Case Report

Attenuation of phenotypical expression of severe hemophilia A in presence of simultaneous prothrombotic Factor V mutation: The debate continues

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Abstract

The effect of coexistence of the prothrombotic Factor V Leiden mutation on the phenotypical expression in hemophilia is still debatable. Six-year-old boy with severe hemophilia A had presented with large soft tissue hematoma, treated with Factor VIII concentrate. Simultaneous Factor V Leiden mutation had resulted in attenuation of clinical features.

Keywords: Factor V Leiden mutation, hemophilia A, phenotypical expression

Introduction

The definitive effect of the prothrombotic Factor V Leiden mutation on the phenotypical expression in hemophiliacs is still not clear. A magnitude of current literature suggest that the prothrombotic mutation may compensate for the low Factor VIII levels resulting in increased thrombin generation and attenuation of clinical symptoms. However, some investigators differ in this regard. We report a 6-year old boy with severe hemophilia A presenting with soft tissue hematoma resulting from blunt trauma. He was treated by Factor VIII replacement therapy. Although severely depleted with Factor VIII clotting activity (<1%), he did not have any features of severe hemophilia such as spontaneous bleeding or hemarthrosis. His need for Factor VIII replacement therapy was minimal and infrequent only in the presence of active bleeding like in the current admission. A simultaneous prothrobotic mutation (heterozygous for Factor V Leiden) was responsible for transformation in the clinical expression of this severe hemophilia of child to a milder variant.

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Case Summary

A 6-year-old boy had presented with a large bluish swelling over left lower abdomen [Figure 1] since 2 days following mild blunt trauma from the edge of bed while playing at home. He also had a small bruise on his forehead and another over left elbow for 5 days. There was no history of abdominal pain, vomiting, and passage of blood in stools or urine. He was admitted at 1-year age with oral bleed from frenal tear and was diagnosed with hemophilia A. The Factor VIII activity at the time of initial diagnosis was less than 1% and he was diagnosed to be suffering from severe hemophilia A. However, he never had any severe bleed or hemarthrosis, but at the age of 2 year 10 month, he needed hospitalization for epistaxis (following a blunt trauma of his nose) and was given Factor VIII concentrate infusion. A thrombophilic screen performed during the course of his illness had suggested that he was a heterozygous for the prothrombotic Factor V Leiden mutation. Thereafter, he had minor bruises on limbs or forehead that resolved with rest, ice compressions and elevation of local parts. However, desmopressin nasal spray was not very effective during bleeding episodes. At 5 years, he was admitted with weakness in both lower

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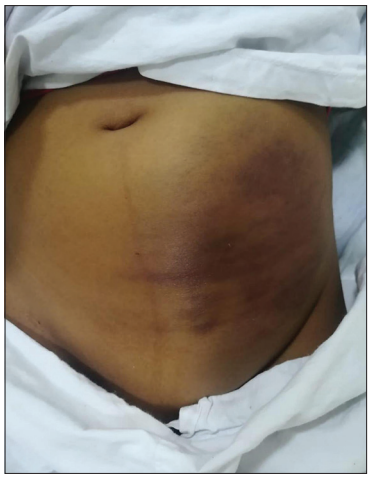

