

Catastrophic Presentation of Sodium Valproate Induced Pure Red Cell Aplasia in a Child with Absence Seizure

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Abstract

Sodium valproate is an effective antiepileptic drug used as monotherapy or adjuvant/alternative with other antiepileptic drugs. Haematological toxicity of this drug, though rare, is now an established fact and comprises mainly of neutropenia, thrombocytopenia and aplastic anemia. Very few cases of Pure Red Cell Aplasia (PRCA) following valproate therapy were reported in last 35 years but none presented as acute emergency. We report a case of a 7-year-old child suffering from absence seizure who developed features of acute heart failure due to anemia after 2 months of sodium valproate monotherapy. No underlying haematological or cardiological cause was found. Bone marrow study showed evidence of PRCA. After discontinuation of the drug patient improved gradually and never relapsed again. This case highlights the importance of haematological evaluation both clinically and by laboratory investigation during follow up visits after starting sodium valproate therapy.

Keywords: Anemia; Child; Red-cell aplasia; Valproic acid

Abbreviations: PRCA: Pure Red Cell Aplasia; NYHA: New York Heart Association; MCV: Mean Corpuscular Volume; MCHC: Mean Corpuscular Hemoglobin Concentration; ME: Myeloid Erythroid

Introduction

Sodium valproate is an effective drug used as antiepileptic for indications like generalised, tonic clonic, atonic, myoclonic, absence seizure, as treatment and prophylaxis of migraine and also as mood stabiliser in cases of bipolar disorder and mania.

Due to lack of availability of ethosuximide in India it is the mainstay of therapy for absence seizures in children of school-going age. Several adverse effects have been described for this drug.

Neutropenia, thrombocytopenia, aplastic anemia are known haematological manifestations [1]. We present a case of severe symptomatic Pure Red Cell Aplasia (PRCA) secondary to sodium valproate monotherapy prescribed for absence seizure.

Case Report

A 7-year-old male Indian child presented with gradually increasing pallor over last 2 weeks and respiratory distress for last 4 days. There was history suggestive of exercise intolerance for last couple of days (NYHA Class II).

There was neither any history of fever/blood transfusion/bleeding from any site/respiratory distress in the past nor any haematological/respiratory/cardiac disease in any family member.

There was past history of repeated episodes of brief duration of staring episodes with unresponsiveness 2 months back, not associated with any abnormal movements of limbs or loss of consciousness.

For this parents visited a neurologist and his electroencephalogram showed characteristic 3 Hz spike-and-wave pattern suggestive of absence seizure. Due to unavailability of ethosuximide patient was started on oral sodium valproate in a dose of 20 mg/kg/day in two divided doses.

After this child did not have any staring episode. On admission general examination revealed visible distress, severe pallor, bipedal pitting edema; Heart rate-148/min, regular rhythm; Respiratory rate-40/min, regular pattern, accessory muscles of respiration working; he preferred sitting position rather than lying down; Neck veins were engorged, jugular venous pulsation noted 4 cm above sternal angle. There was no cyanosis, jaundice, lymphadenopathy or bleeding spots. Oxygen saturation was maintained in room air.

Systemic examination revealed hyperdynamic circulation with gallop rhythm without any heart murmur, bilateral basal crepitations on chest auscultation. The liver was palpable 4 cm below right subcostal margin in midclavicular line with liver span of 15 cm. Neurological examination was within normal limits.

Initial investigations revealed: Hb-4 g%, red blood cells- $1.9 \times 10^{12}/L$, Reticulocyte count 0.6%, MCV-86 fL, MCHC-30 g/dL, Total leukocyte count- $5600 \times 10^6/L$ (Neutrophil-53%, Lymphocyte-40%), Platelet $487 \times 10^9/L$; Peripheral blood smear showed normocytic normochromic anemia. Serum iron, ferritin, total iron binding capacity, vitamin-B12, folate, creatinine, lactate dehydrogenase, complement levels, liver function tests, C-reactive protein, electrolytes were within normal ranges. Fetal hemoglobin was 0.7%.

Direct coombs test, Celiac disease screening, serum assay for Parvovirus B19, antinuclear antibody, urine and stool for occult blood, blood and urine culture were negative.

Analysis of bone marrow aspiration sample revealed: Erythroid hypoplasia with dyserythropoiesis, M:E ratio being 9:1 with normal

white blood corpuscle and platelet precursors suggestive of Pure Red Cell Aplasia (PRCA) (Figure 1).

