Case Report

Combined factor V and factor VIII deficiency: the report of two cases

Cengiz Demir[a], Murat Atmaca[b], Eyüp Taşdemir[c], Mustafa Yılmaz[b], İmdat Dilek[c]

[a]*Department of Division of Hematology Internal Medicine,Yuzuncu Yil University Faculty of Medicine*
[b] *Department of Internal Medicine, Yuzuncu Yil University Faculty of Medicine,*
[c] *Department of Internal Medicine, Division of Hematology Ankara Atatürk Research and Education Hospital*

Abstract. Combined FV and FVIII deficiency is a rarely seen hereditary coagulation disease. Here, we presented two cases diagnosed with combined FV and FVIII deficiency. Factor V levels were 12% and 3% and FVIII levels were 7% and 2%, respectively. For both cases, prothrombin time and activated partial thromboplastin time were prolonged. The first case presented with nasal bleeding while the second case was diagnosed with an abdominal hemorrhage. These cases make us remember that when a hereditary bleeding disorder is considered in the presence of simultaneous prolongation of PT and aPTT, the possibility of combined FV and FVIII deficiency should be considered, although it is seen very rarely.

Key words: Factor V deficiency, Factor VIII deficiency, bleeding

1. Introduction

Congenital coagulation disorders are mostly resulted from decreased or defective synthesis of one of the coagulation factors. Von Willebrand disease and hemophilia A and B are the most common diseases of hereditary bleeding diathesis, followed by FXI and FVII deficiencies. Deficiencies of other coagulation factors and combined coagulation factor deficiencies are much more rare which show autosomal recessive traits (1,2). The incidence of combined factor V and VIII deficiency is 1/1.000.000. Of 6 types of combined hereditary coagulation factor deficiencies, combined FV and FVIII deficiency is the most commonly seen type (1). Combined FV and FVIII deficiency was firstly defined by Oeri and colleagues in 1954 and, thereafter, new cases were reported (3). Although combined FV and FVIII deficiency is seen worldwide, it is more frequently seen in Mediterranean countries (4,5). There were some reports coming from Turkey as well (6). Here, we presented 2 cases diagnosed with rarely seen combined FV and FVIII deficiency, one of whom died.

*Correspondence: Cengiz Demir, MD
Department of Internal Medicine,
Division of Hematology, Faculty of Medicine,
Yuzuncu Yil University, Van, Turkey.
65300 Van/Turkey
E-Mail: drcengizdemir@hotmail.com
Received: 01.07.2010
Accepted: 02.09.2010

2. Case reports

Case 1: A 17-year-old male patient presented to Hematology out-patient clinic with a complaint of frequent nasal bleeding. He had been nasal bleeding since 3-4 years old, 4-5 times a week. He stated that bilateral nasal bleeding events could have been stopped by external pressure. The patient had no history of melenea, hematochesia, hemoptisis, petechia, ecchymosis and hemarthrosis. He was circumcised when he was 6 years old and stayed a week in hospital due to continuing bleeding. In his family, none of the 6 siblings showed a sign of bleeding disorder and his parents were not consanguineous.

Systemic examination revealed no abnormality. Whole blood count was also normal. PT and aPTT, which were measured twice, were found to be respectively 20-19 and 72-70 seconds (normal reference range of PT:12-14sec, aPTT:28-35sec). Bleeding time was normal. aPTT and PT levels measured after mixing patient plasma and normal plasma in a ratio of 1:1 were found to be normal. Therefore, FX level which is a common pathway factor prolonging both PT and aPTT was measured. FX level was 86%. Thereafter, fibrinogen, FII, FV and FVIII levels were

measured and the results were 237 mg/dl, 78%, 12% and 7% respectively. Accordingly, the patient was diagnosed with combined FV and FVIII deficiency.

