Neurol Sci (2013) 34:1003–1004
DOI 10.1007/s10072-012-1153-3

LETTER TO THE EDITOR

Valproate-induced panhypogammaglobulinemia

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Received: 18 April 2012 / Accepted: 3 July 2012 / Published online: 14 July 2012

Abstract Valproate is one of the most used anti-epileptic drugs. Its common side effects are nausea, vomiting, weight gain, hair loss, tremor, changes in behavior, slowed thinking and impaired liver function. Blood dyscrasias are also relatively frequent and a few studies reported changes in serum immunoglobulin concentrations with valproate treatment. We describe a case of panhypogammaglobulinemia with transient pancytopenia due to valproate. Pancytopenia was recovered after discontinuation of valproate but panhypogammaglobulinemia has been persisting. Intravenous immunoglobulin is being administrated monthly. Previous reports describe that other sodium channel blockers, such as phenytoin and carbamazepine, have been associated with hypogammaglobulinemia. This report also suggests that immunodeficiencies can be caused by valproate.

Keywords Valproic acid · Sodium channel blockers · Hypogammaglobulinemia

Dear Editor,

We describe a case of 6-month-old infant with valproate-induced panhypogammaglobulinemia. She was admitted to our hospital for status epilepticus lasting 40 min. Seizure type was generalized tonic–clonic.

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She had a past history of recurrent seizures for 3 months and delayed development. She was prescribed valproate for 3 months. Valproate was increased to 30 mg/kg/day because of recurrent seizures. She could control her head at 6 months and could not yet roll over. Previous electroencephalogram (EEG) and brain magnetic resonance image (MRI) were normal. Previous laboratory studies including complete blood cell counts, glucose, serum electrolytes, blood gas analysis and ammonia showed no abnormality. Otherwise, she had no family and birth history.

Seizure activity stopped after the administration of intravenous diazepam and lorazepam, respectively, twice. Physical examination revealed petechiae on her face and extremities. Laboratory findings included leukocyte count 10,400/μL (segmented neutrophil 51.7 %, lymphocyte 25.1 %), hemoglobin 10.2 g/dL, platelet count 17,000/μL, prothrombin time 72 % (international normalized ratio, 1.19), activated partial thromboplastin time 31.1 s, AST 69 IU/L, AST 16 IU/L, ammonia 141 μmol/L, and valproate drug level >148 μg/dL. Repeated brain MRI and EEG revealed normal. Valproate was discontinued and phenobarbital was substituted. On hospital day (HD) 4, repeated laboratory tests were as follows: leukocyte count 7,300/μL (segmented neutrophil 33.9 %, lymphocyte 50 %), hemoglobin 9.0 g/dL (MCV 81.5 fL, MCH 37.4 pg), platelet count 42,000/μL, AST 50 IU/L, AST 15 IU/L, ammonia 82 μmol/L and valproate drug level 90.7 μg/dL. The immunoglobulin (Ig) assay revealed panhypogammaglobulinemia: IgG 125 mg/dL, IgA < 23 mg/dL, IgM 9.5 mg/dL and IgE < 10 IU/mL. Antiplatelet antibody test was negative. On HD 7, follow-up laboratory tests were as follows: leukocyte 4,890/μL (segmented neutrophil 17 %, lymphocyte 61 %), hemoglobin 8.6 g/dL (MCV 80.1 fL, MCH 36.7 pg), platelet count 80,000/μL, serum iron 73 μg/dL, serum ferritin

55.1 ng/mL, total iron binding capacity 314 μg/dL, reticulocyte 1.86 % and immature reticulocyte 16.3 %. The peripheral blood smear showed pancytopenia. The repeated Ig assay also revealed hypogammaglobulinemia: IgG 132 mg/dL, IgA < 23 mg/dL, IgM 25.3 mg/dL and IgE < 10 IU/mL. On the same day, she developed seizure attack for 10 min and the dose of phenobarbital was increased. Seizure type was generalized tonic–clonic and progressed to right-sided clonus. On HD 8, she developed additional right-sided clonic seizure for few seconds. Seizure attack was not observed from HD 9 and she was discharged on HD 11. One month later, she visited our outpatient clinic. Follow-up laboratory findings were as follows: leukocyte 8,000/μL (segmented neutrophil 19.3 %, lymphocyte 66.6 %), hemoglobin 8.8 g/dL (MCV 71.8 fL, MCH 23.5 pg), platelet count 369,000/μL, serum iron 13 μg/dL, serum ferritin 9.9 ng/mL, total iron binding capacity 341 μg/dL and valproate drug level 3.6 μg/dL. Normochromic normocytic anemia progressed to iron deficiency anemia (IDA). IDA was recovered later by iron supplement. Hypogammaglobulinemia remained: IgG 176 mg/dL, IgA < 23 mg/dL, IgM 39.6 mg/dL and IgE < 10 IU/mL. For hypogammaglobulinemia, monthly intravenous Ig infusions were being administrated for about 1 year on our hospital. Recurrent seizures remained intractable and she was diagnosed as Dravet's syndrome by SCN1A polymorphism on another hospital.

Many reports have been published concerning the effects of treatment with anti-epileptic drugs (AEDs), e.g., phenytoin, carbamazepine, and valproate, on humoral and cellular immunity [1]. From these studies, it became clear that selective IgA deficiency might occur in some patients receiving phenytoin [2]. Phenytoin was associated with low serum IgA concentrations in multivariate analysis [3].

And other sodium channel blockers have been associated with hypogammaglobulinemia. It is speculated that the divergent development of Ig class concentration in patients treated with carbamazepine and valproate, respectively, might be associated with a different effect of these AEDs on B cell maturation, either directly at the B cell level or at the level of regulatory T lymphocytes [1]. Ozaras et al. [4] reported a case of a 37-year-old man with carbamazepine-induced hypogammaglobulinemia recently. Similarly, a 59-year-old man with lamotrigine-induced common variable immunodeficiency has been also reported by Smith et al. [5].

To our knowledge, this is the first report of valproate-induced panhypogammaglobulinemia and suggests that immunodeficiencies can be caused by valproate. It is reasonable that valproate caused panhypogammaglobulinemia in our patient because (1) valproate drug level was high on admission; (2) there was accompanying pancytopenia which is relatively a frequent side effect of valproate, and as above mentioned (3) other sodium channel blockers, such as carbamazepine and phenytoin, have been associated with hypogammaglobulinemia [2].

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