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RESEARCH ARTICLE

A CASE REPORT OF BERNARD-SOULIER SYNDROME IN DIFFERENTIAL DIAGNOSIS OF IMMUNE THROMBOCYTOPENIC PURPURA.

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Abstract

Bernard-Soulier Syndrome (BSS)is a rare hereditary disorder.Platelets in patients with BSS are unable to adhere, leading to an increased bleeding tendency. BSS cases are often misdiagnosed as idiopathic thrombocytopenic purpura (ITP). We report here a seven years old girl diagnosed as Bernard-Soulier syndrome with homozygous deletion of 39 nucleotides in the exon 2 of GP1BA. Bernard–Soulier syndrome should be considered before the patient is diagnosed with immune thrombocytopenia.

Introduction:-

Bernard-Soulier syndrome (BSS) was first known by two French hematologists – Jean Bernard and pierresoulier. They found out a patient from a consanguineous family with severe bleeding episodes, thrombocytopenia and very large platelets [1]. It is a rare hereditary disorder (1:1000000)[2].Platelets in patients with BSS are unable to adhere, leading to an increased bleeding tendency [3].BSS is a platelet function disorder, transmitted in an autosomal recessive manner. Caused by defects in the glycoprotein (GP)Ib/IX/V complex [4]. These genes stand for a group of linked proteins normally found on the surface of the platelets [5].Composed of four subunits, GPIbα disulphide-linked to two GPIbαβ subunits, GPIX and GPV in a ratio of 2:4:2:1, respectively [5]. The genes for each of these subunits have been cloned and are located in Chromosome (ch). 17p12 (GPIBA)[6], ch.22q11.2 (GPIBB) [7], ch3q21 (GP9)[8] and ch.3q29 (GP5)[9]. BSS cases are often misdiagnosed as idiopathic thrombocytopenic purpura (ITP) [5]. In this case report, we present one girl with causative mutations in GP1BA.

Case History:-

A seven years old Saudi girl previously healthy until the age of 5 years old when she presented on 15/1/2015 complaining of petechiae all over face, chest, arms, abdomen, and legs. Another systemic review was unremarkable. She was not on any medications. On examination she was conscious, alert, oriented, not distress. No enlarged lymph nodes were palpable in any part of her body. Her abdomen was not distended, and her spleen and liver were not palpable other systemic examinations were unremarkable.

Laboratory finding were; CBC (HG: 11.7, RBC: 4.19, WBC: 11.2, PLATELET: 80). Blood film: many large and giant platelets seen. Serologic examinations for Human Immunodeficiency Virus and hepatitis B and C were all negative. Also, ANA and direct coombs test were negative.

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The patient diagnosed as idiopathic thrombocytopenia. Received IVIG and discharged in good condition**.**In addition, she had multiple admissions due to the same complain petechiae and low platelet count. She received IVIG many times, and she responded as platelet count increase at least by 30.000 but after two to four weeks platelets drop again even below 10.000. There was no respond to steroids. She responded to anti-D once for four weeks. She received four doses of rituximab there was no respond until 16 weeks. Bone marrow aspiration and biopsy were done on 30/3/2015 before receiving steroids; the result was cellular normal marrow. Normal megakaryocytes content on the marrow. No pathology on the marrow to explain the thrombocytopenia.

She was diagnosed as chronic ITP with frequent admission and poor response to treatment and due to hospital logistic issues platelets aggregation and flow cytometry not done.The doctor arranged an appointment for follow-up and genetic analysis for Bernard-Soulier syndrome. The result of Molecular genetic analysis of the genes GP1BA, GP1BB, GP9 showed a presence of a homozygous deletion of 39 nucleotides in the exon 2 of GP1BA. Finally, she diagnosed as Bernard-Soulier Syndrome (BSS).

Discussion:-

Bernard-Soulier syndrome is an autosomal recessive disorder. Bernard-Soulier syndrome affects both males and females [10].In Bernard-Soulier syndrome, thrombocytopenia is associated with morphologically abnormal large platelets and platelet dysfunction. The clinical manifestation is variable and includes purpura, epistaxis, gingival bleeding, menorrhagia, occasional gastrointestinal bleeding, hematoma, or hematuria.The diagnosis of platelet function disorders needs a detailed medical history and a series of laboratory tests.

In people with Bernard-Soulier syndrome:

- The bleeding time is difficult to perform in young children.
- The closure time is prolonged.
- Larger platelets.
- Platelets appear on the blood film.
- There are usually fewer platelets than normal.
- Platelets do not clump together normally in the presence of ristocetin.
- GPIb/IX/V is not detectable by flow cytometry [10].

Reasons to suspect hereditary thrombocytopenia[11] (See Table 1)
Classification schemes for hereditary thrombocytopenia [11] (See Table 2)
On (Table 3 and 4) showed Mutations Identified and some diseases associated in Patients with Bernard-Soulier Syndrome, their ages ranged from 1 to 70 years. They had platelet counts from 22 to 178 × 10^9/L. The mean value of MPV was 12.6 fL, with a range from 10.4 to 17.2 fL[92].

