Wilson Disease Manifested Primarily as Amenorrhea and Accompanying Thrombocytopenia

TÜLAY ERKAN, M.D., ÇIGDEM AKTUGLU, M.D., E. MAHIR GÜLCAN, M.D., TUFAN KUTLU, M.D., FÜGEN ÇULLU, M.D., HILMI APAK, M.D., AND GÜNGÖR. T. TÜMAY, M.D.

Wilson disease (WD), referred to as hepatolenticular degeneration and occurring primarily as neurological and liver disease, is an inherited disorder that has various clinical presentations [1–3]. The altered gene is localized on the long arm of chromosome 13. Mutations in the Wilson gene are common and include small insertions or deletions. In the cases of unidentified tubular dysfunctions, hemolytic anemias, and urolithiasis, this disease should be kept in mind as the possible etiology. Amenorrhea has been reported in untreated women with WD [1,2,4–8]. Although thrombocytopenia, as a result of hypersplenism and/or as a side effect of D-penicillamin therapy, has been well-documented, the association of idiopathic thrombocytopenia and WD has been published in only one case previously [9].

We present an adolescent patient with secondary amenorrhea, and thrombocytopenia in the absence of hypersplenism as the initial presentation.

CASE

DK, a 14 year-old girl, had amenorrhea for 3 months despite having had regular menses for 2 years. Since the patient refused the gynecologic examination, only an abdominal ultrasound scan was performed which revealed normal findings. No further examination was performed. After 2 months, the patient was admitted to the hospital with pruritus of 2 weeks duration and jaundice for a week. The patient's course has been marked by normal growth (height 90. percentile, weight 25. percentile for age). There was no history of consanguinity in the family. However, 21 years ago, the patient’s 9-year-old sister had died 15 days after the development of jaundice, having been diagnosed as having cirrhosis.

On physical examination, slight jaundice, pretibial edema, and clubbing were recorded. Dry skin with excoration marks were remarkable. She had hepatomegaly of 2 cm and splenomegaly of 1 cm. Breast and pubic hair development was concomitant with Tanner stage 4. The laboratory results were as follows: Hab: 8.2 g/dL, Hct: 26%, WBC: 3500/mm³, platelets: 63,000/mm³ (in subsequent controls; 79,000/mm³, 66,000/mm³ and 87,000/mm³), reticulocytes: 1%, Coombs (–). The platelet function tests were normal and the antithrombocyte antibodies were negative. Erythrocyte sedimentation rate: 55 mm/h. Serum iron: 51 μg/dL, ferritin: 319 μg/dL. Total protein: 6.4 g/dL, albumin: 2 g/dL, total bilirubin: 3.86 mg/dL, direct bilirubin: 2.37 mg/dL. ALT, AST and GGT were elevated 3 times, 6 times, and 4 times normal values, respectively. Alkaline phosphatase and uric acid were slightly decreased (72 IU/L and 2 mg/dL, respectively). Prothrombin activity was 53%. Immunoglobulins were slightly elevated (IgG: 2005, IgA: 626, IgM: 183 mg/dL). Alfa-1 antitrypsin level was normal. Autoantibodies such as ANA, AMA, SMA, LKM1 were negative.
Viral markers including HBsAg, anti-HBc IgM, anti HBs, anti-HAV IgM, IgG, anti-HCV, HCV RNA and antibodies for parvovirus, cytomegalovirus, and Epstein-Barr were found negative. Total serum copper value was normal, ceruloplasmin level was below the normal values (<20 mg/dL; N: 20–55 mg/dL). Twenty-four hour urine excretion of copper was 288.1 µg/dL (N < 100 µg/dL) and the urine examination showed dibasic aminoaciduria. Serum urea and creatitin values were normal. A hormone assay revealed abnormally low concentration of follicular stimulating hormone (FSH) (2.23 mIU/mL), luteinizing hormone (LH) (0.21 mIU/mL) and estradiol (<20 pg/mL). The concentrations of prolactin, T3, T4 and TSH, testosterone, free testosterone and androstenedione were normal.

Ophthalmologic examination with slit-lamp microscopy detected Kayser-Fleischer rings. Abdominal ultrasonographic examination showed minimal ascites with irregular echogenicity of the liver and hydrops of the gallbladder. The dimensions of the uterus were normal and no major follicle in the ovaries was observed. No endometrial echogenicity was recorded.

The needle biopsy of liver showed severe hepato-cellular necrosis, inflammatory changes and fibrosis. Hepatic copper content was 578.18 µg/g (N < 50 µg/g). Upper gastrointestinal tract endoscopy revealed no varices. Cranial tomography was normal, however magnetic resonance imaging showed hyperintensity of the basal ganglia. We had no opportunity for electron micropscopical examination or genetic mutational identification. Two subsequent bone marrow aspirations showed erythroid hyperplasia and normocellularity with normal megakaryocytes, respectively.

