

A 1½ year old girl with excessive bleeding following accidental trauma to the upper labial frenum during playing

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Presentation of Case

Dr. Monwarul Aziz (Dental Surgeon): A 1½ year old girl of a consanguineous parents was brought to the emergency and casualty department of a secondary care military hospital in Chattogram Cantonment (South-East part of Bangladesh), Chattogram, Bangladesh at 0100 hours on 19th January 2018 by her parents with the complaints of excessive bleeding following accidental trauma to the upper labial frenum during playing for the last six hours. The duty medical officer attended the patient and took detail history. The doctor came to know that the baby got accidental trauma to the upper labial frenum during playing at 2130 hours on 18th January 2018 followed by excessive bleeding from the injury site.

As the father of the patient is a paramedic and serving in the same military hospital of Chattogram cantonment, with his medical skill, he made an effort to prevent the bleeding by pressure bandage over the injury site in several times and the bleeding decreased meaningfully. After that, the child dozed but at about 0100 hours on 19th January 2018, the parents noticed that bleeding resumed and blood wetted the bed and mouth of the baby was filled with fresh blood. So, the parents took the baby and rushed to emergency and casualty department of the military hospital.

The attending doctor also examined the injury site and found that the injury was very trivial in nature. There was no need to stitch and he again tried to stop the bleeding by putting pressure bandage and antifibrinolytic agents (tranexamic acid). Initially, the bleeding stopped but after 5-10 min, the bleeding again started. Then he referred the patient to the Military Dental Center. I attended the patient and found that the blood was oozing from the injury site. I again tried to stop the bleeding by putting pressure bandage and local anesthetic agent such as injection adrenaline but it did not work rather more bleeding was observed from the injection site. Then I put hemostatic paste to the injury site and bleeding stopped. As per statement of the parents, the baby was delivered by cesarean section and the baby was

otherwise healthy until this incident as well as the mother recovered well after cesarean section with no history of prolonged bleeding peri- and post-operatively. Her father also underwent operation for deviated nasal septum and recovered well. The patient was immunized as per national immunization schedule and her milestone of development was age proportional. However, during vaccination, the bleeding was observed and it took slightly long time to stop and as it was so minor abnormality that the parents ignored it and did not bring to the notice of the concerned physician. The baby did not suffer from any serious medical and surgical illness in the past. The patient is the only daughter of the parents. Family history revealed no record of bleeding disorder. On general and systemic examinations, no abnormality was detected. No abnormality was detected in the dentures, oral mucosa, gum, lips and tongue on local examination other than a 1 x 1 x 1 cm³ wound in the upper labial frenum. As such, abnormal bleeding from the upper labial frenum was unrelated to dental disorders. Therefore, I referred the case to the child specialist as well as hematologist for further management.

Dr. Bazlur Rahman (Pediatricians): The referred case had reported to the outpatient department of Pediatrics in the morning on 19th January 2018. We discussed the case together and assumed that it might be a case of congenital bleeding disorder. Therefore, we advised for complete blood count, blood grouping, bleeding time, clotting time, prothrombin time and partial thromboplastin time for both the patient as well as parents. The patient was also advised to do serum TSH.

On 20th January 2018, we got the results of the laboratory investigations which showed marked prolongation of bleeding time and partial thromboplastin time of the patient but all other investigations of the patient and parents were within normal limits. Results of the laboratory investigations of the parents were within normal limits. Blood group of the patient was B positive, father O positive and mother B positive. Basing on the history, physical findings and results of the laboratory investigation, we



Table I

Laboratory data

Variable	Reference range, 1 year ¶	In Combined Military Hospital		
		Patient	Father	Mother
Hemoglobin (g/dL)	11.1-13.1	9.0	13.6	9.6
ESR (mm in 1 st hour)	10-20	15		
Hematocrit (L/L)	0.3-0.4	0.3		
RBC (x10 ¹² /L)	3.9-5.1	3.0	4.5	3.2
Mean cell volume (fL)	72-84	80	88	88
White cell count (x10 ⁹ /L)	6.0-16.0	9.8	6.8	7.0
Differential count				
Neutrophils (%)		32	67	50
Lymphocytes (%)		56	26	38
Monocytes (%)		10	5	4
Eosinophils (%)		2	2	8
Platelet count (x10 ⁹ /L)	200-550	440	200	280
Peripheral blood film		Non specific findings		
Bleeding time (min)	5-11	23	3.2	4.3
Clotting time (min)		8.0	8.3	9.4
Prothrombin time (sec)	13	13	13	14
Activated partial thromboplastin time (sec)	30	65	38	32
Von Willebrand antigen (%)	50-160	3		
FVIII activity (%)	60-150	3		
HbsAg		Negative		
Serum TSH (µIU/mL)	0.8-9.1	3.5		
Blood group		B ⁺ ve	O ⁺ ve	B ⁺ ve

¶Reference values are affected by many variables, including the demographics and the laboratory methods used. The ranges used at Combined Military Hospital, Chattogram are for children (1 year) who do not have medical conditions that could affect the results. They may, therefore, not be appropriate for all patients

made an interim clinical impression and referred the case to a tertiary care military hospital, Dhaka cantonment, Dhaka, Bangladesh.