Mutation of the glycoprotein (GP) Ib/IX complex associated with Bernard-Soulier Syndrome (See Table 5) [92]

Idiopathic thrombocytopenicpurpura, leukemia should be included in the differential diagnosis of patients with Bernard-Soulier syndrome. Patients with idiopathic thrombocytopenic may have detectable antiplatelet antibodies. In the past, Inherited thrombocytopenia were, considered very rare. Patients are subject to misdiagnosis of autoimmune thrombocytopenic instead of hereditary thrombocytopenia and inappropriate therapy, such as steroid treatment and splenectomy. [27-29]

Proposed definitions of ITP (Table 6) [30]
Proposed criteria for assessing response to ITP treatments (Table 7) [30]
Individual agents for treatment of ITP and the time to the first and peak responses if using the reported dose range (Table 8) [30]
Refractory ITP (Table 9) [30]

Here, we report one girl with Bernard-Soulier syndrome (BSS) who missed diagnosed as ITP. She demonstrated typical BSS features such as giant platelets and petechial rash.In Conclusion, Bernard–Soulier syndrome should be considered before the patient is diagnosed with immune thrombocytopenia.

Table 1:-Reasons to suspect hereditary thrombocytopenia. [11]

a) Lack of platelet response to therapies including steroids, IVIG, IV anti-D, and splenectomy and, rituximab.
b) A family history of thrombocytopenia.
c) Abnormal size of platelets on blood film.
d) Abnormal bleeding time
in comparison with platelet count.
e) Onset at birth.
f) Associated features such as high tone hearing loss, absent radii, mental retardation**,** renal failure, cataracts, or the development of leukemia.

Table 2:-Classification schemes for hereditary thrombocytopenias.[11]

a) Thrombocytopenia dueto poor production or accelerated destruction.
b) Mode of inheritance: X-linked (wiskottaldrich syndrome) or autosomal dominant.
c) Platelet size on smear: very large, normal, or small (Wiskott Aldrich Syndrome); other findings, e.g. Dohle-like bodies in neutrophils.
d) Associated features including clinical and laboratory findings:
1. findings on exam or by history, e.g., absent radii, renal failure, hearing loss (May Hegglin Anomaly)
2. laboratory abnormalities, e.g., flow cytometry for platelet glycoprotein expression, platelet function testing, assessment of the von Willebrand factor multimer composition.

Table.3:-Mutations Identified in Patients with BSS *[92]

Gene mutation	Nucleotide substitutions	Amino acid Change	Genotype	Initial diagnosis	Splenectomy	References
GPIBαmutation						
7F	deletion of 39 nucleotides in the exon 2		Homozygous	ITP	-	Our Patient
41F	3998-3999delTG	Premature termination	Homozygous	ITP	+	[12]
43M	4444insT	Premature termination	Compound heterozygous	ITP	+	[12]
	4464delA	Premature termination				
26F	4447C>A (TCA>TAA)	Ser444Stop	Homozygous	ITP	-	[13]
34F	4464delA	Premature termination	Homozygous	ITP	+	[14]
14F	4464delA	Premature termination	Homozygous	?	Oophorectomy	[15]
GPIBβ mutation						
37F	777C>T (CGC>TGC)	Arg17Cys	Heterozygous	GPD	-	[16]
6F	949C>G(CCG>CGG)	Pro74Arg	Homozygous	BSS	-	[17]
37F	991A>G (TAC>TGC)	Tyr88Cys	Compound heterozygous	ITP	-	[18]
	1050G>C(GCC>CCC)	Ala10Pro				
20F	991A>G (TAC>TGC)	Tyr88Cys	Homozygous	BSS	-	[19]
37M	1096G>A(TGG>TAG)	Trp123Stop	Homozygous	ITP	+	S.K., et al, unpublished data
1moF	del 22q11.2	unknown	Compound heterozygous	BSS	-	[20]

7M			Homozygous	BSS	-	[62]
4M			Homozygous	BSS	-	[62]
GPIX mutation						
39F	1856T>C (TTT>TCT)	Phe55Ser	Homozygous	ITP	+	[21]
46F	1910G>A (TGT>TAT)	Cys73Tyr	Homozygous	BSS	-	[22]
31M	1910G>A (TGT>TAT)	Cys73Tyr	Homozygous	ITP	-	[22]
46M	1982G>A (TGT>TAT)	Cys97Tyr	Homozygous	ITP	+	[23]
30F	2076G>A(TGG>TGA)	Trp127Stop †	Homozygous	ITP	+	[14,40]
39F	2076G>A(TGG>TGA)	Trp127Stop	Homozygous	ITP	-	[24]
44F	2076G>A(TGG>TGA)	Trp127Stop	Homozygous	ITP	+	[24]

*Nucleotide numbering for GPIb_, GPIb_, and GPIX is according to GenBank accession numbers M22403, U07983, and M80478, respectively. GP indicates glycoprotein; ITP, idiopathic thrombocytopenic purpura; GPD, giant platelet disorders; BSS, Bernard-Soulier syndrome.
†Originally reported as codon 126.

