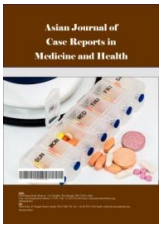

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Severe Anemia Secondary to Valproic Acid Therapy in a Twelve Year Old Girl

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Authors' contributions

This work was carried out in collaboration among all authors. Author KB designed the study, performed the analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MAM and BMB managed the analyses of the study and data collection. Authors JA, SI and NSN managed the literature searches and data collection. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Background: Sodium Valproate is one of the commonest antiepileptic drugs used in the paediatric age group. Haematological side effects of Valproate though rare are an important cause of morbidity. These can include anemia, red cell aplasia and thrombocytopenia. Early recognition of this complication is important for proper management.
Objective: To describe a case of severe anemia caused by chronic therapy with sodium Valproate in a twelve year old girl with seizure disorder.
Presentation of Case: We describe here a case of a twelve year old girl who was a known case of epilepsy on Valproate therapy presenting with severe anaemia. Haematological parameters normalized after stopping Valproate. Through this report, we wish to highlight the importance of periodic monitoring of blood counts in every patient on long term Valproate therapy.

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Keywords: Anemia; valproic acid; epilepsy.

ABBREVIATIONS

PRCA : Pure Red Cell Aplasia
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration
ANA : Anti Nuclear Antibody

1. INTRODUCTION

Sodium Valproate is one of the most common first line anti epileptic drugs used in children in the treatment of epilepsy. There are various side effects of Valproate therapy reported including nausea, transient hepatic enzyme elevations, recurrent hair loss, weight gain, pancreatitis, thrombocytopenia, and renal damage [1]. Thrombocytopenia is the most common hematologic abnormality reported while aplastic anemia, pure red cell aplasia (PRCA), macrocytosis, dimorphic anemia , neutropenia, and coagulopathy are some of the other haematological side effects reported [2]. Anemia caused by sodium valproate is a rare phenomena and there are few case reports in paediatric patients [3]. We present here a case of a twelve year old girl with seizure disorder who developed severe anemia four months after starting Valproic acid therapy. The hemoglobin levels improved after Valproic acid was discontinued.

2. CASE REPORT

This 12 year old girl presented to the Emergency Department with complaints of tiredness and lethargy for two weeks, exertional breathlessness for two weeks and low grade intermittent fever for three days. She also had a history of one episode of non bilious vomiting followed by a transient episode of syncope without any tongue bite or incontinence. Child was a newly diagnosed case of a seizure disorder and had been started on Sodium valproate 200 mg twice daily four months back. She had been on regular treatment with the same with no seizure recurrences. Birth and developmental history were normal and child was immunised for age. There was no history of any similar illness in the past. There was no prior history of any respiratory tract infection. Dietary history was normal. On examination, the child was conscious but lethargic and listless. There was pallor noted in the eyelid and tongue. Peripheral pulses were well felt and there were no signs of dehydration. Capillary refill time was normal. Temperature, pulse rate and blood pressure were within normal limits. Abdominal examination showed hepatomegaly with firm consistency and non tender liver. Nervous system examination showed no focal deficits or meningeal signs. Child was investigated for the pallor. Blood investigations revealed the presence of severe anemia. The values noted were Hemoglobin(Hb) of 1.9 g/dl, Mean corpuscular volume (MCV) of 80 fl, Mean corpuscular hemoglobin (MCH) of 27.1 pg, Total white blood cell count of 8200 per cu mm and Platelet count elevated at 608000/cu mm. Serum Iron and Serum Ferritin were elevated while total iron binding capacity was normal Table 1. Peripheral smear done showed a dimorphic anemia with both microcytes and normocytes with the presence of a reactive thrombocytosis Figs. 1, 2. The red blood cells were widely spaced out as compared to normal blood picture.

