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Journal of Hematology and Allied Sciences

Case Report

Combined factor VIII and IX deficiency: An exceptional case

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Received: 10 September 2023
Accepted: 18 December 2023
Published: 07 February 2024

DOI
10.25259/JHAS_35_2023

Quick Response Code:

ABSTRACT

Familial multiple coagulation factor deficiencies are a group of rare inherited disorders that are characterized by the simultaneous decrease in the levels of two or more coagulation factors. Common synchronous deficiencies are factors VIII and IX and combined deficiency of Vitamin K-dependent coagulation factors (factors II, VII, IX, and X). Here, we report a case of synchronous dual deficiency of factor VIII and IX, which is an extremely rare occurrence and no case report has been mentioned so far to the best of our knowledge. Recognizing such a dual deficiency is very important for proper management of patients.

Keywords: Factor VIII, Factor IX, Hemophilia, Combined, Coagulation

INTRODUCTION

Combined deficiencies of coagulation factors have been identified in the past, with the most common combination being factor V and VIII, which is an autosomal recessive congenital bleeding disorder. Other possibilities are Vitamin K-dependent familial multiple coagulation factor deficiencies. Recent progress has led to a better understanding of the molecular mechanisms underlining the combined deficiency of Vitamin K-dependent clotting factors (VKCFD) and combined deficiency of factor (F)V and FVIII (F5F8D).

CASE REPORT

A 16-year-old male presented with a painful, swollen left knee joint for seven days. He also gave the history of such painful swollen joints on and off after trivial trauma for two years. On examination, the left knee joint was swollen and tender, and the overlying skin was reddish brown. X-ray of the left knee joint showed soft-tissue swelling, and ultrasound of the left knee joint also revealed fluid collection there.

His hemoglobin was 11 g/dL, total white blood cell count was 8900/cu mm, and platelet count was 1.8 lacs/cumm. Liver and kidney function tests were within normal limits. Prothrombin time was 13.4 s (normal range 12–15 s) while his activated partial thromboplastin time (aPTT) was raised, and it was 87 s (normal range 25–35 s). The platelet aggregation test was normal. Factors VIII and IX assays were performed, and both were <1%. Mixing studies were performed, and aPTT was corrected, which suggested factor VIII or IX deficiency and ruled out the presence of any inhibitors. Factor assays confirmed the deficiency of both these coagulation factors. Hence, he was diagnosed with dual deficiency of factors VIII and IX, which is quite rare to happen,

making this case worth reporting. However, a detailed family history did not reveal any history of bleeding episodes, which was quite unusual. There was no consanguinity noted as well. A platelet aggregation test was performed to rule out any platelet function disorder. Platelet agonists added were ristocetin, adrenaline, adenosine diphosphate, and collagen and platelet function studies were normal. Due to a lack of genetic testing at our center, it was not done.

He was therapeutically given an infusion of both factors VIII and IX, after which his levels came within normal limits. He was also treated with fresh frozen plasma. Physiotherapy exercises were started. On follow–up, the patient is doing fine and his symptoms have improved.

DISCUSSION

A series of uncommon inherited illnesses known as familial multiple coagulation factor deficits are characterized by the concurrent decline in the levels of two or more coagulation factors.[1] The likelihood of this condition developing is higher in areas with a high proportion of consanguineous marriages or in gated communities. The majority of instances are concentrated in the Mediterranean region, particularly in Israel, Iran, and Italy.[1,2] Recent developments regarding these entities have improved our understanding of the molecular mechanisms underlying F5F8D and VKCFD.[1,2]

Vitamin K and c-carboxylation c-glutamyl carboxylase catalyze the post-translational modification of glutamate residues into c-carboxyglutamate residues, which activate FII, FVII, FIX, and FX, as well as the anticoagulant factors protein C, protein S, and protein Z. This process is intricate and complex.[3,4]

All Vitamin K-dependent clotting factors are deficient in VKCFD, an autosomal recessive condition. In 1966, a baby girl who had bled for in the first week of birth was reported to have had the first instance of VKCFD.[5] Her FII, FVII, FIX, and FX levels were low to undetectable, and there was no sign of liver injury or malabsorption. The clotting factors (FII, FVII, FIX, and FX) were partially restored by high doses of Vitamin K.