Table 4:-Bernard-Soulier Syndrome Associations

Association	**Age**	**Gender**	**Reference**
Angiodysplasia	39 years old	Female	[31]
	-	Female	[32]
	14 years old	Male	[33]
Angiodysplasia + breast cancer + Hepatitis C	48 years old	Female	[34]
Tuberculosis	14 years old	Female	[35]
Hepatitis	42 years old	Female	[36]
Coronary artery disease	68 years old	Male	[37]
Atherosclerosis and unstable angina	66 years old	Male	[38]
Pregnancy	Variable	Female	[39]
Aquagenicurticarial	18 years old	Male	[45]
Developmental dysplasia of her left hip (DDH)	40 years old	Female	[46]
Acute myeloid leukemia	21 years old	Female	[25]
Myocardial infarction	60 and 64 years old	Male	[26]

Table 5:-Mutation of the glycoprotein (GP) Ib/IX complex associated with Bernard-Soulier Syndrome [92]

Mutation	**Nucleotide Substitution**	**Amino acid change**	**References**
GPIbα Mutations	3172delA	Premature termination	[63]
	3233-3236delTGAG	Premature termination	[64]
	3285C>T	Leu57Phe	[65]
	3309T>C	Cys65Arg	[66]
	3343delT	Premature termination	[67]
	3502T>C	Leu129Pro	[68-69]
	3583C>T	Ala156Val	[70-71-72]
	3621-3656del	Premature termination	[72]
	3651-3653delCTC	del Leu179	[73]
	3741T>A	Cys209Ser	[74-75]
	3998-3999delTG	Premature termination	[12]
	4145G>A	Trp343stop	[76]
	4444insT	Premature termination	[12-14-75]

	4447C>A	Ser444stop	[13]
	4464delA	Premature termination	[12-14]
	4591-4592delAt	Premature termination	[77-78-79]
	4610G>A	Trp498stop	[66-80]
GPIbβ Mutations	del 22q11.2	-	[81-82-83]
	220C>G	Loss of GATA1 site	[81]
	777C>T	Arg17Cys	[16]
	790G>A	Trp21stop	[85]
	945C>G	Pro74Arg	[17]
	963delC	Premature termination	[86]
	991A>G	Tyr88Cys	[18-19]
	1050G>C	Ala108Pro	[18]
	1096G>A	Trp123stop	S.K., et al., unpublished data
GPIX Mutations	1717T>C	Cys8Arg	[87]
	1757A>G	Asp21Gly	[88]
	1811T>C	Leu40Pro	[89]
	1826A>G	Asn45Ser	[88-90-91]
	1856T>C	Phe55Ser	[84-21]
	1910G>A	Cys73Tyr	[22]
	1982G>A	Cys97Tyr	[23]
	2076G>A	Trp127stop	[14-24]
*Nucleotide numbering for GPIbα, GPIbβ_, and GPIX is according to GenBank accession numbers M22403, U07983, and M80478, respectively.			

Table 6:-Proposed definitions of disease[30]	
Primary idiopathic thrombocytopenic	• It is an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count <100 x 109/L) in the absence of other causes that may be associated with thrombocytopenia. No confirmed clinical or laboratory parameters are currently available to establish its diagnosis with accuracy.
Secondary ITP	• All immune-mediated thrombocytopenia except primary ITP*
Phases of the disease	• Newly diagnosed ITP: within three months from diagnosis • Persistent ITP: between 3 to 12 months from diagnosis. • Chronic ITP: More than 12 months. • Severe ITP: Presence of bleeding symptoms at presentation need treatment, or occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose.

Table 7:-Proposed criteria for assessing response to ITP treatments[30]
Quality of response
• CR: platelet count>100 x10^9/L and absence of bleeding.
• R: Platelet count >30 x 10^9/L and at least 2-fold increase the baseline count and absence of bleeding.
• Time to response: time from starting treatment to time of achievement of CR or R.
• NR: platelet count <30 x 10^9/L or less than 2-fold increase of baseline platelet count or bleeding
• Loss of CR or R: Platelet count<100 x10^9/L or bleeding (from CR) or <30 x 10^9/L or less than 2-fold increase of baseline platelet count or bleeding (from R)
Timing of assessment of response to ITP treatments
• Variable depends on the type of treatment (see Table 8)**.**
Duration of response
• Measured from the achievement of CR or R to loss of CR or R**.**

For response criteria in refractory ITP, see Table 9.