Previous hemoglobin four months back before starting Valproic acid was 14 grams/dl. Serological tests for HIV, HBV and HCV done were negative. ANA was normal as were Vitamin B 12 levels. Stool for occult blood was negative and an ultrasound abdomen showed mild hepatomegaly. ESR was normal and reticulocyte count was reduced. Liver function tests were normal. Bone marrow study was planned but could not be done as the patient and attenders were not willing for the same. Serum valproic acid levels were within normal limits.

Since the patient had severe anemia and was symptomatic for the same, she was transfused with multiple units of packed red blood cells until her hemoglobin levels improved. Since the child had normal levels of hemoglobin before Valproic acid therapy, the possibility of a Valproate induced anemia was considered likely. Valproic acid was immediately stopped and was replaced by levetiracetam for seizure control. The child had improvement in general condition and sensorium following transfusion. She was continued on levetiracetam therapy for seizures. Follow up was done after one month and repeat hemoglobin was found to be 13 gm /dl. Child remains asymptomatic and seizure free at follow up .All repeat values of Hemoglobin remain within normal limits.

3. DISCUSSION

Sodium Valproate is one of the commonest anticonvulsants used in the pediatric age group

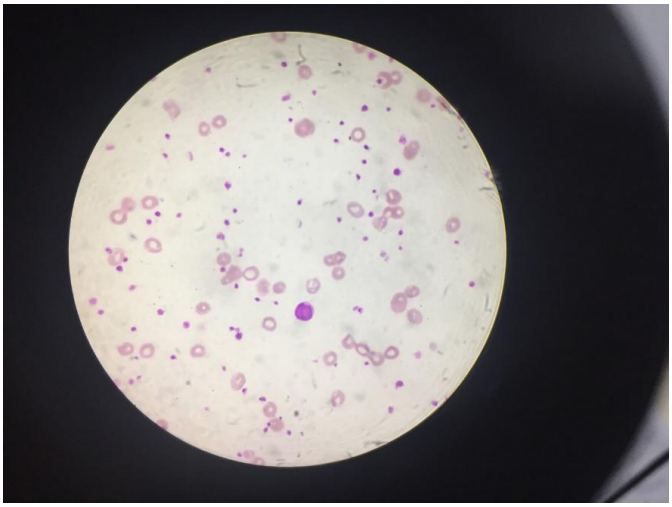

Fig. 1.

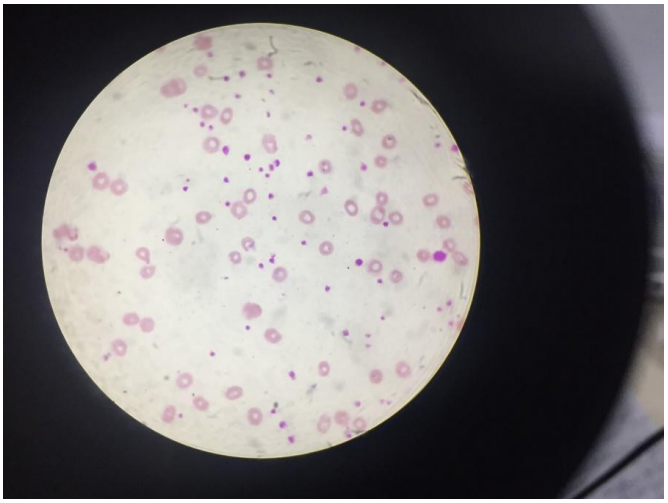

Fig. 2.

Figs. 1 and 2. Showing dimorphic blood picture-both microcytic and normocytic red blood cells that are widely spaced out as compared to normal blood picture