Dr. Mohammad Mizanur Rahman (Hematologist): After reporting to me, I have re-evaluated the case and carefully dissected the history, family pedigree, physical findings and laboratory investigations so far done. As the patient presented only with prolonged and excessive bleeding from the upper labial frenum, no family history of bleeding disorders, platelet count was 440,000/cmm, bleeding time was 20 min and PTT was 60 sec, so my clinical impression was Von Willebrand disease. I referred the case to army referral laboratory, Dhaka cantonment, Dhaka, Bangladesh for von Willebrand factor antigen and factor VIII assay.

Provisional Diagnosis

Inherited bleeding disorder

Differential Diagnosis

Dr. Rahman: Several factors were considered while constructing the differential diagnosis. First, age and sex of the patient. Second, sudden onset of prolonged and excessive bleeding following minor trauma. Third, consanguineous marriage of the parents and absence of bleeding disorders in the family. Fourth, results of first line coagulation tests and blood group of the patient. Fifth, pedigree analysis. Keeping such factors in mind and after evaluating the clinical and initial laboratory investigations, the following differential diagnoses were considered.

Immune thrombocytopenic purpura

Immune thrombocytopenic purpura is defined as low platelet count with either normal bone marrow or megakaryocytic hyperplasia in bone marrow and absence of other causes of thrombocytopenia. Patients with immune thrombocytopenic purpura presents with distinct purpuric rash, an increased tendency to bleed, easy bruising and ecchymoses in the skin and mucous membrane.¹ Immune thrombocytopenic purpura may be presented as acute in which children are mainly affected and usually follows a viral infection of the upper respiratory tract.

Acute immune thrombocytopenic purpura usually resolves spontaneously within two months. Chronic immune thrombocytopenic purpura usually occurs in adults without a known etiology and persists longer than six months.² Acute immune thrombocytopenic purpura in children is usually mild and self-limited but life threatening intracranial hemorrhage may occur when the platelet count is less than 10,000/cmm.³ Such grave situation may be experienced in day to day practice in about 0.5-1.0% cases. However, half of these cases are fatal.⁴ In immune thrombocytopenia, platelets are destroyed in the peripheral circulation through an immune mediated mechanism. An abnormal auto-antibody, usually IgG with specificity for platelet membrane glycoprotein IIb-IIIa or Ib-IX is produced and binds to circulating platelets.⁵⁻⁷ Such antibody coated platelets are destroyed through Fc-mediated phagocytosis by mononuclear macrophages, primarily but not exclusively in the spleen.⁸ Spleen plays a significant role in the pathogenesis of immune thrombocytopenic purpura, not only because platelet auto-antibodies are produced in the white pulp but also because mononuclear macrophages in the red pulp phagocytes and destroy immunoglobulin-coated platelets.⁹ In about 60 percent of cases, auto-

antibodies against platelets are detected.¹⁰ The incidence of immune thrombocytopenia has seasonal variation, with a peak in winter and a nadir in summer. Persistence or chronicity occurred in 36% of children compared with 67% of adults.¹¹ Immune thrombocytopenic purpura is more common in boys than in girls in case of children.¹² Usually women are prone to be affected more than men when immune thrombocytopenic purpura occurs in middle-aged individuals.³ The peak incidence of immune thrombocytopenic purpura in children is between 1–6 years whereas in adults it may occur at any age but most cases are diagnosed in between 30–40 years of age.¹²

In this case, the age of the patient and presence of superficial bleeding suggests the diagnosis of immune thrombocytopenic purpura but sex of the patient, absence of previous history of infection, normal platelet count and no purpura and ecchymoses are the points against the diagnosis of immune thrombocytopenic purpura.

Acute leukemia

Acute leukemia is a neoplasm of bone marrow hemopoietic stem cells which proliferate uncontrolled and replace the normal hemopoietic cells of the marrow. According to cell line involved, acute leukemias are divided into two groups—acute myeloblastic leukemia and acute lymphoblastic leukemia.¹³ Acute lymphoblastic leukemia is more frequent form of leukemia in children and comprises 75% of pediatric leukemia cases. Regarding the etiology of acute leukemia, very little is known and most patients have no identifiable risk factors. However, radiation exposure predisposes to the development of acute myeloblastic leukemia rather than acute lymphoblastic leukemia. Patients having prior history of Hodgkin lymphoma, small cell carcinoma and ovarian cancer are more susceptible to develop acute myeloblastic leukemia.¹⁴ The incidence of acute lymphoblastic leukemia is also low among children with high level of social activity, especially those attending early daycare nursery than those living in more isolated communities and have a reduced exposure to common infections in the first year of life.¹⁵ Pathogenesis of acute lymphoblastic leukemia varies and a significant portion of acute lymphoblastic leukemia are initiated by genomic mutations that occur during development in utero. Significant susceptibility locus in GATA3:3824662 have been identified in younger adults with acute lymphoblastic leukemia. Individuals with some single nucleotide polymorphism (SNP) in germline such as arylamine N-acetyltransferases 1 and 2, MNP-8 promoter genotypes, HLA alleles, ARID5B, IKZF1, CEBPE, CDKN2A, PIP4K2A, LHPP and ELK3 are prone to develop acute lymphoblastic leukemia.¹⁶⁻¹⁹ Patients with acute lymphoblastic leukemia most commonly presents with signs and symptoms of bone marrow failure such as generalized weakness