Table 8:-Individual agents for treatment of ITP and the time to the first and peak responses if using the reported dose range[30]

Agent/treatment	Reported dose range	Time to initial response*	Time to peak response*
Prednisone [46,47]	1-4 mg/kg PO daily x 1-4 wk	4-14 d	7-28 d
Dexamethasone[48,49]	40 mg PO or IV daily x 4 d for 4-6 courses every 14-28 d	2-14 d	4-28 d
IVIg[50,51,52]	0.4-1 g/kg per dose IV (1-5 doses)	1-3 d	2-7 d
Anti-D [53,54]	75 ug/kg per dose IV	1-3 d	3-7 d
Rituximab [55,56,57]	375 mg/m2 per dose IV (4 weekly doses)	7-56 d	14-180 d
Splenectomy[58]	Laparoscopic	1-56 d	7-56 d
Vincristine [46]	up to 2 mg/dose IV (4-6 weekly doses)	7-14 d	7-42 d
Vinblastine [46,59]	0.1 mg/kg per dose IV (6 weekly doses)	7-14 d	7-42 d
Danazol[46,60]	400-800 mg PO daily	14-90 d	28-180 d
Azathioprine [60]	2 mg/kg PO daily	30-90 d	30-180 d
AMG53 [61,41,42]	3-10 ug/kg weekly SC	5-14 d	14-60 d
Eltrombopag[43]	50-75 mg PO daily	7-28 d	14-90 d

In the times to the initial and peak responses, the first number of days is the first time that a response could be reasonably expected and the second number of days is the time after which a response to this particular agent becomes less likely when administered at the dose and schedule listed in the table. Dosages, where not given on kilogram/body weight basis, are intended for adults.
PO indicates per oral administration; IV, intravenous infusion; and SC, subcutaneous infusion.

Table 9:-Refractory ITP [30]
Definition (all should be met)
Failure to achieve at least R or loss of R aftersplenectomy*
Need of treatment(s) (including, but not limited to, low dose of corticosteroids) to minimize the risk of clinically significant bleeding. † Need of on-demand or adjunctive therapy alone does not qualify the patient as refractory.
Primary ITP confirmed by excluding other supervened causes of thrombocytopenia.
Definition of on-demand therapy
Any therapy used to temporarily increase the platelet count sufficiently to safely perform invasive procedures or in case of major bleeding or trauma‡
Definition of adjunctive therapy
Any non-ITP specific therapy that may decrease bleeding (e.g., antifibrinolytic agents, hormonal agents, DDAVP, recombinant factor VIIa, fibrin sealants). Platelet transfusion is also included.
Definition of response to therapy in refractory ITP
Ability to maintain a platelet count sufficient to prevent clinically significant bleeding†§
Ability to decrease toxic therapy (e.g., corticosteroids) does not qualify for response but should be reported
Definition of response to on-demand therapy
Control of bleeding in the specific situation
Achievement of a platelet count sufficient to perform procedure or minimize bleeding from trauma

DDAVP indicates deamino arginine vasopressin.
*May not be applicable in children or in patients with accessory spleen.
†Bleeding symptoms measured by a validated scale whenever possible (requires further studies).
‡Specific platelet thresholds cannot be provided, but in most instances, a platelet count of 50-70 x 10^9/L would fulfill this criterion.
§A strict definition of response in terms of predefined platelet count cannot be given and may not be appropriate when considering the risk/benefit ratio in refractory ITP, because the trade off between efficacy of a specific treatment and its short- and long-term toxicity varies among patients.