Table 1. Laboratory values

	At presentation	After one month of stopping valproate	Normal range
Haemoglobin	1.9 gm/dL	13 gm/dL	12-15 gm/dL
MCV	80.0 fl		82-92 fl
MCH	27.1		27-32 pg
Total WBC count	6200 / cu mm	8000 / cu mm	4000-11000/cu mm
Platelet count	6.08 lakhs/cu mm	4.2 lakhs/cu mm	1.4-4.5 lakhs / cumm
Serum iron	428 mcg/dL		37-170 mcg/dL
Serum ferritin	282 ng/mL		6-137 ng/mL

for the treatment of focal and generalised seizures. It is known to be associated with a wide range of haematological side effects such as bone marrow toxicity, which can cause life-threatening complications. Hepatic enzyme elevations are the most commonly reported side-effects of sodium valproate therapy. The frequency of the same is noted to be maximum during the first three months of treatment. Hematological abnormalities described include thrombocytopenia, leukopenia, aplastic anemia, and pure red cell aplasia [4]. The pathogenesis of the hematological dysfunction caused by valproic acid is not clear and drug-induced immunological dysfunction or DNA damage is thought to be the most likely explanation [5]. Direct toxicity of Valproic acid on the erythroid bone marrow has also been postulated as one of the mechanisms [6]. Other mechanisms postulated include immune dysfunction with antibodies directed against erythroid precursor cells and also T-cell mediated suppression of erythropoiesis.

Most cases of valproic acid induced anemia and pure red cell aplasia are described within the paediatric population [7]. In most of these cases, the serum levels of Valproate were within normal limits thereby excluding drug overdosage. The time interval between initiation of therapy and onset of anemia is known to be variable and can be from 3 months to 13 years. In our case, the interval was found to be around 4 months. In most of the cases, hemoglobin improved upon cessation of Valproate therapy. Sodium valproate therapy can cause direct bone marrow suppression leading to aplastic anemia. It is also known to produce peripheral cytopenia affecting one or more cell lines [8]. Myelodysplastic syndromes [9] and even a clinical picture resembling acute promyelocytic leukemia have also been seen. A variety of bleeding disorders are known to be associated with valproate use. These may include thrombocytopenia, abnormal platelet function, and acquired von Willebrand disease . Another rare syndrome described in the pediatric age group includes autoimmune hemolytic anemia reported by Watanabe [10] et al which happened in a 2-year-old girl, which occurred during long term treatment with Sodium Valproate. There is no specific association noted between the occurrence of anemia and the dose of valproate given. The dosage of valproate leading to anemia used in the literature is about 10 to 20 mg/kg/day and the serum concentrations of valproate are reported normal in most cases [11]. In the present case, serum levels of Valproic acid were found to be normal in keeping with this.

Our patient had a normal hemoglobin before initiation of Valproic acid and was asymptomatic during the same time. She presented with very severe anemia and lethargy and syncope secondary to the low hemoglobin. Work up for secondary causes of anemia was negative. In view of the history of treatment with valproate, the possibility of a valproic acid induced anemia was considered most likely. She was treated symptomatically with blood transfusions to improve her clinical status. Valproic acid was stopped and changed to Levetiracetam for further seizure control. The child had normalization of hemoglobin levels following the discontinuation of valproic acid. Repeat hemoglobin within one month of stoppage of Sodium valproate had reached normal levels Table 1.

The hemoglobin after Valproate therapy in this case had dropped to very low levels-1.9 grams/dl which to our knowledge has not been reported in any of the other cases of Valproate hematotoxicity. This study shows that severe anemia is a potentially life threatening adverse effect of valproic acid therapy which must be checked for periodically. The main limitation of this study was that bone marrow examination could not be done due to lack of patient consent. We would like to stress therefore upon the periodic monitoring of hemoglobin and blood counts along with liver function tests in all children on chronic Valproic acid therapy.

4. CONCLUSION

Anemia is a rare but deadly complication of chronic therapy with sodium Valproate. Any child who is on Sodium Valproate, irrespective of dose and duration should be clinically monitored for evolving signs of anemia during regular follow up. If anemia or other haematological abnormalities are found on laboratory testing, the drug should be promptly withdrawn. Timely diagnosis is the key to avoid any fatal complications.

CONSENT

All authors declare that ‘written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images’.

ETHICAL APPROVAL

All necessary institutional ethical approval taken and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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