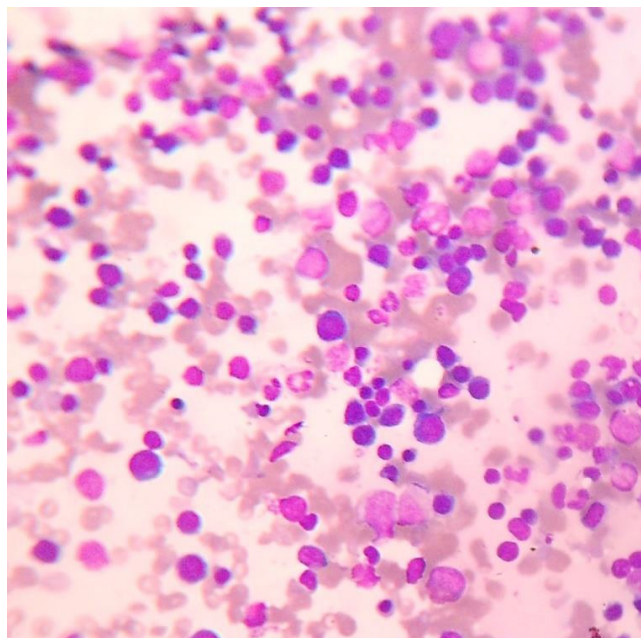


Figure 1: Bone marrow smear showing increased myeloid cells and dyserythropoiesis (H&E, X400).

Chest X-ray showed features of mild pulmonary edema. Electrocardiogram, 24 h holter monitoring did not show any significant anomaly, 2-D Echocardiogram only revealed an ejection fraction of 43%. Ultrasonogram of whole abdomen showed hepatomegaly. Apart from standard protocol for acute heart failure patient was transfused with packed red blood cells (two aliquots of 5 ml/kg slow transfusion over 4 h), following which Hb level increased to 8 g% after 48 h only to decrease again to 7.2 g% after 2 days with no apparent cause. At this point after re-evaluation of the scenario was done and sodium valproate was stopped and oral lamotrigine was started at a dose of 2 mg/kg/day in two divided dose. After 2 weeks of discharge, investigations showed: Hb-8.1 g%, red blood cells $2.3 \times 10^{12}/L$, and reticulocyte count-2.8%, MCV-100 fL. After 3 weeks of discharge, 2-D echocardiogram showed ejection fraction of 63%. The patient is in follow up for last 12 months and showed no relapse.

Discussion

There are several drugs that have been implicated to cause PRCA: antibiotics (linezolid, isoniazid, rifampin, chloramphenicol), antivirals (interferon alpha, lamivudine, zidovudine, ribavirin), immunosuppressants (azathioprine, antithymocyte globulin), drugs used in rheumatological disorders (chloroquine, allopurinol and gold), anticancer drug (fludarabine) etc. [1]. Among anticonvulsant drugs diphenylhydantoin, carbamazepine are documented to cause PRCA. Pathogenesis is thought to be by immune dysfunction with antibodies directed against erythroid precursor cells or erythropoietin, or due to T-cell mediated suppression of erythropoiesis [1]. Aplastic anemia, leukopenia and thrombocytopenia are some of the serious hematological adverse effects of valproic acid therapy cited in the literature [2,3]. Handoko et al. [4] reported that the use of valproic acid

is associated with a nine-fold risk of aplastic anemia. Chateauvieux et al. [5] in experimental K562 cell lineage by microarray analysis confirmed that valproic acid is able to alter hematopoiesis by inhibition of erythroid differentiation by modifying the cell population balance in the myeloid compartment. According to our review of available literature, PRCA secondary to valproate was first reported by MacDougall [6], since then patients (all age groups) developing PRCA due to valproate therapy globally were less than ten in number and nearly half were children and adolescent patients [2,6-8]. Almost none had any catastrophic presentation. Very few of them received monotherapy with sodium valproate and duration of treatment with the drug and dosage were also variable. Zaccara et al. [3] confirmed that the incidence of pure red cell aplasia is sporadic. In our case, the patient presented to us with signs of impending heart failure [after 8 weeks of monotherapy with sodium valproate at minimal dose] due to acute development of anemia without suppression of other cell lineages, required blood transfusion for alleviation of symptoms and recovered like most previous cases after discontinuation of the drug responsible for the condition, sodium valproate. Our patient had normocellular bone marrow with qualitative aberration of erythropoiesis unlike those reported by other authors like hypocellularity, myelodysplasia, changes resembling promyelocytic leukemia etc. [2,9,10]. Increase in haemoglobin, transient reticulocytosis and increased mean corpuscular volume during early weeks of follow up indicated recovery of erythroblast series. Follow up echocardiogram, done after 3 weeks, also showed near normal ejection fraction. There was no relapse of similar event in one year follow up period which favours our description of the causality. No other cause of anemia and impending heart failure could be found even after extensive investigation.

Conclusion

Therefore, according to our opinion, any patient who is started on sodium valproate, irrespective of dose and duration should be clinically looked for evolving signs of anemia during follow up visits and if corroborated by laboratory parameters, drug should be promptly withdrawn. Timely diagnosis is the key to avoid such catastrophic outcome.

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