References:-

1. Pham A, Wang J. Bernard-Soulier Syndrome: An Inherited Platelet Disorder. Arch Pathol Lab Med. 2007;131:1834-6.
2. Sumitha E, Jayandharan GR, David S, Jacob RR, Devi GS, Bargavi B, et al. Molecular basis of Bernard–Soulier syndrome in 27 patients from India.J Thromb Haemost. 2011;9:1590-8.
3. Cattaneo M. Inherited platelet-based bleeding disorders. J ThrombHaemost 2003;1:1628–36.
4. Savoia A, Pastore A, De Rocco D, Civaschi E, Di Stazio M, Bottega R, et al. Clinical and genetic aspects of Bernard-Soulier syndrome: searching for genotype/phenotype correlations. Haematologica. 2011;96:417-23.
5. Berndt MC, Andrews RK. Bernard-Soulier syndrome. Haematologica. 2011;96:355.
6. Lopez JA,Chung DW, Fujikawa K, Hagen FS, Papayannopoulou T**,** Roth GJ. Cloning of the alpha chain of human platelet glycoprotein Ib: a transmembrane protein with homology to leucine-rich alpha 2**-**glycoprotein. Proc Natl AcadSci U S A 1987; 84: 5615–9.
7. Yagi M, Edelhoff S, Disteche CM, Roth GJ. Structural characterization and chromosomal location of the gene encoding human platelet glycoprotein Ib beta. J BiolChem 1994; 269: 17424–7**.**
8. Hickey MJ, Deaven LL, Roth GJ. Human platelet glycoprotein IX**.** Characterization of cDNA and localization of the gene to chromosome.3 FEBS Lett 1990; 274: 189–92**.**
9. Yagi M, Edelhoff S, Disteche CM, Roth GJ. Human platelet glycoproteins V and IX: mapping of two leucine-rich glycoprotein genes to chromosome 3 and analysis of structures. Biochemistry 1995;34**:**16132–7.
10. Bernard-Soulier syndrome - World Federation of Hemophilia [Internet]. Wfh.org. 2012 [cited 2016 Oct 5]. Available from:http://www.wfh.org/en/page.aspx?pid=657
11. Cines DB, Bussel JB, McMillan RB, Zehnder JL. Congenital and Acquired Thrombocytopenia. ASH Education Program Book. 2004;2004(1):390-406.
12. Kanaji T, Okamura T, Kurolwa M, et al. Molecular and genetic analysis of two patients with Bernard-Soulier syndrome:identification of new mutations in glycoprotein Ibgene.ThrombHaemost. 1997;77:1055-61.
13. Kunishima S, Miura H, Fukutani H, et al. Bernard-Soulier syndrome Kagoshima:Ser 444—>stop mutation of glycoprotein (GP) Ib resulting in circulating truncated GPIb and surface expression of GPIb and GPIX.Blood.1994;84:3356-62.
14. Mitsui T,YokoyamaS,YazakiN,etal.Severe bleeding tendency in a patient with Bernard-Soulier syndrome associated with a homozygous single base pair deletion in the gene coding for the human platelet glycoprotein Ib . J PediatrHematolOncol. 1998; 20:246-51 **.**
15. Noda M, Fujimura K,Takafuta T, et al. Heterogeneous expression of glycoprotein Ib, IX and V in platelets from two patients with Bernard-Soulier syndrome caused by different genetic abnormalities.Thromb Haemost.1995;74:1411-15.
16. Kunishima S, Naoe T, Kamiya T, Saito H. A novel heterozygous missense mutation in the platelet glycoprotein Ib_ gene associated with isolated giant platelet disorder. Am J Hematol. 2001;68: 249-55.
17. KunishimaS,TomiyamaY,HondaS,etal.Homozygous Pro74—>Arg mutation in the platelet glycoprotein Ib gene associated with Bernard-Soulier syndrome. ThrombHaemost. 2000;84:112-17.
18. Kunishima S, Lopez JA, Kobayashi S, et al. Missense mutations of the glycoprotein (GP) Ib gene impairing the GPIb / disulfide linkage in a family with giant platelet disorder. Blood. 1997;89: 2404-12.
19. KurokawaY,IshidaF,KamijoT,et al.A missense mutation (Tyr88 to Cys) in the platelet membrane glycoprotein Ib gene affects GPIb/IX complex expression: Bernard-Soulier syndrome in the homozygous form and giant platelets in the heterozygous form. Thromb Haemost.2001;86:1249-56.
20. Nakagawa M,OkunoM,OkamotoN,FujinoH,KatoH.BernardSoulier syndrome associated with 22q11.2 microdeletion. Am J Med Genet.2001;99:286-288.
21. Suzuki K, Hayashi T,Yahagi A, et al. Novel point mutation in the leucine-rich motif of the platelet glycoprotein IX associated with Bernard-Soulier syndrome.Br J Haematol.1997;99:794-800.