Case 2: A 17-year-old male patient was presented to emergency room with the complaints of abdominal distension and joint pain. His oral mucosa and conjunctiva were pale, his blood pressure was 80/60 mmHg and he had tachycardia. He had sensitivity and rebound on abdominal examination. His both knees and left elbow showed slight flexion contracture. Laboratory investigations showed normal biochemical parameters. In the blood count, WBC was $11.6x10^9$/L, Hb was 7.4 g/dL, Hct was 22.8%, Plt was 238 $x10^9$/L, PT was 20.1 seconds and aPTT was 90.3 seconds D-dimer was negative. The abdominal ultrasound showed intra-abdominal disseminated fluid. His medical history revealed that he had experienced gingival bleeding and, occasionally, swelling in left elbow and in both knees. He had been using non-steroidal anti-inflammatory drugs very frequently due joint pains and swelling. He had been circumcised as a child and got a long bleeding then. His parents were not consanguineous.

The surgical consultation mandated an emergency surgical intervention for the patient. Before the operation, the plasma sample was obtained for the study of FX, FII, FV, FVIII, FIX and fibrinogen levels to explain simultaneous prolongation of PT and aPTT. As prolonged PT and aPTT levels was normalized by mixing patient plasma and normal plasma in a ratio of 1:1, factor deficiency was considered and 20 mL/kg fresh frozen plasma (FFP) infusion was initiated for the patient. Thereafter, FFP was continued at a dose of 10 mL/kg for 12 hours. Patient's PT and aPTT levels were normalized. The patient underwent operation after transfusion of 3 units of erythrocyte, the intra-abdominal hematoma was drained, no additional pathology was detected. The laboratory results were obtained after the operation; all were normal except factor VIII (2%) and factor V levels (3%). The patient was diagnosed with combined FV and FVIII deficiency. Therefore, the treatment with FFP and factor VIII concentrate were continued. He did not recover after the operation, his general status deteriorated progressively and died at the 5^{th} day in intensive care unit. There was no obvious sign of hemorrhage (intraabdominal, intracranial or intrathoracic). No post-mortem investigation was allowed by the family, hence cause of death remained unknown.

3. Discussion

Diseases accompanied by hereditary coagulation factor deficiencies are generally caused by the deficiency of one of the coagulation proteins. Combined coagulation factor deficiencies are very rarely seen and they are most commonly seen in the form of FV and FVIII combination. Two genes account for the combined FV and FVIII deficiency. LMAN1 gene is localized on the long arm of Chromosome 18 and MCFD2 gene is localized on the short arm of Chromosome 2. LMAN1 and MCFD2 protein complex is essential for the transportation of FV and FVIII from endoplasmic reticulum to Golgi apparatus. The deficiency of these two subunits leads to combined FV and FVIII deficiency (2,4,7-9). Molecular tests could not be done in present cases.

In homozygous cases with FV and FVIII deficiency, factor levels are reported to be 5-30%, 15% on average (2,4,8,10). The factor levels were below the reported mean levels in our cases (FV and FVIII levels were respectively 12% and 7% in the first case and 3% and 2% in the second case). The second case had lower factor levels and got a fatal course.

The patients with homozygous combined factor deficiency may show spontaneous or post-traumatic bleeding. In these cases, most common symptoms were menorrhagia, nasal bleeding, gingival bleeding and easy bruising (2,11). Approximately 20% of the post-traumatic cases may show bleeding. Hematuria, gastrointestinal system bleeding and intra-cranial hemorrhage are seen less commonly. Excessive bleeding may be observed after tooth extraction and after a surgical intervention. Majority of pregnant cases show post-partum bleeding (4). Our first case had mild nasal bleedings from the ages 3-4 and a severe bleeding after the circumcision. The second case, which had lower factor levels, had a history of gingival bleeding, joint bleeding and bleeding after the circumcision. He presented with intra-abdominal bleeding.

It is reported that the Jewish neonates with FV and FVIII deficiency generally do not experience bleeding during the circumcision performed when they are 8 days old (4). However, during the circumcisions performed at 5-7 years old, as it is the case in our cases, severe bleeding is observed. The two cases reported from Turkey were circumcised using desmopressin (6). It is reported that, though rare, heterozygous cases may show notable bleeding as well (4). Although there is no

adequate evidence to understand the role of haemostatic factor levels in combined factor deficiencies, it is reported that factor levels should be about 30% (4). For our second case who died following a severe bleeding, both factor levels were below 5%. Although no correlation was reported between factor levels and bleeding intensity, the mortality of the second case may suggest us that the condition is better to be monitored like a case of severe hemophilia A, if factor levels are below 5% in a combined deficiency.

