Bernard-Soulier Syndrome Like Platelet Defect in a Patient with Noonan Syndrome; A Case Report

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ABSTRACT

Noonan's Syndrome (NS) is characterized by dismorphic facial features, short stature, short or webbed neck, congenital heart defects and testicular abnormalities. Various bleeding disorders in Noonan Syndrome have been reported. Bernard-Soulier Syndrome (BSS) is a rare congenital bleeding disorder characterized by thrombocytopenia and giant platelets. There is not any reported case of Noonan syndrome associated with BSS in literature. We report here a four-year-old male patient with Noonan Syndrome and BSS like platelet defect.

Key Words: Bernard-Soulier syndrome, Bleeding diathesis, Noonan syndrome, Platelet function.

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INTRODUCTION

Noonan's Syndrome (NS) is characterized by short stature, short or webbed neck, facial anomalies, congenital heart defects and testicular abnormalities[1-5]. Various bleeding disorders in Noonan Syndrome associated with coagulation factor deficiencies and qualitative or quantitative platelet disorders have been reported[2,6-9,10].

Bernard-Soulier Syndrome (BSS) is a rare congenital bleeding disorder characterized by thrombocytopenia and giant platelets[11,12]. A qualitative or quantitative deficiency in the platelet membrane glycoprotein (GP) Ib/ IX receptor complex, a major receptor for the von Willebrand factor (vWF), is the cause of the syndrome[13,14].

There is no reported case of BSS associated with Noonan syndrome. Here, we report a patient with Noonan Syndrome and BSS association.

CASE REPORT

A four-year-old male was brought with a nose bleeding history from six months of age and he had received blood transfusion at four times because of bleeding. He had no petechia-purpura and hemarthrosis, but he had easy bruising in history. His father and brother had no bleeding disorder, but his mother had a moderate-severe postpar-

tum hemorrhage, and one sister and one brother of mother had died because of bleeding when they were two years old.

In physical examination, short stature (height and weight below 3rd percentile, head circumference at 25th percentile), increased mid face height, mild hypertelorism and ptosis, antimongoloid slant of palpebral fissures, lower nasal bridge, prominent upper lip, low set and mildly malformed ears were found. His right testicle was undescended. His mother and father were at normal height and weight, but his mother had mildly antimongoloid slant to the eyes.

In laboratory evaluation; hemoglobin was 7.5 g/dL, hematocrit 23%, white blood cell count 7000/mm^3, platelet count 98.000/ mm^3, mean platelet volume 11.7 fL, bleeding time 15 minutes, prothrombin time (PT) 13 seconds, activated partial thromboplastin time (aPTT) 31 seconds, Factor VIII 168%, and vWF 60%. There were giant platelets on a stained peripheral-blood smear. Platelet aggregation with adenosine diphosphate (ADP) and collagen were normal, but agglutination with ristocetin was absent. His mother's and father's bleeding times were normal. According to this result, the patient was diagnosed as BSS. He was also diagnosed as Noonan syndrome according to Sharland et al criteria[5].

DISCUSSION

The patient had three of Sharland's criteria to diagnose Noonan syndrome[5]. He had typical facial appearance, short stature, and right undescended testicle. He had also prolonged bleeding time, moderate thrombocytopenia, large platelets, normal PT and aPTT, platelet aggregation was normal to collagen and ADP, but abnormal for ristocetin. According to these findings, the patient was diagnosed as BSS and Noonan syndrome.

A common association between bleeding disorders and Noonan syndrome have been reported[6-9,16,17]. Sharland et al reported that 65% of NS had a history of abnormal bruising or bleeding, and 50% had specific abnormalities in the intrinsic pathway of coagulation[7]. The most frequently described coagulation factor deficiencies are Factor XI: C, VIII: C, XII: C deficiencies and their combined deficiencies[6-9,16].

Thrombocytopenia has firstly been noted by Noonan[2]. Evans et al reported amegakaryocytic thrombocytopenia in an infant with Noonan syndrome[10]. Hathaway noted bleeding disorder due to platelet function defect[17]. Witt et al reported thrombocytopenia in one patient, concomitant coagulation and platelet defects in three patient, and platelet function defects in five patients[6]. Singer et al reported a patient with Noonan syndrome and amegakaryocytic thrombocytopenia[9]. But, Noonan syndrome associated with BSS like platelet defects was not reported previously in literature.

Positive family history for bleeding diathesis and coagulation factor abnormality in first degree relatives with NS have also been reported[6,7]. Postpartum hemorrhage of mother and bleeding disorders of her relatives may be related with NS.

In BSS, platelet aggregation responses to physiologic agonist such as ADP and collagen are normal, but there is an impaired platelet agglutination response to ristocetin[18,19]. In the heterozygous form of BSS, the platelet count, platelet function and clinical hemostasis are normal[18,20].

