Five-year-old girl with tongue bleeding

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Case

A five-year old girl presented to our clinic with the complaint of unstoppable bleeding following biting of her tongue when bleeding continued despite suturing. The patient who had no known history of bleeding was born by cesarean section in the 28th gestational week as twin sister with a birth weight of 1 180 g and was followed up in the neonatal intensive care unit for three months after delivery. The patient had a head trauma one year before presentation, but no bleeding was observed on the site of suture. In the familial history, it was learned that the parents were first degree relatives. There was no familial

history of bleeding. Her aunt was lost after a diagnosis of aplastic anemia was made. Her physical examination findings were found to be normal, but oozing of blood at the site of the sutures on the tongue continued. The laboratory findings were as follows: prothrombin time (PT): 26.7 s, PT activity: %31.2, INR: 2.3, activated partial thromboplastin time (aPTZ): 79 s. Inhibitor effect was not observed in the mixing test and the results were considered in favour of factor deficiency. After a blood sample for factor levels was obtained, fresh frozen plasma (FFP) and tranexamic acid were given to the patient (by obtaining consent from the patient's mother and father.)

Diagnosis - Discussion

Combined Factor V and Factor VIII Deficiency

The other factor levels were found to be normal in the patient who had a Factor (F) V level of 4.5% (normal range: 70-150%) and a FVIII level of 18.5 % (normal range: 50%-150%). A diagnosis of combined Factor V and Factor VIII deficiency was made. In the follow-up, the patient had no complaint of bleeding. Outpatient follow-up and topical treatment with tranexamic acid primarily in case of bleeding were recommended.

Hemorrhage may be related with a regional cause or a disease which causes predisposition to hemorrhage (hemostatic disorder). Hemostasis disorders which are manifested with hemorrhage may arise from vascular causes, platelet count or function disorders, coagulation disorder or excessive or rapid resolving of coagulum (fibrinolysis).

In patients who are found to have prolonged prothrombin time and aPTT, hepatic disorders and vitamin K deficiency which are observed more commonly should be considered primarily in differential diagnosis. If vitamin K deficiency is considered in patients who are found to have normal hepatic function tests, PT and aPTT tests are repeated following intramuscular administration of vitamin K, since vitamin K level cannot be measured (1). If no improvement is found, deficiency of mutual pathway factors (fibrinogen, prothrombin, FV and FX) or inhibitor which develops against these factors should be considered. In patients in whom these tests are found to be normal, rarer factor deficiencies may be considered.

In combined Factor V and Factor VIII deficiency, PT and aPTT are found to be prolonged, but FV prolongs both PT and aPTT, while FVIII prolongs only aPTT. Therefore, prolongation of aPTT is not in parallel with PT. The diagnosis is made with measurement of factor levels. Factor levels vary by age, but not by gender. However, FV and FVIII levels in the neonatal period are similar to the levels in adulthood. Thus, the diagnosis can be made early (2). In a similar case report, a cephalhematoma with a size of 6-8 cm was found in a newborn girl following spontaneous vaginal delivery, PT and aPTT were found to be prolonged in the patient who had no familial history of bleeding and a diagnosis of combined FV and FVIII deficiency was made when the FV and FVIII levels were found to be low (FV: 26%, FVIII: 8.8%) (3).

Among congenital bleeding disorders, the most common coagulation disorders include von Willebrand factor deficiency, hemophilia A and hemophilia B. Rarer diseases include fibrinogen deficiency, prothrombin (FII) deficiency, FV deficiency, combined FV and FVIII deficiency, FVII deficiency, FX deficiency, FXI deficiency and FXIII deficiency. While hemophilia shows X-linked inheritance, rare bleeding disorders usually have autosomal recessive inheritance. When the data of the World Federation of Hemophilia are examined, it is observed that the most common rare bleeding disorders are FXI deficiency (37%) and FVII deficiency (23%) and the least common rare bleeding disorder is FII deficiency (2%). In a study conducted by Peyvandi et al. (4) with 489 patients who had rare bleeding disorders, combined FV and FVIII deficiency was observed in 20 patients and it was found that the frequency of bleeding increased as the factor levels decreased.