due to anemia, recurrent infections due to neutropenia, bleeding manifestations due to thrombocytopenia, CNS, testes and organ involvement (lymphadenopathy, splenomegally) or bone pain due to leukemic infiltration.²⁰ For the diagnosis of acute lymphoblastic leukemia, WHO and National Comprehensive Cancer Network (NCCN) guidelines are the demonstration of $\geq 20\%$ bone marrow lymphoblasts, morphological assessment of bone marrow aspirate smears for blasts population, comprehensive flow cytometric immunophenotyping and baseline characterization of leukemic clone to unclog ensuing minimal residual disease (MRD) analysis. It is also important to find the risk stratification and treatment planning in patients with acute lymphoblastic leukemia. For this, NCCN advises further analysis of peripheral or bone marrow lymphoblasts by G-banded metaphase chromosome study, interphase fluorescence in situ hybridization (FISH) for BCR-ABL, MLL, TEL/AML-ETV6/RUNX1, CEP4 and CEP10, RT-PCR and aCGH for aneuploidy or failed karyotype.²¹ The presence of gum bleeding in this patient favors the diagnosis of acute lymphoblastic leukemia but absence of anemia, fever, lymphadenopathy and organomegaly, no immature white cell in peripheral blood as well as normal platelet count disfavors the diagnosis of acute lymphoblastic leukemia.

Aplastic anemia

Peripheral blood pancytopenia and bone marrow hypoplasia in the absence of abnormal infiltrate and without increase in reticulin are the features that define aplastic anemia.²² In 1888, Paul Ehrlich introduced the concept of aplastic anemia but Anatole Chauffard named this disorder aplastic anemia in 1904.²³ It is thought that aplastic anemia is more common in Asia than the West. In Europe, the incidence is two cases per million population.²⁴ A prospective study conducted in Thailand revealed the incidence of approximately 4 to 6 cases per million populations. This increased incidence in this area may be due to more exposure to environmental factors such as pesticides, fertilizers, dyeing agents as well as toxic chemicals used in the garment and other industries. The increased incidence of aplastic anemia is not observed among the Asians living in United States indicating that genetic factors are more responsible for aplastic anemia in USA and the West.²⁵ No racial predisposition of aplastic anemia is reported in USA and both sexes are equally affected. Biphasic age distribution is observed with peaks at 20–25 years and another over 60 years.²² The primary defects in or damage to the stem cells or the marrow microenvironment is the theoretical basis of bone marrow failure. Clinical and laboratory observations suggest that aplastic anemia is an autoimmune disease.²⁶⁻²⁸ In aplastic anemia, bone marrow examination revealed hemopoietic stem cell elements which are less than 25% and replaced by fat cells. CD34 cell population

analyzed by flow cytometry are significantly reduced in the aplastic anemia.²⁹ However, in most cases of aplastic anemia, the cause is unknown. The search for an etiology is often unproductive and should obtain detailed work history including exposure to environmental factors as well as family and infectious disease history.³⁰ The chance of having inherited bone marrow failure is less in the absence of overt phenotypic features of inherited aplastic anemia such as Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond syndrome, congenital amegakaryocytic thrombocytopenia, Bloom syndrome, Diamond-Blackfan syndrome.³¹ The onset of aplastic anemia is usually insidious and usually presents with symptoms related to anemia, thrombocytopenia or signs of infection. Pallor, headache, palpitation, dyspnea, fatigue are the symptoms of anemia. Gingival bleeding, purpura, ecchymoses or petechial rashes occur due to thrombocytopenia.

Leucopenia, especially neutropenia leads to mouth or pharyngeal ulceration, recurrent or overt infections with fever. Presence of lymphadenopathy or organomegaly as well as immature red or white cells in the peripheral blood film excludes the diagnosis of aplastic anemia.³² Patient should also be searched for the presence of hyperpigmentation, short stature, malformations of the thumb and forearms, skeletal anomalies, small head or eyes, renal problems, hearing defect, heart disease, gastrointestinal difficulties and hypogonadism.³¹ Aplastic anemia is diagnosed by blood and bone marrow studies. Peripheral blood examination usually shows pancytopenia or bicytopenia and bone marrow biopsy including aspiration is done to assess the cellularity of the bone marrow. Usually a hypoplastic marrow is found in aplastic anemia. Cytogenetic study and flow cytometric analysis of the bone marrow should be done to find out the genetic factors as well as the presence of PNH clone.²⁴ Therapy for aplastic anemia consists of supportive care only or immunosuppressive therapy or hemopoietic stem cell transplantation (HSCT). Severe aplastic anemia and very severe aplastic anemia are hematologic emergency as they have a mortality rate of greater than 70%. Therefore, treatment should be initiated immediately.³³

Gingival bleeding, absence of lymphadenopathy and organomegaly in this case supports the diagnosis of acquired aplastic anemia but absence of congenital abnormalities, fever, symptoms of anemia and normal peripheral blood findings are the points against both acquired and congenital aplastic anemia.

