Should we consider Addison's disease in the differential diagnosis of persistent hypertransaminasemia ? A case report

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To the editor

A 29 year-old Caucasian male was admitted to our department in order to investigate persistent hypertransaminasemia (3-4-fold the normal values) for at least 1 year, along with a symptomatology of progressive fatigue and weight loss (6 kg/6 months). No remarkable data were revealed from the individual and family history. Physical examination demonstrated hyperpgimentation, atrophy of the upper and lower limbs, hypotension (100/70 mmHg on supine and 80/50 mmHg on upright position) and enlargement of cervical lymph nodes.

Laboratory testing on admission revealed : elevated aminotransferases [AST : 107 IU/L and ALT : 175 IU/L (range 5-40)] and cholestatic enzymes [γ-glutamine transferase (γGT) : 128 IU/L (range 9-50), alkaline phosphatase (ALP) : 169 IU/L (range 40-120)], hyperkalemia (K^+ : 5.6 mEq/L), hyponatriemia (Na^+ : 130 mEq/L), mild lyphocytocis and monocytosis. Other markers of liver function, were normal. Further investigation towards abnormal liver biochemistry, including viral markers and tumor markers, was negative. His autoimmune profile was normal, except for anti-smooth muscle antibodies (ASMA), with a titre of 1/160. The levels of α-1-antithrypsin and immunoglobulins (IgA, IgG and IgM) were also normal. Ophthalmologic examination did not show evidence of Kayser-Fleischer ring and serum ceruloplasmin along with the levels of copper of 24-hour urine were normal. Tuberculin skin test (Mantoux) was negative. Imaging of the upper and lower abdomen as well as upper endoscopy did not show any remarkable signs. Finally a liver biopsy was performed. On histological examination, the hepatic architecture was well-preserved. A few portal tracts were slightly enlarged, while most of them had normal size (Fig. 1). Some hepatocytes showed hydrophic degeneration. The orcein-shikata staining for cooper-associated protein was negative. No signs of autoimmune liver disease were identified.

Judging by the patient's symptomatology and the electrolyte abnormalities, Addison's disease was suspected. Serum cortisol levels at 08:00 a.m. were low (2.2 μg/dL, normal 7-25) and adrenocorticotropic hormone (ACTH) levels were extremely high (1591 pg/mL, normal range 9-52). A cosyntropin-stimulation test confirmed the diagnosis of Addison's disease. The patient was placed on hydrocortisone (20-10 mg) plus 0.1 mg fludrocortisone per day, with a concomitant resolution of his symptomatology and normalization of liver enzyme levels within the following weeks.

Addison's disease may coexist with autoimmune hepatitis as a part of autoimmune polyglandular syndrome (APS) type I, in about 5-31%, usually with positive antibodies against liver and kidney microsomes (anti-LKM). These antibodies are present even in 25% of patients with APS type I without alterations in their liver function tests (1). Our patient had negative anti-LKM antibodies and liver biopsy did not show any evidence of autoimmune hepatitis. Moreover, there was no evidence of other autoimmune diseases.

Addison's disease has rarely been associated with elevated liver enzymes in the absence of autoimmune hepatitis. We pulled out 17 patients from the literature. In each patient, administration of hydrocortisone resulted in normalization of transaminase levels (2-10). Of note, in 3 cases a cosyntropin-stimulation test unmasked a state of hypocortisolism, despite apparently normal baseline cortisol levels (8). The exact pathogenetic role of hypocortisolism in inducing liver dysfunction is not clear. Some explanations have been suggested, such as hypoperfusion or weight changes as the responsible mechanisms. However, these are rarely severe enough to cause liver damage (7,10). The most convincing mechanism seems to be hepatocellular apoptosis and necrosis due to lymphocytic infiltration and subsequent cytokine release (7). In another point of view, cortisol inhibits the mediators of inflammation in normal states and therefore its deficiency induces lymphocyte recruitment, cytokine release and concomitant liver damage (10). Another hypothesis is increased iron deposition, which was

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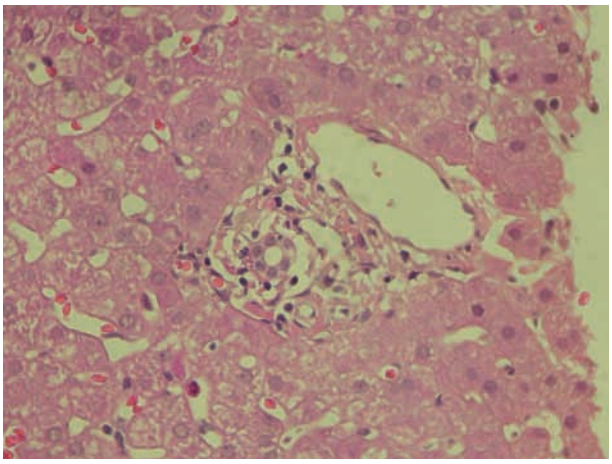

Fig. 1. — Liver biopsy showing portal tract of normal size. H&E × 400.

described in a case of Addison's disease, along with increased ferritin levels, which were reversible after treatment with glucocorticosteroids (6). Our patient's ferritin levels were at the upper high normal level at diagnosis (286 ng/mL, normal range 10-291) and decreased to 63 ng/mL, after administration of hydrocortisone at 18 months of follow-up. Nonetheless, there were no signs of iron deposition on liver biopsy and we must also consider the role of ferritin as marker of inflammation. Hence, we could not provide a plausible explanation for the exact mechanisms in Addison's disease -induced hypertransaminasemia.

Conflict of interest

This paper was written independently ; no company or institution supported it financially. Some of the authors have attended conferences, given lectures and participated in advisory boards or trials sponsored by various pharmaceutical companies.

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