22. Noda M, Fujimura K,Takafuta T, et al.A point mutation in glycoprotein IX coding sequence (Cys73 (TGT) to Tyr(TAT)) causes impaired surface expression of GPIb/IX/V complex in two families with Bernard-Soulier syndrome. ThrombHaemost. 1996;76: 874-8.
23. KunishimaS,Tomiyama Y, Honda S, et al. Cys97—>Tyr mutation in the glycoprotein IX gene associated with Bernard-Soulier syndrome.Br J Haematol.1999;107:539-45.
24. Iwanaga M, Kunishima S, Ikeda S,Tomonaga M, NaoeT.Vulnerable mutation Trp126—>stop of glycoprotein IX in Japanese Bernard-Soulier syndrome.Eur J Haematol.1998;60:264-6.
25. Adlekha S, Chadha T. Bernard Soulier Syndrome associated with acute myeloid leukemia. Indian J Med Sci. 2013;67:145-7.
26. Girolami A, Vettore S, Vianello F, Berti de Marinis G, Fabris F. Myocardial infarction in two cousins heterozygous for ASN41HIS autosomal dominant variant of Bernard-Soulier syndrome. J Thromb Thrombolysis. 2012;34:513-7.
27. Kurtjens R, Bolt C, Vossen M, Haanen C. Familial thrombopathic thrombocytopenia. Br J Haematol. 1968;15:305-17**.**
28. Nayean Y, Lecompte T. Genetic thrombocytope- nia with autosomal dominant transmission: a re- view of 54 cases. Br J Haematol. 1990;74:203- 8
29. Noris P, Spedini P, Belletti S, Magrini U, Balduini CL. Thrombocytopenia, giant platelets, and leu- kocyte inclusion bodies (May-Hegglin anomaly): clinical and laboratory findings. Am J Med. 1998;104:355-60.
30. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113:2386-93.
31. Yuksel O, Koklu S, Ucar E, Sasmaz N, Sahin B. Severe recurrent gastrointestinal bleeding due to angiodysplasia in a Bernard-Soulier patient: an onerous medical concomitance. Dig Dis Sci. 2004;49:885-7.
32. Otrock ZK, Degheili JA, Sibai H, Salem ZM. Recurrent jejunal bleeding due to angiodysplasia in a Bernard-Soulier patient. Blood Coagul Fibrinolysis. 2013;24:428-9.
33. Kaya Z, Gürsel T, Dalgic B, Aslan D. Gastric angiodysplasia in a child with Bernard-Soulier syndrome: efficacy of octreotide in long-term management. PediatrHematolOncol. 2005;22:223-7.
34. Okita R, Hihara J, Konishi K, Osaki A, Yoshida K, Yamaguchi Y, et al. Intractable gastrointestinal bleeding from angiodysplasia in a patient of Bernard-Soulier syndrome--report of a case. Hiroshima J Med Sci. 2005;54:113-5.
35. Hasanzad M. Bernard–Soulier Syndrome (BSS) &tuberculosis: A case report. Int J Mycobacteriol. 2014;3:283-5.
36. Suzuki K, Hayashi T, Akiba J, Yoshino M, Tajima K, Satoh S, et al. Successful intravenous interferon-beta treatment of chronic hepatitis C in a patient with Bernard-Soulier syndrome. Thromb Res. 2000;100:149-52.
37. Bilal RH, Moideen I, Pyke L, Makahleh Z, Fernandez-Jimenez P, Hasan R. Off-pump coronary artery bypass grafting in a patient with Bernard-Soulier syndrome. Ann Thorac Surg. 2010;90:284-5.
38. Humphries JE, Yirinec BA, Hess CE. Atherosclerosis and unstable angina in Bernard-Soulier syndrome. Am J ClinPathol. 1992;97:652-5.
39. Peitsidis P, Datta T, Pafilis I, Otomewo O, Tuddenham EG, Kadir RA. Bernard Soulier syndrome in pregnancy: a systematic review. Haemophilia. 2010;16:584-91.
40. Arai M,YamamotoN,AkamatsuN,etal.Substantial expression of glycoproteins IX and V on the platelet surface from a patient with Bernard-Soulier syndrome.Br J Haematol.1994;87:185-8.
41. Newland A, Caulier MT, Kappers-Klunne M, et al. An open-label, unit dose-finding study of AMG 531, a novel thrombopoiesis-stimulating peptibody, in patients with immune thrombocytopenic purpura. Br J Haematol. 2006;135:547-53.
42. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomized controlled trial. Lancet. 2008;371:395- 403.
43. Bussel JB, Cheng G, Saleh MN, Psaila B, Kovaleva L, Meddeb B, et al. Eltrombopag for the Treatment of Chronic Idiopathic Thrombocytopenic Purpura. N Engl J Med 2007;357:2237-47.
44. Kai AC, Flohr C. Aquagenic urticaria in twins. World Allergy Organ J. 2013;6:2.
45. Stuart Bisland and Frank Smith.Total Hip Arthroplasty in A Young Patient with Bernard-Soulier Syndrome .J Orthop Case Rep. 2014; 4: 38–41.
46. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods of American Society of Hematology. Blood. 1996;88:3-40.

