Report of a rare co-incidence of congenital factor V deficiency and thalassemia intermedia in a family

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Factor V (FV) is a critical component of the coagulation cascade. A single-chain glycoprotein procofactor activated by thrombin cleavage to FVa, it acts as a cofactor for activated factor X (FXa). FXa, FVa, and calcium ions on a phospholipid surface form the prothrombinase complex, which activates prothrombin to thrombin. FVa also serves as a target for the anticoagulant-activated protein C, which cleaves FVa to inactive FVi. The liver is the major site for synthesis of plasma FV (representing about 80% of synthesis), whereas platelet FV is thought to be synthesized in situ by megakaryocytes (the remaining 20%, which is stored in alpha granules).[1] Congenital deficiency of FV is a rare disorder with an estimated incidence of 1 in one million.[2] The disorder is transmitted in an autosomal recessive way, but in some families it is autosomal dominant. Heterozygous patients generally have no symptoms. Homozygotes present with spontaneous or postoperative bleeding. About one-half of patients are diagnosed in adulthood. The severity of bleeding symptoms is only partially related to the degree of FV deficiency in plasma.[3]

-thalassemia is an inherited hemoglobin disorder caused by a defect in the synthesis of the -globin chain resulting in hemolytic anemia. Depending on clinical severity, three forms of thalassemia are known: thalassemia major (TM), thalassemia intermedia (TI) and thalassemia minor. In countries where consanguineous marriages are frequent, such as Muslim countries and southern India, recessively inherited coagulation deficiencies are more prevalent and can occur approximately 10 times more frequently than in Western countries. In most of these countries where thalassemia is also prevalent, we expect to have a higher co-incidence of thalassemia and FVD. To our knowledge, only one case of TI and congenital FVD has been reported.[4] We report a second case.

Case

Our patient was a 20-year-old woman diagnosed with -thalassemia intermedia (Hb pattern: AFA2, genotype CD 29/CD 29]. She had been transfusion-dependent since the age of one year (2 units of packed red blood cells every three months). At the age of 12 years, she underwent allogeneic bone marrow transplantation in Italy. During her work up before transplantation, she was found to have FVD with a plasma FV antigen level of 21%. FVD was confirmed by reverse transcription-polymerase chain reaction. She had no bleeding history except for an episode of severe menorrhagia at the age of 16 years. Her 17-year-old brother was also known to have TI and required blood transfusion every three months. He was also heterozygous for FVD with a plasma FV antigen level of 18%. At the age of 11 years, he underwent open-heart surgery for an atrial septal defect repair. His surgery was complicated with a non-hemorrhagic pericardial effusion during the second week. No bleeding history was documented. The 43-year-old mother also discovered to be homozygous for FVD with a plasma FV level of 6%, had no history of bleeding.

Discussion

FVD or parahemophilia is a very rare coagulation disorder. There are only 150 cases reported in the literature.[5] The detection of FVD is usually incidental since in most cases only homozygotes tend to be symptomatic. In homozygotes, the levels of plasma FV are usually below 10%, and they present with mild, moderate or severe bleeding. Even in severe presentation, bleeding is manageable and rarely fatal. Heterozygotes have FV levels above 20% and uncommonly present with bleeding manifestastions. The majority of cases are phenotypically characterized by a concomitant deficiency of FV activity and antigen (type I deficiency), but approximately one-quarter have normal antigen levels, indicating the presence of a dysfunctional protein (type II deficiency).[6] The FV gene is located on chromosome 1. It is characterized by a large size (80 kb) and complexity.[7] A total of 26 distinct mutations have been identified.

M. Lak et al. analyzed the clinical manifestations of 35 Iranian patients with congenital FVD.[3] The most prevalent

bleeding symptoms in these patients were epistaxis and oral cavity bleeding (57% for each), menorrhagia (50%), post-operative and post-partum bleeding (43%), muscle hematoma (29%), hemarthrosis (26%), hematuria, and gastrointestinal and central nervous system bleeding (6% each). In most patients, bleeding symptoms first develop during the first 6 years of life, but only one case has been reported with bleeding from the umbilical stump.

Our patients did not exhibit bleeding symptoms. Although the episode of menorrhagia may have been a manifestation of FVD, this could be merely a part of pubertal development and not related to FVD. The second patient developed a non-hemorrhagic pericardial effusion 2 weeks post open-heart surgery and no bleeding complications were observed. Although most patients with FVD are asymptomatic or suffer from mild to moderate bleeding disorders, a report was found of a family with FVD in whom the propositus presented with recurrent thrombosis.[8]

-thalassemia, especially TI, is a common hereditary disorder in Mediterranean countries. Approximately one third of thalassemia patients in Lebanon have TI.[9] Our patients expressed typical symptoms of this disorder. In countries where consanguineous marriages are frequent, such as the Muslim countries and southern India, recessively inherited coagulation deficiencies are more prevalent and can occur approximately 10 times more frequently than in Western countries. In most of these countries where thalassemia is also prevalent, we would expect a higher coincidence of thalassemia and FVD. After an extensive review of the literature only one case report of concomitant TI and congenital FVD was found.[4] The association between these two deficiencies is most likely incidental. However, most if not all heterozygote patients with FVD are asymptomatic. The association between these two disorders may be more prevalent in countries where intermarriages are common, but the association may be missed.

FV is the only inherited bleeding disorder for which no concentrate is available for treatment. Since the most frequent bleeding in FVD is epistaxis and oral cavity bleeding, local measures are usually sufficient and replacement therapy is rarely necessary. In patients suffering from spontaneous hemorrhages in soft tissues or post-operative bleeding, fresh frozen plasma is the mainstay of treatment.

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