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The first case report of a patient with coexisting hemophilia B and Down syndrome

TO THE EDITOR: Hemophilia B, also known as Christmas disease, is an X-linked disorder caused by either the absence or reduced biosynthesis of clotting factor IX. This disorder affects approximately 1 in 30,000 male individuals worldwide [1]. It is five times less common than hemophilia A. On the other hand, Down syndrome (DS), the most common human chromosomal anomaly, results from trisomy of chromosome 21 and leads to mental retardation. Besides, it represents many consistent phenotypes including characteristic facies, intellectual disability, congenital heart diseases, and gastrointestinal abnormalities. In particular, hematological abnormalities include transient abnormal myelopoiesis, acute megakaryoblastic leukemia, and transient thrombocytopenia/polycythemia/neutrophilia [2]. We present a case with a rare phenotype, i.e., the coexistence of hemophilia B and DS: one X-linked disorder and the other a chromosomal disorder. Here, we also describe the management of this rare coexistence.

A 2-year-old male child born of a non-consanguineous marriage with a mixed ethnic background (father is a Punjabi and mother is from Orissa), visited to the pediatric emergency department with a history of spontaneous gum bleeding over the previous 4 days which was not resolved by general remedies. In addition, the patient suffered from episodic ecchymotic patches over the anterior abdominal wall in the previous month. There was no history suggestive of any bleeding disorders in close relatives (maternal/paternal sides). He was the second born child with an asymptomatic elder sister. On physical examination, the child had delayed developmental milestones, mongoloid slant, flat occiput, depressed nasal bridge, short hands, and simian crease, all suggestive of the DS phenotype. However, no abnormality was found in review of systems.

Karyotype analysis confirmed DS (47, XY, +21). Imaging studies confirmed the absence of any renal or cardiac malformations. Thyroid profile showed normal T3, T4, and thyroid stimulating hormone levels of 1.72, 10.57, and 3.5 units, respectively. Complete blood cell count (CBC) revealed hemoglobin level of 13.0 g/dL, white blood cell (WBC) count of 5.6×10^9/L, and platelet count of 292×10^9/L. Coagulation test showed normal prothrombin time (PT), 14 sec (reference range, 12–16 sec); prolonged activated partial thromboplastin time (aPTT), 85 sec (reference range, 26–32 sec); and normal fibrinogen level, 1.75 g/L (reference range, 2–4 g/L). Mixing study using normal pooled plasma and patient's plasma was suggestive of factor IX deficiency. Factor IX quantitative assay revealed a concentration of <1%, indicative of severe deficiency (Hemophilia B). Sequence analysis of peripheral blood for the *F9* gene (exon 7) revealed c.760G>A (p.Gly254Ser). This mutation has been predicted as pathogenic variant by in silico program, Polyphen-2 (http://genetics.bwh.harvard.edu/pph2), and multiple sequence alignment has shown the glycine to be conserved across multiple species. The mother and sister of the patient were also found to be the carriers of the same mutation. The child, given two units of fresh frozen plasma along with vitamin K supplements, became stable and was discharged after a hospital stay of 7 days. Currently, he grows up 5 years old with regularly attending speech as well as physiotherapy clinics, and shows normal growth parameters except for small head, occasional skin bleedings, and joint bleedings. His parents have been counseled regarding the carrier state of his sister and further prenatal diagnosis.

The hematological abnormalities in DS have been studied in order to understand their pathophysiology. The spectrum of these abnormalities includes benign conditions (neutrophilia, thrombocytopenia, and polycythemia) which usually resolve by 3 weeks of age, as well as malignancies like acute megakaryoblastic leukemia [3]. The likely explanation for all these manifestations may be secondary to the extra copy of chromosome 21 or because of mutations involving the *GATA1* gene [2]. The exact mechanism of how trisomy

21 leads to alter hematopoiesis is still not clear.

Hemophilia B results from variants in the *F9* gene, located on Xq27 chromosome. Currently, there are >1,000 pathogenic mutations in the *F9* gene, the most common being point mutations [4]. The patients suffer from coagulopathies such as prolonged bleeding, easy bruising, and mucosal bleeding. They are classified as severe (<1 IU/dL), moderate (1–5 IU/dL), or mild (5–40 IU/dL) hemophilia B patients based on residual factor IX activity. The patients should be managed with factor IX concentrates during bleeding episodes. The mutation found in this case was firstly reported by Mukherjee *et al.* in 2004 [5]. It is partially generic and affects the catalytic domain of *F9* resulting in its severe deficiency.

To the best of our knowledge, this is the first report of the coexistence of DS with hemophilia B. On the other hand, there are only two reported cases of DS with hemophilia A [6, 7]. Though some authors argued that transient bone marrow dysfunction in DS causes the imbalance of releasing hematopoietic elements, this hypothesis cannot be applied to this case [8]. The underlying mechanism of *F9* mutation occurring in the DS patient or vice versa, or the two conditions were coincidental, is still unclear.

In conclusion, we report here the first case of DS with hemophilia B managed with appropriate therapy. These patients should be followed up closely for preventing the disabilities as well as early detection of other complications in DS.

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