47. Bellucci S, Charpak Y, Chastang C, Tobelem G. Low doses v conventional doses of corticoids in immune thrombocytopenic purpura (ITP): results of a randomized clinical trial in 160 children, 223 adults. Blood. 1988;71:1165-9.
48. Andersen JC. Response of resistant idiopathic thrombocytopenic purpura to pulsed high-dose dexamethasone therapy. N Engl J Med. 1994; 330:1560-4.
49. Mazzucconi MG, Fazi P, Bernasconi S, et. al. Therapy with high-dose dexamethasone (HDDXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: a GIMEMA experience. Blood. 2007;109:1401-7.
50. Godeau B, Chevret S, Varet B, et al. Intravenous immunoglobulin or high-dose methylprednisolone,with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicenter trial. Lancet. 2002;359:23-9.
51. Godeau B, Caulier MT, Decuypere L, Rose C, Schaeffer A, Bierling P. Intravenous immunoglobulin for adults with autoimmune thrombocytopenic purpura: results of a randomized trial comparing 0.5 and 1 g/kg b.w. Br J Haematol. 1999; 107:716-19.
52. Bussel JB, Pham LC, Aledort L, Nachman R. Maintenance treatment of adults with chronic refractory immune thrombocytopenic purpura using repeated intravenous infusions of gammaglobulin. Blood. 1988;72:121-7.
53. Newman GC, Novoa MV, Fodero EM, Lesser ML, Woloski BM, Bussel JB. A dose of 75 microg/kg/d of i.v. anti-D increases the platelet count more rapidly and for a longer period of time than 50 microg/kg/d in adults with immune thrombocytopenic purpura. Br J Haematol. 2001;112:1076-8.
54. Tarantino MD, Young G, Bertolone SJ, et al. Single dose of anti-D immune globulin at 75 microg/ kg is as effective as intravenous immune globulin at rapidly raising the platelet count in newly diagnosed immune thrombocytopenic purpura in children. J Pediatr. 2006;148:489-94.
55. Arnold D, Dentali F, Crowther MA, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med. 2007;146:25-33.
56. Godeau B, Porcher R, Fain O, et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: results of a prospective multicenter phase 2 study. Blood. 2008;112:999-1004.
57. Cooper N, Stasi R, Cunningham-Rundles S, et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. Br J Haematol. 2004;125:232-9.
58. Kojouri K, Vesely SK, Terrell D, George J. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. Blood. 2004;104:2623-34.
59. Facon T, Caulier MT, Wattel E, Jouet JP, Bauters F, Fenaux P. A randomized trial comparing vinblastine in slow infusion and by bolus i.v. injection in idiopathic thrombocytopenic purpura: a report on 42 patients. Br J Haematol. 1994;86:678-80.
60. Boruchov DM, Gururangan S, Driscoll MC, Bussel JB. Multiagent induction and maintenance therapy for patients with refractory immune thrombocytopenic purpura (ITP). Blood. 2007;110:3526-31.
61. Klaassen RJ, Blanchette VS, Barnard D, et al. Validity, reliability, and responsiveness of a new measure of health-related quality of life in children with immune thrombocytopenic purpura: the Kids' ITP Tools. J Pediatr. 2007;150:510-15.
62. Madani H, Nazer M, Alotibi W. Bernard-Soulier Syndrome; Case Study .Int J Health Sci (Qassim). 2016;4:156-9.
63. Li C, Pasquale DN, Roth GJ. Bernard-Soulier syndrome with severe bleeding:absent platelet glycoprotein Ib due to a homozygous one-base deletion.Thromb Haemost.1996;76:670-4.
64. Afshar-Kharghan V, Craig FE, Lopez JA. Bernard-Soulier syndrome in a patient doubly heterozygous for two frameshift mutations in the glycoprotein Ib gene. Br J Haematol. 2000;110: 919-24.
65. Miller JL, Lyle VA, Cunningham D. Mutation of leucine-57 to phenylalanine in a platelet glycoprotein Ib leucine tandem repeat occurring in patients with an autosomal dominant variant of Bernard-Soulier disease. Blood.1992;79:439-46.
66. Kenny D, Jonsson OG, Morateck PA, Montgomery RR. Naturally occurring mutations in glycoprotein Ib that result in defective ligand binding and synthesis of a truncated protein. Blood.1998;92: 175-83.
67. SimsekS,AdmiraalLG,ModdermanPW,van-der-SchootCE,vondem-Borne AE. Identification of a homozygous single base pair deletion in the gene coding for the human platelet glycoprotein Ib causing Bernard-Soulier syndrome.Thromb Haemost.1994;72: 444-9.