The clinical signs and symptoms of VKCFD change with the amount of procoagulant proteins. In the majority of cases, but not always, high doses of Vitamin K can somewhat alleviate symptoms.[4,5] In the first few weeks of life, bleeding can involve cerebral hemorrhage, which can occasionally result in a deadly outcome and death. Hemarthrosis and mucocutaneous bleedings may be observed due to antibiotic therapy, leading to decreased Vitamin K production by gut bacteria. Skeletal defects have been reported in some patients, presumably resulting from under-carboxylation of bone Gla-proteins. Diagnosis of familial VKCFD requires differentiation from acquired forms of the disorder that can be caused by accidental ingestion of warfarin products, intestinal malabsorption of Vitamin K, and liver dysfunctions.[3,5]

Another combined FV and FVIII deficiency, known as F5F8D, is discovered. These two big plasma glycoproteins serve as crucial cofactors for the proteolytic activation of prothrombin and FX, respectively. FV, a 330-kDa single-chain polypeptide present in plasma and platelet granules, is largely generated in hepatocytes and megakaryocytes.[5] On the other hand, identifying the primary tissue source for the production of FVIII has long been a source of uncertainty, even though earlier findings had indicated that a large source of circulating FVIII came from liver sinusoidal endothelial cells. Low quantities of FVIII are generated, and upon secretion, it undergoes processing to form a heterodimer with an 80-kDa light chain linked to a 200-kDa heavy chain fragment.[1,3]

Classic hemophilia A is caused by a genetic FVIII deficiency, whereas a rare autosomal recessive disorder called para-hemophilia is caused by an inherited FV deficiency.[5] Ghosh *et al.* first identified a combined lack of FV and FVIII as an autosomal recessive illness in 1954.[4] Plasma FV and FVIII antigen and activity levels in patients with this illness are between 5% and 30% of normal. The signs of bleeding are comparable to those seen in patients with isolated FV or FVIII deficiency.[1,4] Epistaxis, menorrhagia, and profuse bleeding during or following trauma, surgery, or childbirth are the most frequently reported. Unlike the coinheritance of both FV deficiency and FVIII deficiency, the inheritance of F5F8D is autosomal recessive.

To our knowledge, 81 families and at least 140 patients have received a diagnosis of F5F8D, with more than half hailing from the Mediterranean region. F5F8D is probably underdiagnosed, in part because its bleeding symptoms are so frequently mild.[4,5]

It is possible that some F5F8D patients receive incorrect diagnoses of mild hemophilia or para-hemophilia. According to estimates of 1:100,000, this disorder appears to be particularly common among Middle Eastern Jews and non-Jewish Iranians.[5] This high frequency is likely caused, at least in part, by these populations' high consanguineous marriage rates. Estimates place the prevalence of persons with hemophilia in developing nations like India between 10% and 80%[5]

Hemophilia cases, however, continue to be underdiagnosed, and many cases go unreported. One would anticipate India to have close to 100,000 hemophilia cases given that the incidence of hemophilia A is one in 5,000 and hemophilia B is one in 30,000, as in the US. However, only 13,448 patients are registered, according to the most recent survey conducted by the World Federation of Hemophilia and data supplied by the Hemophilia Federation of India.[1,3]

CONCLUSION

Because simultaneous factor VIII and IX deficiency is extremely rare and, to the best of our knowledge, has not yet been reported, and this makes our case all the more worth reporting.

This combined deficiency can be accurately and quickly diagnosed, which can result in prompt treatment and a reduction in morbidity and mortality.

Ethical approval

The authors declare that they have taken the Institutional Ethics Committee approval and the approval number is IEC/IGIMS/34-23.

Declaration of patient consent

Patient's consent is not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Jamal I, Jeelani KA. Combined factor VIII and IX deficiency: An exceptional case. J Hematol Allied Sci. 2023;3:161-3. doi: 10.25259/JHAS_35_2023.