Hemophilia

Hemophilia is mainly an inherited genetic disorder that hampers the capability of the body to make blood clot that is needed to stop bleeding.^{34, 35} A deficiencies or abnormality of a single plasma

protein results in inherited coagulation disorders. Due to such unique feature, most of the inherited coagulation disorders produce similar signs and symptoms.³⁶ Hemophilia is mainly of two types, such as hemophilia A and hemophilia B. Hemophilia A is an X-linked recessive disorder due to deficiency of clotting factor VIII (FVIII). Hemophilia B is also an X-linked, inherited, recessive disorder that results in deficiency of functional coagulation factor IX. Both hemophilia A and B may result from spontaneous mutation and acquired immunologic processes.³⁴ Hemophilia has worldwide distribution and affects all ethnic groups. The overall incidence of hemophilia A is about 1 case per 10,000 births (1 in 5,000 male births), with about one third of affected individuals does not have family history of hemophilia A. On the other hand, hemophilia B occurs in about 1 in 50,000 births. Hemophilia B is relatively less frequent than hemophilia A. Of all hemophilia cases, 80-85% is hemophilia A, 14% is hemophilia B and the rest are various other clotting abnormalities.

Among the genetic coagulation disorders, hemophilia A is the most frequent X-linked mendelian disease and second most common coagulation disorder after Von Willebrand disease. Others type of hemophilia include hemophilia C which is due to deficiency of FXI and parahemophilia due to deficiency of FV.^{37, 38} As hemophilia A and B are both X-linked recessive disorders, females are rarely severely affected. Some females with non-functional gene on one of the X chromosome may be mildly symptomatic. In both hemophilia A and B, spontaneous bleeding may occur with normal bleeding and prothrombin time but a prolonged partial thromboplastin time. Clinically hemophilia is classified as mild when factor activity is >5-40%, moderate when 1-5% and severe when factor activity is <1%. Patients with severe hemophilia presents with bleeding in the joints and hematoma in soft-tissue without precipitating trauma. Severe disease is more common in children less than 1 year and comprises 40-75% of hemophilia A cases. Children between 1 and 2 years usually present with moderate disease and are about 18-28% of cases. Mild disease occurs in children over than 2 years and accounts for 15-31% of cases.³⁹ Patients with severe hemophilia present with manifestations of neonatal bleeding (e.g., after circumcision). Few neonates may have intracranial hemorrhage. However, most neonates may present with severe hematoma and prolonged bleeding from the cord or umbilical area. Just after neonatal period, bleeding is infrequent in infants until they become toddlers, when injury-induced soft-tissue hematoma occurs.

During teeth eruption, old children may also experience oral bleeding. It is really problematic for the concerned physicians to manage bleeding from gum and tongue lacerations because blood oozing may continue in spite of adopting supportive

measures. As the time passes and hemophilic patients mature and begin to take part in various physical activities, hemarthroses and hematomas occur. If joint bleeding occurs recurrently, chronic arthropathy usually complicate in a target joint. Treatment of patients with hemophilia involves preventive and supportive measures, management of bleeding episodes, treatment of FVIII inhibitors, if developed and treatment and rehabilitation of hemophilic arthropathy.⁴⁰ The presence of oral bleeding in this girl is in favor of the diagnosis of hemophilia but sex of the patient, absence of bleeding disorders in the family as well as the absence of hemorrhage characteristic of hemophilia disfavor the diagnosis of hemophilia.

Vitamin K deficiency

Vitamin K is an important lipid-soluble vitamin which takes part in the vitamin K cycle for the production of vitamin K-dependent coagulation factors. Green, leafy-vegetables and oils such as soybean, cottonseed, canola and olive oils are the rich sources of vitamin K but colonic bacteria also synthesize it.⁴¹ Four coagulation factors (FII, FVII, FIX, FX) in the liver are synthesized with the help of VK. Production of protein C and S, which are anticoagulant proteins, also depends on vitamin K.⁴² The etiology of vitamin K deficiency differs in infants and adults. In infants, the notable cause is liver prematurity, lack of vitamin K in breast milk, sterile guts in neonates and low transplacental transfer of vitamin K.⁴³⁻⁴⁶ Neonatal cholestasis leading to malabsorption of vitamin K can also result in vitamin K deficiency.⁴² In adults, malabsorption syndrome, infectious diarrhea, parenchymal liver disease, inflammatory bowel disease, cholestatic disease, malnutrition, chronic illness, prolonged parenteral nutrition, massive transfusion and multiple abdominal surgery are the etiologies of vitamin K deficiency.⁴⁷ No age is immune for the development of vitamin K deficiency but infants are most commonly affected.⁴² Infants younger than 5 days may develop vitamin K deficiency without bleeding manifestation. The prevalence of typical hemorrhagic disease of newborns and infants due to vitamin K deficiency is 0.3-1.7%.⁴⁸

