Familial thrombocytopenia associated with ovarian agenesis, umbilical hernia, bicuspid aortic valve, patent ductus arteriosus and epilepsia

Ovaryen agenez, umblikal herni, biküspis aortik kapak, patent duktus arteriyozus ve epilepsi ile birliktelik gösteren ailesel trombositopeni

Ayşe Nur Torun, Alptekin Gürsoy, Neslihan Başçıl Tütüncü, Nilgün Güvener Demirağ
Department of Endocrinology and Metabolism, Başkent University Faculty of Medicine, Ankara, Turkey

To the Editor,

Familial thrombocytopenias constitute an uncommon and heterogeneous group of disorders in the context of inheritance pattern and phenotypic diversity [1]. Although acquired thrombocytopenias are common, familial thrombocytopenias represent a very small percentage of the thrombocytopenias. Family history, platelet size on smear, lack of platelet response to autoimmune thrombocytopenia therapies, and the presence of certain "associated features" that are identified along with the thrombocytopenia are the major triage points in the diagnosis of familial thrombocytopenias [1]. Velocardiofacial syndrome, MYH9 gene-related disorders and Jacobsen syndrome (JBS) are well-known inherited syndromes of thrombocytopenias, in which platelets are increased in size and affected probands have unique phenotypic expressions such as cardiovascular, renal, skeletal and gonadal anomalies [2].

We describe herein a Turkish ancestry 18-year-old female familial thrombocytopenia patient who presented with additional disease features of umbilical hernia, bicuspid aortic valve, patent ductus arteriosus (PDA), ovarian agenesis and epilepsia. Her parents were nonconsanguineous and family pedigree included one familial thrombocytopenia affected sister who did not show any associated disease features. The patient's parents and youngest brother were clinically normal with normal platelet count.

The proband was born with umbilical hernia. At two years of age, she was operated for correction of PDA and umbilical hernia and she also had bicuspid aortic valve. At 10 years of age, the proband was admitted to the hospital for evaluation of hemoptysis. After serial diagnostic evaluations including aggregation tests and bone marrow biopsy, the proband and her sister were diagnosed as familial thrombocytopenia. The laboratory evaluation revealed hemoglobin 11.6 g/dl and hematocrit 33.5%, white blood cell count 4.5 cells/mm^3, and platelet count 31.3 x 10^3/ml. Low platelet count was confirmed in subsequent measurements and large platelets were observed on blood smear. At 14 years of age, a gynecology consultation was sought when physical examination showed retarded secondary sexual characteristics and amenorrhea. The examination revealed apparent eunuchoid status, breast development delay, and scant axillary and pubic hair. On imaging studies, both ovaries were absent and the uterus was small. Her karyotype analysis was 46,XX. Hormonal assessment supported the diagnosis of hypergonadotropic hypogonadism with serum estradiol 20 pg/ml (normal range: 10-50 pg/ml), luteinizing hormone 35.18 mIU/ml (normal range: 1.7-8.6 mIU/ml), and follicle-stimulating hormone 138.1 mIU/ml (normal range: 0.7-11.4 mIU/ml). The patient was diagnosed with hypergonadotropic hypogonadism, and was treated with oral estrogen. After three months, she began to menstruate regularly, and secondary sexual characteristics had developed at her first-year follow-up visit. Soon after, she experienced two tonic-clonic seizures that necessitated an anticonvulsant therapy.

Address for Correspondence: Dr. Ayşe Nur Torun, Department of Endocrinology and Metabolism, Başkent University Faculty of Medicine, Ankara, Turkey
Phone: +90 312 212 29 12 E-mail: aysenurizol@yahoo.com

Familial thrombocytopenia represents a very small portion of the cases of thrombocytopenia seen in clinical practice. The patient in this report had thrombocytopenia with increased platelet size, which was a phenotype shared with her younger sister. Inheritance pattern of thrombocytopenias with increased platelet size may be autosomal dominant, recessive or X-linked [2]. Velocardiofacial syndrome is a well-known inherited thrombocytopenia in which the inheritance pattern is autosomal recessive and the anomalies other than platelets include cleft palate, cardiac anomalies and learning disabilities [3]. Our patient also seemed to have an autosomal recessive disorder, but she shared only the cardiac anomaly with velocardiofacial syndrome. Another form of large platelet thrombocytopenia in which affected siblings show mental retardation and cardiac and facial anomalies is JBS, and the inheritance pattern is autosomal dominant [4]. JBS is unlikely in our patient because of its inheritance pattern and phenotype. MYH9 gene-related disorders are a group of autosomal dominant thrombocytopenias with large platelets in the newborn, and the affected siblings develop hearing loss, cataracts and glomerulonephritis [5]. The inheritance trait of MYH9 gene-related disorders and their phenotypic appearance are different from our patient. To our knowledge, our patient seems to represent the first co-occurrence of familial thrombocytopenia, umbilical hernia, bicuspid aortic valve, PDA, ovarian agnesis and epilepsia.

We conclude that our patient may represent a new variant of familial thrombocytopenia syndrome,or that this combination is a novel disorder. The most likely mode of inheritance for familial thrombocytopenia in this family is autosomal recessive, because the syndrome was manifested in multiple sibs from clinically normal nonconsanguineous parents. The core phenotype defining this condition is probably limited to thrombocytopenia. The phenotypic heterogeneity of the disease in both sisters reflects the possibility of the underlying genetic heterogeneity of this disorder.

References

1. Balduini CL, Iolascon A, Savoia A. Inherited thrombocytopenias: from genes to therapy. Haematologica 2002;87:860-80.
2. Geddis AE, Kaushansky K. Inherited thrombocytopenias: toward a molecular understanding of disorders of platelet production. Curr Opin Pediatr 2004;16:15-22.
3. Shprintzen RJ, Goldberg RB, Young D, Wolford L. The velo-cardio-facial syndrome: a clinical and genetic analysis. Pediatrics 1981;67:167-72.
4. Obregon MG, Mingarelli R, Digilio MC, Zelante L, Giannotti A, Sabatino G, Dallapiccola B. Deletion 11q23-->qter (Jacobsen syndrome). Report of three new patients. Ann Genet 1992;35:208-12.
5. Lalwani AK, Goldstein JA, Kelley MJ, Luxford W, Castelein CM, Mhatre AN. Human nonsyndromic hereditary deafness DFNA17 is due to a mutation in nonmuscle myosin MYH9. Am J Hum Genet 2000;67:1121-8.