correct diagnosis in order to save unnecessary therapy and to take due precautions for prevention of bleeding

Keywords: *Bernard soulier syndrome, bleeding, giant platelets, platelet aggregation, flowcytometry*

Introduction

Management of bleeding disorders in children requires not only an understanding of the unique characteristics of paediatric hemostasis but also the myriad number of rare congenital disorders in children, which may present a diagnostic challenge. Amongst the inherited bleeding disorder, Bernard soulier syndrome (BSS) is one disorder which is often missed due to incomplete work up/follow up of the patient. Bernard–Soulier syndrome (BSS), is a rare bleeding disorder first described in 1948 by two French haematologists – Jean Bernard and Jean Pierre Soulier. [1] It is caused by a defect in platelet glycoprotein- Gp Ib- IX- V complex which is the receptor for von willebrand factor (VWF). The exact incidence of BSS is difficult to estimate due to frequent misdiagnosis and under reporting. [1,2] Inheritance of the BSS is usually autosomal recessive and is often associated with consanguinity. [2]

BSS is a dual quantitative and qualitative bleeding disorder characterized by abnormally large platelets, mild thrombocytopenia and platelet dysfunction. Patients usually present early in life with bleeding symptoms like epistaxis, ecchymosis, cutaneous, gingival bleeds and rarely with menorrahagia and gastrointestinal bleedings. [3] Heterozygous carriers are usually asymptomatic or can have mild bleeding symptoms. [2] Platelet counts may range from very low (30,000/μL) to marginally low or normal (200,000/μL) and in individual patients, the count may fluctuate considerably over a period of years. [3]

The GP Ib-IX-V complex has two important roles in platelet function that explain the often severe bleeding observed in BSS: it mediates adhesion of platelets to the blood vessel wall at sites of injury by binding VWF and it facilitates the ability of thrombin at low concentrations to activate platelets. [4] Furthermore, the GP Ib-IX-V complex may have important roles in the process by which platelets are generated and possibly in platelet turnover, as evidenced by the decreased

number and abnormal size of platelets from BSS patients. [4,5] A variety of mutations have been described leading to the defect (biosynthetic or functional) in Glycoprotein GP Ib IX V complex responsible for the clinical heterogeneity. [4]

Diagnosis of BSS, require high clinical suspicion in a suitable clinical settings with a positive family history or consanguinity. Extended investigations like platelet aggregation and flowcytometry are required to clinch the diagnosis. [6] Here, we present a case of 11 month old child who was initially wrongly diagnosed as immune thrombocytopenic purpura (ITP) and was started on steroids. No response to therapy led the clinician to explore the alternate diagnosis and the patient was later confirmed to have Bernard soulier syndrome.

Case History

A 11 months old boy who was brought by his parents from Afghanistan for evaluation and treatment of his bleeding symptoms. He was apparently well till 5 months of age when he developed fever for about 1 week alongwith upper respiratory tract illness. His complete blood count showed Hb- 12.5 gm/dl, TLC – 5,500/cmm DLC – P45 L 40 M8 E7 and low platelet count of 80,000/cmm with presence of many giant platelets. The mother also noticed occasional bruising over lower limbs and small ecchymotic patches (around 0.5 -1 cm in size and 3-4 in number) over trunk. However, there was no history of joint bleeds, hematoma after vaccination or active bleeding from any other site. Systemic examination showed no abnormality. In the setting of fever and upper respiratory infection, followed by thrombocytopenia and presence of large platelets on peripheral smear, a diagnosis of ITP was considered and the patient was started on oral prednisolone. The platelet count repeated after 4 weeks of therapy showed no improvement in counts. Meanwhile, patient was reported to have occasional episode of mild epistaxis which was managed conservatively.

Further history was sought in detail which revealed the parents to have second degree consanguineous marriage. The mother gave history of having borderline platelet counts all her life and occasional ecchymotic patches over limbs/ trunk however the father and other two siblings of the patients were completely asymptomatic. In order to rule out inherited bleeding disorder, a screening coagulogram was ordered which came back normal (PT 12/13 sec, APTT 28/30 sec, TT 16/ 16 sec, fibrinogen 380mg/dl). Repeat peripheral smear examination showed mild thrombocytopenia (platelet count – 1 lakh/cmm) and presence of mostly large platelets with occasional giant platelets also (Fig.1)

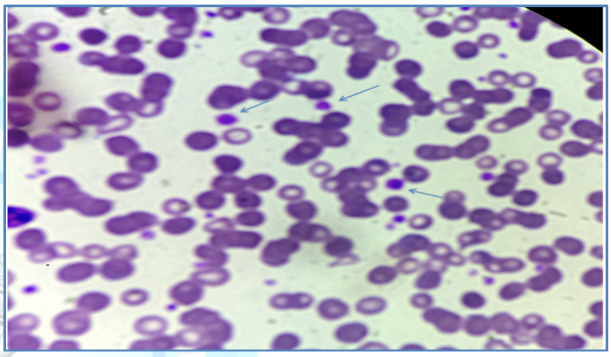

Fig.1 Leishman Giemsa stained peripheral smear (100x) showing giant platelets (arrow)

Date	Test Type	Details	PA	PS	SA	SS	AUC*	LP	DA	MA	PA
1/24/2017	ADP		69	39	0	0	279	0	0	69	67
1/24/2017	AA		66	38	0	0	270	0	0	66	64
1/24/2017	RIPA		5	0	0	0	24	0	0	5	4
1/24/2017	AA ADR		45	23	0	0	153	18	0	45	43