The presenting clinical features are related to hypoprothrombinemia and hemorrhage is the main clinical symptom, especially in response to minor trauma. Any parts of the body may be involved but the prime presentations are mucosal and submucosal bleeding such as gum bleeding, epistaxis, hematoma, hematemesis, melena, menorrhagia, hematuria and oozing from the venipuncture sites or umbilical stump. Treatment of vitamin K deficiency depends on the severity of associated bleeding, underlying disease state and risk of inducing a local hematoma at the vitamin K injection site. In life threatening bleeding, fresh frozen plasma should be administered before vitamin K

injection. vitamin K injection in the form of phytonadione (VK1) may be administered intravenously/ intramuscularly in a dose of 1-25 mg in case of adult and 0.5 to 1 mg in case of infant.⁴⁹ Gum bleeding following trauma is the only symptom in this patient that may be considered as a feature of vitamin K deficiency but absence of prematurity and no history of bleeding from the umbilical stump after delivery as well as normal prothrombin time are the features that nullify the diagnosis of vitamin K deficiency.

Dr. Maksuda Begum (Pediatrician): I received the patient on 7th February 2018 as a referred case from a secondary level military hospital, Chattogram, Bangladesh in a stable state with the past history of excessive prolonged bleeding from the upper labial frenum following minor trauma got during playing. The patient was thoroughly evaluated and reviewed all clinical and physical findings as well as laboratory investigations done in the military hospital, Chattogram. As the patient had no clinical and physical findings at present, therefore I advised to repeat the complete blood count with PBF, bleeding time, clotting time, prothrombin time, activated partial thromboplastin time, factor VIII and vWF:Ag assay. On 8th February 2018, I got the investigation reports which are shown in Table I. Analyzing the results of laboratory investigations as well as the initial patient's clinical findings I arrived at a diagnosis of Von Willebrand disease. At the same time, to find out from which type of Von Willebrand disease the patient has been suffering, I advised to perform Ristocetin Induced Platelet aggregation (RIPA) studies, Ristocetin cofactor activity (VWF:RCo), collagen binding activity (VWF:CB) and Von Willebrand factor gene mutation.

Dr. Aziz's Diagnosis

Von Willebrand disease

Discussion

Dr. Rahman: Von Willebrand disease is a congenital coagulation disorder caused by the deficiency of synthesis of defective Von Willebrand factor. As a result, the primary hemostatic defect ensues due to defective interaction between the platelets and the vessel walls.⁵⁰ Von Willebrand factor is a large multimeric glycoprotein, circulates in plasma at a concentration of 10 mg/dL and carries FVIII in a non-covalently bound complex. Von Willebrand factor plays vital roles in the synthesis, action, stabilization, conformation and immunogenicity of FVIII.⁵¹ Von Willebrand factor is released from the storage granules in platelets and endothelial cells in response to various stimuli such as stress, estrogens,

pregnancy, malignancy and thyrotoxicosis that cause endothelial activation.

Two main functions of the Von Willebrand factor are: a) It mediates the adhesion of platelets to the site of traumatized blood vessels and b) it fixes and stabilizes the FVIII, thereby preventing its degradation. The plasma half-life of FVIII in presence of normal Von Willebrand factor concentration is 12 hours but in the absence of the factor, the half-life of FVIII-C (FVIII-coagulant) is reduced to 2 hours.⁵²

Von Willebrand disease is categorized into three main types: a) type 1 (quantitative deficiency of Von Willebrand factor), b) type 2 (qualitative deficiency of Von Willebrand factor) and c) type 3 (complete deficiency of Von Willebrand factor).⁵³

The inheritance of the disease is autosomal dominant except type 3 which is inherited as autosomal recessive manner. The prevalence is only 1% in general population. About 125 persons per million populations are affected by clinically significant Von Willebrand disease but the prevalence of severe disease is approximately 0.5–5.0 persons per million population.

Males and females are equally affected but the phenotypic features are more frequently detected in women because of increased bleeding tendency during menstruation. ABO blood groups of the affected individual also determine severity of the Von Willebrand disease, being severe in people of blood group 'O'.⁵⁴ The incidence of type 1 disease is 60–80% of cases, type 2 disease 20–30% of cases and type 3 disease accounts for less than 5% of all cases.⁵⁵

Mutations in Von Willebrand factor gene which is situated on the short arm of chromosome 12 are responsible for the disease in most cases. More than 300 mutations have been detected in Von Willebrand factor gene. In severe cases, the genetic changes in Von Willebrand factor gene are common whereas in mild form of type 1, full range of molecular pathology together with polymorphisms of Von Willebrand factor gene may be seen. Individuals with type 1 disease have low levels of Von Willebrand factor due to mutations affecting the expression of Von Willebrand factor gene. As a result of mutations, the intracellular passage of Von Willebrand factor sub-units is impaired leading to severe, dominantly form of type 1.⁵⁶ In type 1, there is also rapid clearance of Von Willebrand factor from the plasma providing less cleavage time of circulating Von Willebrand factor multimer by ADAMTS-13.⁵⁷

