To the editor:

Diamond-Blackfan anemia responding to valproic acid

Diamond-Blackfan anemia (DBA) is a congenital macrocytic anemia characterized by severely reduced erythroid precursors with normal megakaryocytic and granulocytic differentiation.1 There is also reticulocytopenia and increased red blood cell (RBC) fetal hemoglobin (HbF).2 About 25% of patients harbor a mutation on chromosome 19 that involves the gene encoding ribosomal protein S19.3 Many patients initially respond to corticosteroids, but others may require lifelong RBC transfusions. Other therapeutic modalities include androgens, cyclosporine, interleukin-3, metoclopramide, and bone marrow transplantation.4 We report a case of DBA who markedly improved on valproic acid.

A 19-year-old female was diagnosed with DBA at age 16 months. She received different treatment regimens including prednisone (40 mg daily) for 13 years, and methotrexate (5 mg daily) and cyclosporine (15 mg/kg per day) for the last 3 years. Despite this, she required frequent blood transfusions. She developed autoimmune hemolytic anemia, underwent splenectomy, and lately started to receive least incompatible blood transfusions. One year ago, she received metoclopramide (30 mg daily) for 4 months, but transfusion requirements did not improve and the mean hemoglobin level remained at 64 g/L (6.4 g/dL) and reticulocytes, .001 (0.1%).

Eight months ago, she was admitted for fever, pneumonia, and urinary tract infection, which were treated with antibiotics. She was still taking prednisone, methotrexate, and cyclosporine in addition to alendronate and calcium. The hemoglobin level was 64 g/L. She received 2 units of least incompatible packed red blood cells after a bolus of steroids. She developed generalized tonic-clonic seizures 10 days later. Computed tomography of brain was normal. Valproic acid was started and she was discharged at a dose of 500 mg thrice a day (30 mg/kg per day) with good seizure control. Blood valproic acid levels were therapeutic, ranging between 0.5 and 1.0 g/L.

Since then, the patient has required no further blood transfusions. Hemoglobin level stabilized with a mean value of 126 g/L (12.6 g/dL), and reticulocytes count increased to .04 (4%). Serial HbF levels have been 1.1% to 1.4%, and mean corpuscular volume, 92 to 96.

Valproic acid, also known as 2-propylpentanoic acid or n-dipropylacetic acid, has been used for the treatment of epilepsy since 1978. It is structurally related to butyric acid analogs, such as arginine butyrate, which have been shown to increase HbF.2-4 Valproic acid was also shown to increase the percentage of red blood cells that contained HbF in patients with epilepsy.5 Another study of 4 adults with sickle cell disease treated with valproic acid reported a 3-fold increase in HbF in 3 patients over 2 to 13 weeks.6 In another study, valproic acid was as effective as hydroxyurea in increasing the concentration of HbF in patients with sickle cell disease.7 Furthermore, in patients with sickle cell disease there was a modest increase in both mean HbF concentration and the number of cells containing increased HbF after valproic acid treatment.8 The mechanism of induction of fetal hemoglobin synthesis by valproate is possibly through modulation of the mitogen-activated protein kinase (MAPK) signal transduction system.9 In our patient, initiation of valproic acid therapy was temporally associated with an improvement in the hemoglobin concentration, without an increase in HbF. A search of the literature did not reveal any previous use of valproic acid in the treatment of DBA. We recommend considering the use of valproic acid in treating DBA if there is no response to other therapies. Further studies are needed to confirm the potential benefits of this drug in DBA.

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