Fig.2 platelet aggregation summary showing normal aggregation with ADP(67%), AA(64%) , ADR(43% but absent aggregation with Ristocetin(4%)

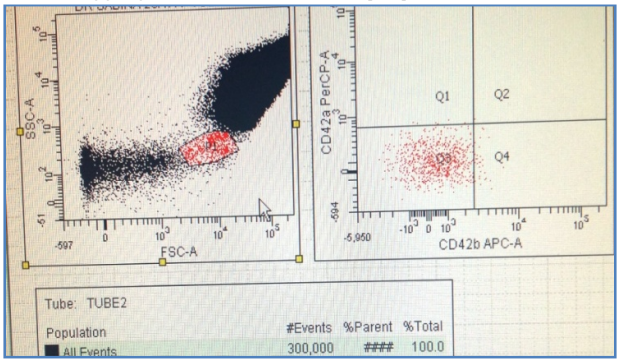

Fig.3 Platelet flowcytometrty- selected platelet population (in Red) showing absence of CD 42a and CD 42b (Gp 1b)

The mean platelet volume (MPV) on automated counter was 13 fL against normal MPV range of 7-11 fL. Platelet aggregation test was done using platelet rich plasma and showed normal aggregation with ADP, AA, AR and absent aggregation with ristocetin which did not correct on addition of normal plasma (Fig.2) With a high suspicion of Bernard soulier syndrome, flowcytometry for platelets was ordered which showed absence of CD 42a(Gp Ib) and CD 42b on platelets of thereby confirming the diagnosis of BSS. (Fig.3) The parents were counselled about the treatment and prevention of bleeding. The family went back to their country reassured with correct diagnosis and knowledge of management required.

Discussion

BSS has frequently been misdiagnosed as ITP based on a prolonged bleeding time, thrombocytopenia, large platelets, and is often treated unsuccessfully with steroids or splenectomy. [7] In order to avoid misdiagnosis, clinical evaluation should thus begin with taking a careful history about child's age, sex, clinical presentation, past history, and family history. Further evaluation for bleeding disorders should include general screening tests that assess hemostasis (PT, APTT, TT, fibrinogen levels, clot solubility test) and additional specific testing as required (platelet aggregation study flowcytometry etc).

In BSS, platelet aggregation study is helpful but cannot be performed in patients who present with severe thrombocytopenia (<1 lakh/cmm) or history of recent platelet transfusion [8] Flowcytometry is confirmatory and should be ideally done on platelet rich plasma in order to avoid confusion with RBCs (large platelets can be confused for Red cells). [9] Genetic mutation is rarely ordered due to general unavailability of the test but is gold standard and can differentiate biosynthetic or functional defects of GP IB IX V receptor. [4]

Management of BSS includes supportive measures (platelet transfusion) for uncontrolled bleeding/ prophylaxis during surgery. [10] Alloimmunization and platelet refractoriness remain a problem in frequently transfused patients. Desmopressin and recombinant factor VIIa (rFVIIa) are other available alternatives. [10] Counselling of patients to avoid trauma, aspirin containing medications and other platelet antagonists is paramount in order to avert serious bleeding. [10] In conclusion, BSS is rare bleeding disorder with highly variable clinical phenotype and is likely to be misdiagnosed and mismanaged. Platelet aggregation studies and more definitely flowcytometry can provide an accurate diagnosis and timely institution of adequate therapy.

References

1. Nurden AT. Qualitative disorders of platelets and megakaryocytes. J Thromb Haemost 2005;3:1773–82.
2. Bragadottir G, Birgisdottir ER, Gudmundsdottir BR, Hilmarsdottir B, Vidarsson B, Magnusson MK, et al. Clinical phenotype in heterozygote and biallelic Bernard-Soulier syndrome--a case control study. Am J Hematol 2015;90:149-53.
3. Pham A, Wang J. Bernard-Soulier syndrome: an inherited platelet disorder. Arch Pathol Lab Med 2007;131:1834-6.
4. Lopez JA, Andrews RK, Afshar-Kharghan V, Berndt MC. Bernard-Soulier Syndrome. Blood 1998;91:4397–418.
5. Feng S, Christodoulides N, Kroll MH. The glycoprotein Ib/IX complex regulates cell proliferation. Blood 1999;93:4256-63.
6. Diz-Kucukkaya R. Inherited platelet disorders including Glanzmann thrombasthenia and Bernard-Soulier syndrome. Hematology Am Soc Hematol Educ Program 2013;2013:268-75.
7. Young G, Luban N, White JG. Giant platelet disorders in African-American children misdiagnosed as idiopathic thrombocytopenic purpura. J Pediatr Hematol Oncol 1999; 21:231-6.
8. Kirchmeir CM, Pilliteri D. Diagnosis and Management of Inherited Platelet Disorders. Transfus Med Hemother 2010;37:237–46.
9. Linden MD, Frelinger AL, Barnard MR, Przyklenk K, Furman MI, Michelson AD. Application of flow cytometry to platelet

disorders. Semin Thromb Hemost 2004;30:501-11.
10. Balduini CL, Lolascon A, Savoia A. Inherited thrombocytopenias: From genes to therapy. Haematologica 2002;87:860–80.

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