For the cases who show menorrhageia, gingival bleeding and nasal bleeding due to combined factor FV and FVIII deficiency, anti-fibrinolytic therapy, such as tranexamic acid and epsilon amino caproic acid, may be efficient. In cases that show factor levels between 10 and 15%, FFP generally provides haemostasis. FFP must be used instead of factor replacement in the patients who have combined factor V-VIII deficiency because there was no factor V extract available yet. Because of factor V is a labile protein, FFP should be as fresh as possible. In the cases with severe bleeding, FFP and cryoprecipitate or FVIII concentrates should be used. Desmopressin may elevate the level of FVIII but not to a degree that is not enough for a major surgery. In surgical cases, it is recommended to continue the replacement for 7-10 days postoperatively. Post-surgical factor levels should be kept above 50% (4).

As a result, in the cases with a suspect of hereditary bleeding disorder who show simultaneous prolongation of PT and aPTT possibility of combined FV and FVIII deficiency should be considered. The cases with factor levels below 5% should be monitored closely, like the patients with severe hemophilia.

References

1. Mansouritorgabeh H, Rezaieyazdi Z, Pourfathollah AA, Rezai J, Esamaili H. Haemorrhagic symptoms in patients with combined factors V and VIII deficiency in north-eastern Iran. Haemophilia 2004; 10: 271-275.
2. Thompson AR. Congenital bleeding disorders from other coagulation protein deficiencies. In: Young NS, Gerson SL, High KA (eds). Clinical Hematology, Mosby Elsevier Philadelphia 2006, pp 855–866.
3. Oeri J, Matter M, Isenschmid H, Hauser F, Koller F. Congenital factor V deficiency (parahemophilia) with true hemophilia in two brothers. Bibl Paediatr 1954; 58: 575-588.
4. Seligsohn U, Zivelin A, Inbal A. Inherited deficiencies of coagulation factors II, V, VII, X, XI and XIII and combined deficiencies of factors V and factor VIII and of the vitamin K-dependent factors. In: Lichtman MA, Beutler E, Kıpps T, et al. (eds). Williams Hematology, Mc Graw-Hill Comp New York 2006, pp 1887–1907.
5. Mansouritorgabeh H, Rezaieyazdı Z, Rezai J. Reduced Bone density in individuals with combined factors V and VIII deficiency. Haemophilia 2007; 13: 340-343.
6. Devecioğlu O, Eryilmaz E, Celik D, et al. Circumcision in a combined factor V and factor VIII deficiency using desmopressin (DDAVP). Turk J Pediatr 2002; 44: 146-147.
7. Neerman-Arbez M, Johnson KM, Morris MA, et al. Molecular analysis of the ERGIC-53 gene in 35 families with combined factor V-factor VIII deficiency. Blood 1999; 93: 2253-2260.
8. Zhang B, McGee B, Yamaoka JS, et al. Combined deficiency of factor V and factor VIII is due to mutations in either LMAN1 or MCFD2. Blood 2006; 107: 1903-1907.
9. Mohanty D, Ghosh K, Shetty S, et al. Mutations in the MCFD2 gene and a novel mutation in the LMAN1 gene in Indian families with combined deficiency of factor V and VIII. Am J Hematol 2005; 79: 262-266.
10. Seligsohn U, Zivelin A, Zwang E. Combined factor V and factor VIII deficiency among non-Ashkenazi Jews. N Engl J Med 1982; 307: 1191-1195.
11. Peyvandi F, Tuddenham EG, Akhtari AM, Lak M, Mannucci PM. Bleeding symptoms in 27 Iranian patients with the combined deficiency of factor V and factor VIII. Br J Haematol 1998; 100: 773-776.