In type 2, plasma Von Willebrand factor level is normal but have structural and functional defects on which basis type 2 is divided into four subtypes. Either defective Von Willebrand factor multimer assembly or increased cleavage of the multimer by

ADAMTS -13 is responsible for type 2A disease. Homozygous or heterozygous mutations in Von Willebrand factor gene may result in defective multimer assembly preventing multimerization of Von Willebrand factor in the Golgi apparatus. As a result, there is selective loss of large and medium-sized multimers leading to decreased Von Willebrand factor mediated platelet adhesion.⁵⁸ Type 2B is characterized by the loss of large multimers. Multimer assembly is not hampered by the mutations that cause type 2B disease but the multimers after their secretion, get bound to the platelets after which they become cleaved by ADAMTS-13. The defect in type 2B is that Von Willebrand factor-Gp1b complex could not bind to subendothelial tissue. As a result, the large multimers-platelet Gp1b complex is rapidly cleared from the plasma resulting in thrombocytopenia.⁵⁹ Type 2M is characterized by decreased Von Willebrand factor dependant platelet adhesion but the plasma concentration of HMW Von Willebrand factor multimer is normal. The mutations that cause type 2M disease leads to a defect in the functions of Von Willebrand factor resulting in the interference of Von Willebrand factor-platelet adhesion.

As a result, there is less exposure of Von Willebrand factor to ADAMTS-13 preserving the large multimers of Von Willebrand factor in the same concentration as secreted from endothelial cells.⁶⁰ Von Willebrand disease type 2N is featured by remarkable decline in the binding affinity for FVIII due to mutations. The FVIII level is reduced and leads to the misdiagnosis of hemophilia A. Von Willebrand disease type 3 is caused by recessive mutations either missense or nonsense of the Von Willebrand factor gene resulting in undetectable plasma level of Von Willebrand factor.⁶¹ Besides mutations, epigenetic factors such as ABO blood group causing defects in other genes may influence the circulating Von Willebrand factor level.⁵³ Type 3 Von Willebrand disease is a severe form of the three, characterized by severe mucosal bleeding, hemarthrosis and muscle hematoma and affect 1–2 per million populations.⁶²

Von Willebrand disease may be acquired resulting from the development of antibodies to Von Willebrand factor. Conditions that may cause acquired Von Willebrand disease are hypothyroidism, aortic stenosis, Eisenmenger syndrome, myeloproliferative disorders, Wilms tumor and IgG and IgM paraprotein. It develops by a variety of mechanisms in such acquired disorders but typically resolves with the treatment of the underlying disease or cause.⁶³ Several factors influence the symptoms of Von Willebrand disease: Plasma level of residual Von Willebrand factor activity, disease type and subtype and also age and sex of the patient. Bruising and epistaxis are the prominent symptoms in children with Von Willebrand disease. Pediatric-

specific bleeding in Von Willebrand disease are cephalohematoma, cheek bleeding, post-circumcision and post-venipuncture bleeding, conjunctival bleeding and umbilical stump bleeding.⁶⁴ In adult the most common presenting symptoms are hematomas, menorrhagia and bleeding from minor wounds. Bleeding following surgery or dental extraction are the symptoms presented by majority (60–80%) of patients.⁶⁵ Five to 20% of women having menorrhagia are diagnosed as Von Willebrand disease⁶⁶ and on the other hand 70% of women with Von Willebrand disease have increased blood loss during menstrual cycle.⁶⁷ Although hemarthrosis is not a significant problem in patients with Von Willebrand disease but patients with type 2N and type 3 may present with hemarthrosis. Risk of joint bleeding depends on the level of residual Von Willebrand factor in plasma, severity of the disease and patients with type 3 Von Willebrand disease who has reduced FVIII level.⁶⁸

Von Willebrand factor rise physiologically throughout life but such age-dependant increase in Von Willebrand factor does not provide protection to alleviate bleeding symptoms.⁶⁹ However, patients with Von Willebrand disease are at reduced risk of developing cardiovascular disease and ischemic stroke.⁷⁰

The early diagnosis of Von Willebrand disease type 1 and type 2 is difficult as the patients do not present with major bleeding manifestations. Type 3 usually presents with severe bleeding, so early diagnosis is relatively simple and easy. The disease is usually diagnosed on the basis of personal and family history of bleeding along with laboratory test results. The first line laboratory investigations are: Estimation of hemoglobin level, hematocrit, platelet count, prothrombin time and activated partial thromboplastin time and more importantly Von Willebrand disease profile testing (VWF: Ag, VWF: RCo, FVIII: C), ABO blood group. Second line tests if initial test results suggest Von Willebrand disease are: Von Willebrand factor multimer analysis, VWF:CBA, VWF:FVIIIIB, RIPA and Genetic tests.⁷¹ In type 3, patients present with severe bleeding and laboratory investigations such as bleeding time is markedly prolonged, prothrombin time is normal, activated partial thromboplastin time is also prolonged. VWF: Ag and FVIII level are very low (≤ 5 IU/dL).⁷²

