Megaloblastic Anemia And Hyperhomocysteinemia Possibly Secondary To Vitamin B-12 Due To Sodium Valproate

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Citation

Abstract

INTRODUCTION
Long-term administration of sodium valproate is associated with vitamin deficiencies (1). To our knowledge, sodium valproate induced vitamin B-12 deficiency in the adult population has never been reported in the literature. We present a patient with megaloblastic anemia and hyperhomocysteinemia due to vitamin B-12 deficiency secondary to sodium valproate.

CASE REPORT
A 36-year-old male with long standing history of epilepsy (since 1973) and treated with sodium valproate (500 mg/day) since 2001 was admitted to our Hematology department with the complaints of fatigue and weakness for the previous 10 days. He did not take other medications. On physical examination he was pale and the spleen was palpable at the costal margin. Neurologic examination was normal. His chest X-ray and electrocardiogram was unremarkable. Laboratory data on admission showed hemoglobin (Hb): 4.4 gr/dl (12-16), white blood cell (WBC): 2490 K/mm$^3$, platelet (Plt): 67800 K/mm$^3$ mean corpuscular volume (MCV): 121 fl (80-96), vitamin B-12: 140 pg/ml (157-1059), folic acid: 10.5 ng/ml (3-17), lactate dehydrogenase (LDH): 7570 U/L (200-450), homocysteine: 21.8 µ/L (4.5-15), with normal values of ferritin, iron binding capacity, serum iron, liver-renal enzymes, bilirubine and thyroid function. Two years before starting sodium valproate his complete blood cell count was Hb: 14.4 gr/dl, WBC: 6490 K/mm$^3$, Plt: 267800 K/mm$^3$, MCV: 86 fl. Blood smear analysis demonstrated marked anisocytosis and poikilocytosis together with macroovalocytes, and hypersegmented neutrophils. Bone marrow microscopic examination revealed 54% neutrophils, 40% lymphocytes, 4% monocytes, 2% eosinophils with macrocytosis, poikilocytosis and anisocytosis. Pathology reported hypercellular bone marrow possibly related with megaloblastic anemia. We started vitamin B-12 with the diagnosis of megaloblastic anemia due to vitamin B-12 deficiency secondary to sodium valproate. Two units erithrocyte suspension were given to patient due to anemia. On the third day, a reticulocyte crisis was detected and his Hb, WBC, Plt level progressively increased. Endoscopic examination revealed minimal erythematous gastropathy and a gastric biopsy biopsy was obtained. Stomach pathology reported no abnormalities and no helicobacter pylori. Abdominal ultrasonography showed splenomegaly (150 mm). There was no known data about this in his medical history and in examination nothing was found that may explain splenomegaly other than megaloblastic anemia. In follow-up his laboratory level of complete blood cell count, LDH and homocysteine was normally detected 3 months after valproate cessation later and his splenomegaly (140 mm) was decreased in size.

DISCUSSION
Long-term administration of sodium valproate is associated with vitamin deficiencies (1). Sodium valproate may lead to anemia and hyperhomocysteinemia by affecting the levels of folic acid which has a role in the metabolism of homocysteine (2,3). It is well known that valproate may cause folic acid deficiency but in our case the level of folic acid may have been normal due to nutrition of patient (4). In the literature there is no data about valproate associated vitamin B-12 deficiency. In our case, we excluded all the other causes of megaloblastic anemia (including malabsorption, other medications, parasitic infections, ileal resection, vegetarian diet) other than sodium valproate. In 2001, before starting sodium valproate his complete blood cell count was...
normal. The previous normal laboratory values suggest sodium valproate may be the possible cause of vitamin B-12 deficiency and hyperhomocysteinemia. To our knowledge, this is the first case of vitamin B-12 deficiency and hyperhomocysteinemia secondary to sodium valproate in the adult population. An objective causality assessment using the Naranjo probability scale revealed that the possible cause of this adverse reaction is sodium valproate (5). The mechanism of valproate-induced vitB-12 deficiency is unknown. Splenomegaly occurs in 10% of megaloblastic anemias. Further studies are warranted to clarify the mechanism of this reaction.

CONCLUSION

In conclusion, our case shows that the administration of sodium valproate may induce a decrease of vitamin B-12 and an increase of homocysteine. We advise to measure the serum level of vitamin B-12, folic acid and homocysteine in patients who have anemia and hypersegmented neutrophils in blood smears treated with sodium valproate. This could allow to early detection of patients at risk for vitamin deficiency and hyperhomocysteinemia which could substantially increase the risk of cardiovascular disease in these patients.

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References

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