Zinc treatment was started initially. D-penicillamine was also commenced but, as the patient’s thrombocyte count rapidly fell from 87,000 to 58,000/mm³, the treatment was suspended. Trientine was commenced at a dose of 1 g/day. No clinical or biochemical manifestations of toxicity were observed. Also, the avoidance of foods with high copper content was advocated. At 30 months follow-up, the patient is doing well with normal ovulatory function and with thrombocyte count around 98,000/mm³.

Discussion

The patient was diagnosed as WD owing to the low level of ceruloplasmin, the presence of corneal Kayser-Fleischer rings along with increased level of copper in 24-hour urine excretion and in dry liver tissue. Before treatment, the platelet count was found to be low with lack of increased number of megakaryocytes in the bone marrow aspiration suggesting that the thrombocytopenia was not exclusively owing to hypersplenism. The anemia that was diagnosed initially disappeared without any treatment or transfusion, although thrombocytopenia persisted. It is evident that gross splenomegaly is not necessary to produce hypersplenism, but the patient’s bone marrow aspiration findings did not show hypercellularity suggesting hypersplenism (except erythroid hyperplasia). In patients with portal hypertension, the thrombocytopenia is generally owing to hypersplenism. Also, the absence of anti-thrombocyte and viral antibodies excluded respectively the diagnosis of autoimmune thrombocytopenia and viral infections frequently associated with mild thrombocytopenia.

The platelet function abnormalities in WD have been well-recognized [10,11]. Owen et al. [10] studied platelet function and coagulation profiles of 16 WD patients and observed some abnormality of platelet aggregation in 15. The platelet function tests were normal in our patient. Also, Hoagland et al. [11], reported that 52% of patients with WD had thrombocytopenia and 30% had leucopenia. Twenty-four of these patients, who had thrombocytopenia, did not have splenomegaly. In the literature, there is only one case of an adult patient with idiopathic thrombocytopenia associated with WD [9]. Splenectomy was recommended because of poor response to corticosteroids and the liver biopsy performed during the operation revealed chronic aggressive hepatitis. Further investigations showed low level of serum ceruloplasmin and the presence of Kayser-Fleischer rings and thereupon the diagnosis of WD was made.

In advanced stages of chronic liver disease, serum thrombopoietin level may be decreased [12]. Although it is difficult to speculate in the absence of the serum thrombopoietin, it is possible that low levels might have caused thrombocytopenia. Thrombopoietin is mainly produced by the liver and the regulatory mechanism of thrombopoietin gene expression in hepatocytes is not clear. But Yamashita et al. [13] using various growth factors and cytokines on thrombopoietin mRNA expression in adult rat hepatocytes in primary cultures, showed that among them only hepatocyte growth factor/scatter factor (HGF/SF) enhanced thrombopoietin mRNA expression. On the other hand, HGF is a copper-binding protein [14]. In WD as the copper level in liver rises,
possibly related to the decrease in HGF, thrombopoietin production can decrease and could be the reason for thrombocytopenia in WD. As this has not been studied, it is not possible to know whether the thrombocytopenia in our patient was owing to liver damage or this relationship between copper and thrombopoietin.

Primary or secondary amenorrhea has been reported in women with chronic liver disease and in almost all untreated women with WD [6,7,15]. In these patients, as in ours, because the concentrations of FSH and LH were low, gonadotropin-releasing stimulation test can be done in order to identify pituitary involvement. Liver damage is known to interfere with normal metabolism of estrogen. In this case, the estradiol level was low, owing either to low concentrations of FSH and LH and/or inadequate estradiol production. Estrogen is necessary to sustain granulosa cell mitosis and FSH is required to permit the granulosa cell to aromatize the theca cell to estrogen. So, endocrine microenvironment of the developing follicle remains estrogenic. The amount and activity of aromatase is critical in maintaining the health of the oocyte. Interference of the enzyme system aromatase by copper intoxication would probably cause poor estradiol production and poor ovulation [7]. The liver damage in WD may prevent also the normal breakdown and metabolism of testosterone which, in the presence of a normal production rate, will elevate the total testosterone levels, and these in turn may prevent normal function of the ovulatory mechanism by arresting follicular maturation and producing atretic follicles [16]. In this patient low levels of FSH, LH, and estradiol were found with normal levels of testosterone, free testosterone, and androstenedione. Despite inadequate breakdown and metabolism of testosterone, normal serum testosterone levels in our patient can be explained by the low levels of FSH-LH and the lack of the normal ovarian follicular activity. As a result, the amenorrhea in WD probably originates from the hypothalamic and/or pituitary and/or ovarian levels. In a study from Taiwan, amenorrhea was reported to be relatively more common among WD patients in Asia [5]. The wide spectrum of age of onset of the clinical features in WD may be related to the severity of the gene disruption by mutation. The mutations provide an explanation for some of the wide phenotype variation encountered in WD.

In conclusion, WD is encountered in the differential diagnosis of amenorrhea or thrombocytopenia. Minor manifestations such as isolated thrombocytopenia or amenorrhea as a presenting feature of WD is interesting and extremely unusual. Because treatment is capable of reversing these changes and restoring a normal menstrual cycle, early diagnosis is important. Thus, we support the recommendation that adolescents with amenorrhea or children with thrombocytopenia without any obvious cause, should be evaluated for WD.

References