68. Li C, Martin SE, Roth GJ.The genetic defect in two well-studied cases of Bernard-Soulier syndrome: a point mutation in the fifth leucine-rich repeat of platelet glycoprotein Ib. Blood. 1995;86: 3805-14.
69. Antonucci JV, Martin ES, Hulick PJ, Joseph A, Martin SE. Bernard-Soulier syndrome: common ancestry in two African American families with the GPIb Leu129Pro mutation. Am J Hematol.2000;65:141-8.
70. Ware J, Russell SR, Marchese P, et al. Point mutation in a leucinerich repeat of platelet glycoprotein Ib resulting in the BernardSouliersyndrome. JClin Invest.1993;92:1213-20.
71. Savoia A, Balduini CL, Savino M, et al. Autosomal dominant macrothrombocytopenia in Italy is most frequently a type of heterozygous Bernard-Soulier syndrome. Blood. 2001;97:1330-5.
72. Margaglione M, D'Andrea G, Grandone E, Brancaccio V, Amoriello A, Di Minno G. Compound heterozygosity (554-589 del, C515-T transition) in the platelet glycoprotein Ib alpha gene in a patient with a severe bleeding tendency. Thromb Haemost. 1999;81:486-92.
73. Salle C, Baas MJ, Lanza F, Schwartz A, Hanau D, Chevalier J, et al. A three-base deletion removing a leucine residue in a leucine-rich repeat of platelet glycoprotein Ibα associated with a variant of Bernard-Soulier syndrome (Nancy I). Br J Haematol. 1995;89:386-96.
74. Simsek S, Noris P, Lozano M, et al. Cys209 Ser mutation in the platelet membrane glycoprotein Ib gene is associated with Bernard-Soulier syndrome.Br J Haematol.1994;88:839-44.
75. Gonzalez-Manchon C, Larrucea S, Pastor AL, et al. Compound heterozygosity of the GPIb gene associated with Bernard-Soulier syndrome.Thromb Haemost. 2001;86:1385-91.
76. Ware J, Russell SR, Vicente V, Scharf RE, Tomer A, McMillan R, et al. Nonsense mutation in the glycoprotein Ib alpha coding sequence associated with Bernard-Soulier syndrome. Proc Natl Acad Sci U S A. 1990;87:2026-30.
77. Koskela S, Partanen J, Salmi TT, Kekomaki R. Molecular characterization of two mutations in platelet glycoprotein (GP) Ib in two Finnish Bernard-Soulier syndrome families. Eur J Haematol. 1999;62:160-8.
78. Afshar-Kharghan V, Lopez JA. Bernard-Soulier syndrome caused by a dinucleotide deletion and reading frameshift in the region encoding the glycoprotein Ib transmembrane domain. Blood. 1997;90:2634-43.
79. Afshar-Kharghan V, Craig FE, Lopez JA. Bernard-Soulier syndrome in a patient doubly heterozygous for two frameshift mutations in the glycoprotein Ib gene. Br J Haematol. 2000;110: 919-24.
80. Holmberg L, Karpman D, Nilsson I, Olofsson T. Bernard-Soulier syndrome Karlstad: Trp 498—>Stop mutation resulting in a truncated glycoprotein Ib that contains part of the transmembranous domain.Br J Haematol.1997;98:57-63.
81. Ludlow LB, Schick BP, Budarf ML, et al. Identification of a mutation in a GATA binding site of the platelet glycoprotein Ibpromoter resulting in the Bernard-Soulier syndrome. J Biol Chem. 1996;271:22076-80.
82. Budarf ML, Konkle BA, Ludlow LB, et al. Identification of a patient with Bernard-Soulier syndrome and a deletion in the DiGeorge/velo-cardio-facial chromosomal region in 22q11.2.Hum Mol Genet.1995;4:763-6.
83. Iascone MR, Sacchelli M, Vittorini S, Giusti S. Complex conotruncal heart defect, severe bleeding disorder and 22q11 deletion: a new case of Bernard-Soulier syndrome and of 22q11 deletion syndrome? Ital Heart J. 2001;2:475-7
84. Noris P, Simsek S, Stibbe J, von dem Borne AE.A phenylalanine55 to serine amino-acid substitution in the human glycoprotein IX leucine-rich repeat is associated with Bernard-Soulier syndrome. Br J Haematol.1997;97:312-20.
85. Moran N, Morateck PA, Deering A, Ryan M, Montgomery RR, Fitzgerald DJ, Kenny D. Surface expression of glycoprotein Ibα is dependent on glycoprotein Ibβ: evidence from a novel mutation causing Bernard-Soulier syndrome. Blood. 2000;96:532-9.
86. Kenny D, Morateck PA, Gill JC, Montgomery RR. The critical interaction of glycoprotein (GP) Ib with GPIX:a genetic cause of Bernard-Soulier syndrome.Blood.1999;93:2968-75.
87. Rivera CE,Villagra J, Riordan M,Williams S, Lindstrom KJ, Rick ME. Identification of a new mutation in platelet glycoprotein IX (GPIX) in a patient with Bernard-Soulier syndrome.Br J Haematol.2001;112:105-8.
88. Wright SD, Michaelides K, Johnson DJ, West NC, Tuddenham EG. Double heterozygosity for mutations in the platelet glycoprotein IX gene in three siblings with Bernard-Soulier syndrome. Blood. 1993 May 1;81(9):2339-47.
89. Noris P, Arbustini E, Spedini P, Belletti S, Balduini CL. A new variant of Bernard-Soulier syndrome characterized by dysfunctional glycoprotein (GP) Ib and severely reduced amounts of GPIX and GPV. British journal of haematology. 1998;103:1004-13.
90. Donner M, Karpman D, KristofferssonAC,Winqvist I, Holmberg L. Recurrent mutation Asn45→Ser of glycoprotein IX in Bernard-Soulier syndrome.Eur J Haematol.1996;57:178-9.

91. Vanhoorelbeke K, Schlammadinger A, Delville JP, et al. Occurrence of the Asn45Ser mutation in the GPIX gene in a Belgian patient with Bernard Soulier syndrome.Platelets.2001;12:114-20.
92. Kunishima S, Kamiya T, Saito H. Genetic abnormalities of Bernard-Soulier syndrome. Int J Hematol. 2002;76:319-27.