Letters to the Editors

Pure red aplasia induced by sodium valproate in a patient with Behçet's syndrome

Sirs,

Pure cell red aplasia (PRCA) is an uncommon syndrome characterised by a severe normocytic and normochromic anaemia associated with reticulocytopenia and conspicuous decrease or lack of erythroblasts in an otherwise normal functioning bone marrow (1, 2). PRCA can be congenital or acquired. The acquired form can present as a primary autoimmune antibody-mediated haematological disorder in the absence of any other disease, or can be secondary to infections (particularly B19 parvovirus), haematological malignancies, autoimmune disorders, thymoma and other solid tumours, severe renal failure, ABO-incompatible bone marrow transplantation, pregnancy, drugs and chemical toxic agents. The incidence of transient and reversible PRCA triggered by infections and drugs is probably underestimated due to its self-limiting character.

Sodium valproate is a commonly used anticonvulsant agent that can cause PRCA (3-10). We report the case of a 44-year-old male patient suffering from Behçet's syndrome (BS) who developed transient and reversible severe symptomatic PRCA after the start of sodium valproate therapy.

His BS begun when he was thirty with recurrent oral apthosis, papulo-pustolosis and bilateral panuveitis. He received high doses of oral corticosteroids for 4 years in another hospital. When he came to us, due to persistence of bilateral retinal vasculitis we gave cyclosporine A (CsA) at a dose of 3 mg/kg/day with very good results. Afterwards, the daily dose of cyclosporine was reduced to 2 mg/kg/day due to a mild increase of serum creatinine level.

The disease remained in remission for about 10 years when the patient developed generalised tonic-clonic seizures of epilepsy. Magnetic resonance imaging (MRI) of brain revealed mild dilatation of the subarachnoid cisterns together with hyperintense signal areas on the T2-weighted, PD and fluid-attenuated inversion recovery (FLAIR) sequences involving the pons, thalamus, insula that were not modified by the injection of the contrast-medium. The lesions were interpreted as a result of lacunar infarctions. CsA was withdrawn and substituted with chlorambucil at a dose of 3 mg/day. The patient was also given sodium valproate at a dose of 1000 mg day in two divided doses.

After 4 months an anaemia appeared that did not improve after the withdrawal of chlorambucil.

After more than 4 months, the patient was admitted to the Oncology and Haematological Department of our hospital because of a severe anaemia with marked pallor, fatigue, tiredness and dizziness in the absence of jaundice. He confirmed full adherence to therapy and denied having had any infections and any exposures to environmental toxins or over-the-counter dietary supplements, taking other drugs, smoking cigarettes or drinking alcohol in the period preceding the examination. His haematological parameters were as follows: haemoglobin 6.1 g/dl (normal range 14-18 g/dl); red blood cell (RBC) 1.96 x1012/L (4.5-6.2 1012/L); mean corpuscular haemoglobin (MCV) 85 fl (82-97 fl); mean corpuscular haemoglobin concentration (MCHC) 36.5 g/dl (32-36 g/dl); white blood cells (WBC) 4.7 x109/L (3.6-9.6 109/L); platelets (PLT) 148 x 109/L (140-440 109/L); reticulocyte count <1%. The direct and un-direct Coombs' tests were negative. Serum iron, ferritin, folate, vitamin-B12, complement levels, antinuclear antibodies, lactate dehydrogenase, electrolytes, liver and kidney function tests, thyroid function tests, erythrocyte sedimentation rate and C-reactive protein, were normal. A stool sample for occult blood and upper gastrointestinal endoscopy were negative. Serological tests excluded viral infections. Bone-marrow biopsy showed hypocellularity together with erythroid hypoplasia. The myelopoiesis and the megakariopoiesis were preserved. A diagnosis of valproate-related PRCA was made and the drug was discontinued and substituted with phenobarbital and lamotrigine. The patient received 2 packed blood cell transfusions with the aim to alleviate symptoms. A complete resolution of the haematological damage was observed one month after stopping sodium valproate.

Sodium valproate is a clinically effective anticonvulsant agent that may give bone marrow toxicity leading to life-threatening complications such as thrombocytopenia, leukopenia, aplastic anaemia and PRCA. So far, less than 10 patients of sodium valproate-induced PRCA have been reported (3-10). Approximately half out of these were children or adolescents. Our patient developed PRCA shortly after the initiation of treatment with sodium valproate and the disease resolved spontaneously after the discontinuation of the medication. There was no evidence of any influence of chorambucil on the development of anaemia. Our investigations ruled out the known causes of PRCA. The pathogenesis of PCR-induced PRCA is not known. Current evidence implicates an immune dysfunction leading to specific immunoglobulin G antibodies directed against erythroid precursor cells or erythropoietin, or to a T-cell mediated suppression of erythropoiesis. BS patients had a higher incidence of comorbidities compared to general population (11). The risk of side effects of different drugs and potentially dangerous drug interactions should be kept in mind. In the management of BS patients a strict collaboration between physicians is needed to optimise the care (12).

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