Though we could not perform genetic testing for the molecular confirmation of the Von Willebrand disease but the early onset of severe bleeding and absence of bleeding history in her family which are characteristics of autosomal recessive disorders along with normal platelet count, non-“O” blood group, markedly prolonged bleeding time, moderately prolonged activated partial thromboplastin time, markedly reduced VWF: Ag (3%) and FVIII level (3%) strongly suggests the

diagnosis of Von Willebrand disease type 3. The patient was treated with pressure bandage and tablet tranexamic acid in the secondary care military hospital, Chattogram. Her parents were advised to avoid friction prone games, NASIDs and intramuscular injection.

Dr. Ismail Chowdhury (Medical Specialist): Where the patient was finally diagnosed as Von Willebrand disease type 3?

Dr. Aziz: The patient was referred to CMH, Dhaka after doing first line coagulation screening tests and making provisional diagnosis of Von Willebrand disease. In CMH Dhaka, VWF: Ag and FVIII level were measured and finally diagnosed as Von Willebrand disease type 3.

Dr. Shahinur Rahman (Surgical Specialist): When and how was the bleeding of the patient controlled/stopped?

Dr. Aziz: Bleeding was controlled 30 min to 1 hour of reporting to Military dental Centre, Chattogram Cantonment, after applying hemostatic paste to the site of injury and injection Tranexamic acid.

Dr. Md. Nesar Uddin (Otolaryngologist): What is the mode of treatment of such type of patient and the prognosis of the patient?

Dr. Rahman: Type 3 Von Willebrand disease is usually treated with desmopressin, administered intravenously (0.3 μ g/kg body weight) or intranasally (total dose 300 μ g [150 μ g per nostril), VWF-FVIII or Von Willebrand factor concentrate and tablet tranexamic acid 1 g 3 to 4 times daily.⁶⁵ Majority of patients are of type 1 Von Willebrand disease which is a mild, manageable bleeding disorder and rarely cause life threatening bleeding; most of them have little impact on quality of life or life expectancy. Management with Von Willebrand factor rich FVIII concentrates for severe Von Willebrand disease (type 2 and type 3) usually lead to have a good quality of life (QoL).⁵²

Dr. Mostofa Kamal (Cardiologist): What are the characteristics of autosomal recessive disorders? Does this patient fulfill the criteria of autosomal recessive disorders?

Dr. Rahman: Characteristics of autosomal recessive disorders are: recessive abnormal genes only affect homozygous offspring, heterozygous parents are not clinically affected, no parent to offspring transmission of the phenotypic trait but siblings are affected, horizontal pattern of transmission, onset is frequently early in life and tends to be more severe.⁷³ This child also has the features of autosomal recessive disorders such as early severe onset, parents are not clinically affected. As the patient is the only child of the parents, so regarding siblings and horizontal transmission could not be assessed.

Dr. Md. Ataur Rahman Siddiqui (Surgical specialist): Willebrand disease?
How will you manage menorrhagia and the patient during pregnancy?

Dr. Nazma Siddiquee (Gynecologist): Menorrhagia is a frazzling problem in patients with Von Willebrand disease. However, excessive bleeding during menstruation can be minimized by 50% if tranexamic acid continued for first 3 days of the menstrual cycle. Besides this, combined oral contraceptive pill or levonorgestrel (hormone impregnated) coil is very effective in some patients.⁵²

During pregnancy, FVIII and Von Willebrand factor increases, so rarely presents a problem for type 1 Von Willebrand disease. But Von Willebrand factor level falls immediately after child birth for which patients with type 2 and 3 Von Willebrand disease should be observed for post-partum hemorrhage (PPH). Such patient if bleeding developed may be treated with desmopressin or Von Willebrand factor concentrate to keep the plasma Von Willebrand factor level above 30.0 U/dL. Abnormal HMW multimers in type 2B Von Willebrand disease may cause platelet aggregation and thrombocytopenia in pregnancy. Therefore, use of tranexamic acid in pregnancy in type 2B Von Willebrand disease should be avoided as it may further decrease the platelet count.⁵²

Dr. Mohammad Iqbal Kabir (oral and maxillofacial surgeon): Can Von Willebrand disease be developed without genetic mutations?

Dr. Rahman: Yes, in about 30% of patients with Von Willebrand disease, no genetic mutations are found or identified.⁷⁴ However, the disease may be developed in some disorders called acquired Von Willebrand syndrome. Such disorders are hypothyroidism, aortic stenosis, myeloproliferative disorders, Wilms tumor, IgG and IgM paraprotein.⁶³

Dr. Farhana Jannat (Gynecologist): Why did you label this patient as type 3 Von Willebrand disease not type 1 or type 2?