Acquired BSS like platelet defects were reported in malignancies such as myelodysplastic syndrome (MDS) and acute myeloblastic leukemia (AML)[21]. Our patient did not have any malignant disorder.

The situation of the patient may be Noonan syndrome and BSS association rather than BSS like syndrome, but molecular analysis for BSS could not be done. So molecular studies are needed to say that the cause of platelet defect in this children is BSS or BSS like syndrome.

Various coagulation and platelet abnormalities can be seen in Noonan syndrome. This patient showed that the spectrum of bleeding disorders in Noonan syndrome is quite wide. So, the investigation of patients with NS for platelet functions will be beneficial.

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REFERENCES

1. Noonan JA, Ehmke DA. Associated noncardiac malformations in children with congenital heart disease. J Pediatr 1963;63:468-70.
2. Noonan JA. Hypertelorism with turner phenotype. Am J Dis Child 1968;116:373-80.
3. Mendez HMM, Opitz JM. Noonan syndrome: A review. Am J Med Genet 1985;21:493-506.
4. Sharland M, Burch M, McKenna WM, Patton MA. A clinical study of Noonan syndrome. Arch Dis Child 1992;67:178-83.
5. Sharland M, Morgan M, Smith G, Burch M, Patton MA. Genetic counselling in Noonan syndrome. Am J Med Genet 1993;45:437-40.
6. Witt DR, McGillivray BC, Allanson JE, Hughes HE, Hathaway WE, Zipursky A, Hall JG. Bleeding diathesis in Noonan syndrome: A common association. Am J Med Genet 1988;31:305-17.
7. Sharland M, Patton MA, Talbot S, Chitolie A, Bevan DH. Coagulation-factor deficiencies and abnormal bleeding in Noonan's syndrome. Lancet 1992; 339:19-21.
8. Massarano AA, Wood A, Tait RC, Stevens R, Super M. Noonan syndrome: Coagulation and clinical aspects. Acta Pediatr 1996;85:1181-5.
9. Singer ST, Hurst D, Addiego JE. Bleeding disorders in Noonan syndrome: Three case reports and review of the literature. J Pediatr Hematol Oncol 1997; 19:130-4.
10. Evans DGR, Lonsdale RN, Patton MA. Cutaneous lymphangioma and amegakaryocytic thrombocytopenia in Noonan syndrome. Clin Genet 1991; 39:228-32.
11. Bernard J, Soulier JP. Sur une nouvelle variété de dystrophie thrombocytaire hémorrhagipare parse congénitale. Sem Hop Paris 1948;24:3217-23.
12. Caen JP, Nurden AT, Jeanneau C, Michael H, Tobelem G, Levy-Toledano S. Bernard-Soulier syndrome - a new platelet glycoprotein abnormality. Its relationship with platelet adhesion to subendothelium and with the factor VIII von Willebrand protein. J Lab Clin Med 1976;87:586-96.
13. Beardsley DS, Nathan DG. Congenital disorders of platelet function. In: Nathan DG, Orkin SH (eds). Nathan and Oski's Hematology of Infancy and Childhood. 5th ed. Philadelphia: WB Saunders, 1998: 1609-14.
14. Ruggeri ZM. The platelet glycoprotein Ib-IX complex. Prog Hemost Thromb 1991;10:35-68.
15. Sharland M, Morgan M, Patton MA. Photoantropometric study of facial growth in Noonan syndrome. Am J Med Genet 1993;45:430-6.
16. de Hann M, vd Kamp JJP, Briet E, Dubbeldam J. Noonan syndrome: Partial factor XI deficiency. Am J Med Genet 1988;29:277-82.
17. Hathaway WE. Bleeding disorders due to platelet dysfunction. Am J Dis Child 1971;121:127-34.
18. George JN, Nurden AT, Phillips DR. Molecular defects in interactions of platelets with the vessel wall. N Engl J Med 1984;311:1084-98.
19. Degos L, Tobelem G, Lethiellux P, Levy-Toledano S, Caen J, Colombani J. Molecular defect in platelets from patients with Bernard-Soulier syndrome. Blood 1977;50:899-903.
20. George JN, Reimann TA, Moake JL, Morgan RK, Cimo PL, Sears DA. Bernard-Soulier disease: A study of four patiens and their parents. Br J Haematol 1981;48:459-67.
21. Hicsonmez G, Gumruk F, Cetin M, Ozbek N, Tuncer M, Gursel T. Bernard-Soulier-like functional platelet defect in myelodysplastic syndrome and in acute myeloblastic leukemia associated with trilineage myelodysplasia. Turk J Pediatr 1995;37:425-9.

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