Combined Factor V and FVIII deficiency was described in 1954 for the first time. It is considerably rare in the general population (the prevalence is 1/ 1 000 000). Three percent of rare bleeding disorders are constituted by combined Factor V and FVIII deficiency. The Jews of the Middle East and Iranians are the ethnic groups in which the disease is observed most commonly (the prevalence is 1:100 000) (2). Combined Factor V and FVIII deficiency has an autosomal recessive inheritance and this condition is related with single gene disorder. Combined Factor V and FVIII deficiency occurs as a result of mutation in two different genes including lectin mannose binding protein 1 (LMAN1) (its other name is endoplasmic reticulum and golgi intermediate compartment protein (ERGIC) and multiple coagulation factor deficiency 2 (MCFD2). The factor levels in MCFD2 mutation are found to be lower compared to the levels found in LMAN1 mutation and MCFD2 is a soluble co-receptor of LMAN1 receptor (5). Although mutations have been demonstrated in these two genes in current studies, mutation could not be demonstrated in neither genes in one patient in a study conducted with 13 patients who had combined FV and FVIII deficiency in India. This study suggested that a third gene may have a role in combined FV and FVIII deficiency (6, 7). The ERGIC-53 gene which encodes the protein which controls intracellular entrance and exit of a group of proteins including Factor V and Factor VIII is found on the long arm of the 18th chromosome. Although normal amounts of FV and FVIII are synthesized in hepatocytes, exit of these factors from the cells and release into the circulation are disrupted as a result of ERGIC-53 dysfunction.

Generally, mild-moderate bleeding is found in these patients. Severe bleeding may be observed following surgery or trauma. Gastrointestinal or central nervous system hemorrhages have been reported in a very small number of patients. In a study conducted by the Obstetrics and Gynecology division with 86 women who were diagnosed with combined FV and FVIII deficiency, it was found that 42 patients (49%) had a complaint of menorrhagia (8). Monitoring is important in treatment and treatment in case of hemorrhage is preferred currently. Only FFP is used in replacement treatment for Factor V; there is no specific factor treatment. FFP and recombinant or plasma derived FVIII concentrates may be used for Factor VIII. Since severe hemorrhage is not expected in these patients, there is no need for prophylactic administration of FVIII or FFP. Similarly our patient had no finding of hemorrhage in previous cases of trauma and hospitalization.

There are also case reports in the literature which have reported severe hemorrhage in contrast to our case. In a case report reported by Lanchon et al. (5), preoperative preparation of a patient with combined FV and FVIII deficiency who would undergo tonsillectomy was described. Desmopressin, FFP, tranexamic acid and recombinant FVIII were given to the patient after hemorrhage and the patient was monitored closely in terms of hemostasis. Tests performed by anesthesia unit before surgical operations are important in the diagnosis of rare bleeding disorders, because one of the most common findings in this group of patients is postoperative hemorrhage (5, 9).

The risk of development of inhibitor as a complication of treatment should be kept in mind. Buckner et al. (10) found that inhibitor secondary to replacement treatment with FVIII developed in a patient who had combined FV and FVIII deficiency. In our patient, inhibitor was not found, because factor was not given yet. However, one should be careful in terms of development of inhibitor in patients with combined FV and FVIII deficiency who have received high dose factor replacement treatment.

In conclusion, combined FV and FVIII deficiency is a rare bleeding disorder, but it may be observed more commonly than expected in countries in which consanguineous marriages are prevalent. Since mild hemorrhages are observed clinically, most cases are overlooked. Therefore, combined FV and FVIII deficiency should be considered in differential diagnosis in patients with prolonged PT

and prolonged aPTT especially in our country in which consanguineous marriages are prevalent.

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