Dr. Afroza Akter (Child Specialist): Type 3 disease is an autosomal recessive disorder. We have labelled this patient as type 3 disease because pedigree analysis showed the features of autosomal recessive inheritance such as early onset of severe bleeding and parents are not clinically affected. Laboratory test result such as prolonged bleeding and activated partial thromboplastin time, normal platelet count, non-O blood group, markedly reduced VWF: Ag (3%) and FVIII level (3%) favors the diagnosis of type 3 Von Willebrand disease.⁷⁴

Dr. Sohel Abdullah Imdad Khan (Dental surgeon): What is the management protocol of type 1 and type 3 Von Willebrand disease? Should we give any surgical stitch in the injury site of patients with Von

Dr. Kabir: Patient with Von Willebrand disease should be managed according to the protocol.⁶⁵ Before giving surgical stitch to the injury site in patients with Von Willebrand disease, we should control the bleeding adopting standard procedures.

Dr. Mohammad Abdul Aleem (Anesthesiologist): In the management of patient with Von Willebrand disease, you are recommending tranexamic acid but Von Willebrand disease is due to qualitative or quantitative deficiency of Von Willebrand factor. How does tranexamic acid work in Von Willebrand disease?

Dr. Aziz: In fact, tranexamic acid is one of the supportive measures to stop bleeding in patients with Von Willebrand disease. Tranexamic acid competitively inhibits activation of plasminogen (via binding to the kringle domain), thereby reducing conversion of plasminogen to plasmin (fibrinolysin), an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins, including the procoagulant factors V and VIII. Tranexamic acid also directly inhibits plasmin activity, but higher doses are required than are needed to reduce plasmin formation.⁷⁵

Dr. Md. Bazlur Rahman (Child Specialist): How does desmopressin/DDAVP act in Von Willebrand disease?

Dr. Rahman: Desmopressin raises the plasma concentration of Von Willebrand factor through cyclic AMP-mediated release of Von Willebrand factor from endothelial cell Weibel-Palade bodies.⁷⁶

Dr. Anisur Rahman Howlader: Is there any sex predilection for the incidence of Von Willebrand disease? As we know hemophilia A affects male only but can it affects female?

Dr. Ismail Chowhdury: As Von Willebrand disease is inherited as autosomal recessive inheritance, so both sexes are equally affected. Though hemophilia is a disease of male but it may affect female in conditions such as Turner syndrome (XO) associated with affected hemophilia gene, extreme lyonization (inactivation of the normal FVIII allele in one of the X chromosome), homozygosity for the hemophilia gene (i.e., father with hemophilia and mother who is a carrier, two independent mutations, or some combination of inheritance and new mutations).⁷⁷

Dr. Mohammad Mohsin: As it is an inherited genetic disease, what advices we should provide to reduce the incidence of Von Willebrand disease?

Dr. Rahman: Genetic disorders can be prevented by taking measures such as: Genetic counseling, genetic screening and testing (carrier screening, neonatal screening, prenatal diagnosis and selective abortion), premarital counseling, pre-implantation gene-

tic diagnosis, treatment of genetic disease and education.⁷⁸

Dr. Md. Asaduzzaman: You have told that bleeding time is prolonged but platelet count is normal. Is the platelet count always normal in Von Willebrand disease?

Dr. Abdullah-Al-Baki (Microbiologist): Platelet count is reduced only in type 2B Von Willebrand disease. In type 2B, thrombocytopenia occurs due to rapid clearance of large multimers-platelet Gp1b complex from the plasma.⁵⁹

Dr. Humayun Kabir: What is the relationship between Von Willebrand factor and ABO blood group system?

Dr. Rahman: Plasma level of factor VIII (FVIII) and Von Willebrand factor is dependent on ABO blood group. Blood group O individuals have significantly (approximately 25%) lower plasma levels of both FVIII and Von Willebrand factor. Von Willebrand factor level in plasma ranges from 0.4 to 1.5 U/dL in group O and in non-O it ranges from 0.5 to >2.0 U/dL.⁵² This association is of clinical significance. Low plasma levels of either FVIII or Von Willebrand factor have long been established as causes of excess bleeding.

Dr. Muhammad Ariful Islam Miah (Medical Specialist): Why Von Willebrand factor level is low in blood group "O" individuals?

Dr. Aleem: The underlying mechanism responsible for the low plasma level of FVIII and Von Willebrand factor in individuals with blood group O remains unknown. However, it has been assumed that the ABO effect is primarily mediated through a direct functional effect of the ABO locus on plasma Von Willebrand factor levels. Theoretically, ABO blood group may alter the rate of Von Willebrand factor synthesis or secretion within endothelial cells. Alternatively, ABO group may affect Von Willebrand factor plasma clearance rates.⁷⁸

Dr. Rahman: Why type 3 is more severe than type 1 disease?

Dr. Aziz: In type 3, the plasma level of FVIII and Von Willebrand factor are markedly reduced leading to the development of hemarthrosis and muscle hematoma. But in type 1 and type 2, the reduction of FVIII and Von Willebrand factor are not that much severe to cause hemarthrosis and muscle hematoma.⁶²

Final Diagnosis

Von Willebrand disease type 3

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