Figure 1: Abdominal wall hematoma

limbs after a viral respiratory tract infection and diagnosed as Guillain-Barre syndrome with S1 radiculopathy and given IVIG infusion followed by full recovery. His family members had no history suggestive of any bleeding disorder though his father and elder brother had beta-thalassemia trait but the mother of the patient had not been tested. He was allergic to amoxycillin and his immunization was up to date. There were history of muscle hematomas following intramuscular vaccinations before 1 year of age which resolved spontaneously but after the diagnosis of hemophilia, intramuscular injections were avoided. On admission, the child was not looking very ill and was afebrile but had moderate pallor. He had small ecchymoses on forehead and left elbow with no pain and a large tense soft tissue hematoma over left lower abdomen below umbilicus extending from midline to left flank and extending to left groin. Mild swelling of left side of scrotum without tenderness was noted. Systemic examination was otherwise unremarkable. Investigations revealed hemoglobin level of 6.5 g/dl and moderate elevation of activated partial thromboplastin time, normal prothrombin time and International normalized ratio (INR), normal LFT, and negative septic screen [Relevant data given in Table 1]. Ultrasound examination of abdomen showed no organomegaly or free fluid in peritoneal cavity but a soft tissue hematoma over left lower abdomen superficial to rectus sheath and small fluid collection in left scrotum, and both testis normal in size and vascularity. HPLC, serum iron, and TIBC before blood transfusion were normal. Considering his previous history and baseline Factor VIII level of 1%, he was given intravenous infusion of Factor VIII 40 iu/kg {HUMULIN M - basalta (Baxter inc)} on 3 successive days and 2 units of packed red cells transfusion along with analgesia with paracetamol and was kept in PICU for observation. The abdominal hematoma had gradually resolved and he was discharged with routine advice for Factor VIII replacement sos.

Discussion

Among the prothrombotic mutations, Factor V Leiden mutation causes a reduced ability of activated protein C to inactivate activated Factor V. This is believed to confer an evolutionary selective advantage at least in Caucasian populations where the prevalence of this mutation is particularly frequent.[1] In a review, Franchini and Lippi had summarized the current literature on the clinical effects of the gene-interaction between Factor V Leiden and hemophilia mutations.[2] Some investigators observed that the co-inheritance of Factor V Leiden can influence by ameliorating the clinical phenotype of hemophilia patients.[3,4] However, some other investigators had failed to observe a decreased bleeding frequency in severe hemophiliacs carrying the Factor V Leiden.[5,6] Some reports did suggest that heterozygosity of Factor V Leiden mutations was independently associated with lower factor concentrate utilization, while some others did not find any significant difference in annual factor concentrate consumption. To summarize, activation of protein C inhibits the thrombin production. Hence, the presence of coexisting Factor V Leiden mutation that prevents APC results in a prothrombotic state and minimizes bleeding in hemophilia.[7]

Table 1: Bleeding and thrombophilic parameters

Test	Results	Reference Range	Interpretation
PT and PT control	12.8 s 13.2 s	11.4–13.7 s	Normal
APTT and APTT control	64.1 s 30.2 s	27–40 s	High
Factor VIII activity	1%	60–150%	Low
Factor V Leiden mutation	Heterozygous mutation		Mutation present
Prothrombin gene mutation	Not detected		No mutation
MTHFR gene mutation	Not detected		No mutation

PT: Prothrombin time, APTT: Activated partial thromboplastin time, MTHFR: Methylenetetrahydrofolate reductase

In this case, we have reported a child with severe hemophilia A, which is one of the commonest bleeding disorders often encountered in our primary practice. Hence, it is imperative for clinicians to be aware of the coexisting factors associated with augmentation and attenuation of the clinical expression of this commonly inherited condition. This will be helpful in guidance of treatment protocol and future research in this field.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Lindqvist PG, Dahlbäck B. Carriership of Factor V Leiden and evolutionary selection advantage. Curr Med Chem 2008;15:1541-4.
2. Franchini M, Lippi G. Factor V Leiden and hemophilia. Thromb Res 2010;125:119-23.
3. Franchini M. Thrombotic complications in patient with hereditary bleeding disorders. Thromb Haemost 2004;92:298-304.
4. Van den Berg HM, De Groot PH, Fischer K. Phenotypic heterogeneity in severe hemophilia. J Thromb Haemost 2007;5:151-6.
5. Arbini AA, Mannucci PM, Bauer KA. Low prevalence of the factor V Leiden mutation among "severe" hemophiliacs with a "milder" bleeding diathesis. Thromb Haemost 1995;74:1255-8.
6. Arruda VR, Annichino-Bizzacchi JM, Antunes SV, Costa FF. Association of severe hemophilia A and factor V Leiden: Report of three cases. Haemophilia 1996;2:51-3.
7. Polderdijk SG, Adams TE, Ivanciu L, Camire RM, Baglin TP, Huntington JA. Design and characterization of an APC-specific serpin for the treatment of hemophilia. Blood 2017;129:105-13.