Case Report

Carbamazepine-induced Pure Red Cell Aplasia in a Young Girl

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Abstract

Carbamazepine is a commonly used drug. It is important to be aware of common as well as uncommon adverse effects of commonly used drugs. Apart from the neurological side-effects, haematological side-effects in form of aplastic anemia and agranulocytosis are well-documented. We report a case of pure red cell aplasia (PRCA) following institution of carbamazepine therapy for seizures in a 7-year old girl. PRCA reverted on discontinuation of carbamazepine. PRCA is an uncommon complication of carbamazepine therapy, this being the fifth only case in world literature. It is recommended that blood counts be periodically monitored in patients on carbamazepine.

Key words: Hematologic diseases; pure red-cell aplasia; antiepileptics; carbamazepine

Introduction

A case of carbamazepine-induced PRCA presenting with severe anemia three and half months after initiation of carbamazepine therapy for neurocysticercosis-related seizures is being reported.

Report of case

A 7 year Hindu female first child, born of a non-consanguineous marriage, presented with increasing pallor noticed for 6-7 days and intermittent fever with chills and rigor for 4 days. There was no history of prolonged or profuse bleeding after cuts or injury, petechiae, ecchymoses, bruising etc. Family history was also not suggestive of any bleeding disorder.

Child was on carbamazepine at a daily dose of 11 mg/kg for the last three and half months for generalised tonic clonic seizures, due to multiple neurocysticerci (left frontal and right parietal region). Child had received full course of steroids and albendazole as per protocol. At presentation, GCS was 15/15. Liver was 1.5 cm below costal margin, soft and nontender, spleen was palpable 2 cm below costal margin. There was no lymphadenopathy, no bony tenderness, no ecchymoses, petechiae or bruises. Rest of the systemic examination was unremarkable. Initial investigations revealed- haemoglobin of 3.8 g/dL, total leucocyte count- 15,900/mm^3 (neutrophil 62%, lymphocyte 34%), platelet count- 3,51,000/mm^3, total red cell count- 2,10,000/mm^3, packed cell volume-11.7%, mean corpuscular volume- 84.9 μ^3, mean corpuscular haemoglobin- 27.8 pg, mean corpuscular haemoglobin concentration- 32.7%, red cell distribution width- 16.6, peripheral blood smear showed anisocytosis, poikilocytosis, polychromasia and leukocytosis. Reticulocyte count was 5%, corrected being 1.3%. Patient was started on injection artesunate (4 mg/kg/day for 3 days) keeping a possibility of malaria and transfused packed cells. But tests for malarial parasite were negative. Injection ceftriaxone (75 mg/kg/day) was also added keeping possibility of sepsis and administered for seven days though the sepsis screen was negative. Post-blood transfusion hemoglobin was 8.5 g/dL. Liver function tests were normal, Coomb's test was negative and stool was negative for ova, cysts and occult blood. Serum iron was 152 µg/dL, total iron binding capacity was 306 µg/dL and serum ferritin was 454.7 µg/L suggestive of iron overload state. Bone marrow aspiration revealed hypocellular marrow with erythroid hypoplasia (Figure 1). There was also increase in myeloid-erythroid ratio (8:1), platelet series was normal. Marrow iron stores were normal.

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A possibility of carbamazepine-induced pure red cell aplasia was entertained and carbamazepine stopped on day 3 of hospitalisation. Computed tomography scan of head showed complete disappearance of Taenia cysts. However, electroencephalography showed generalised epileptogenic activity, so the child was started on sodium valproate 15 mg/kg/day and discharged from hospital.

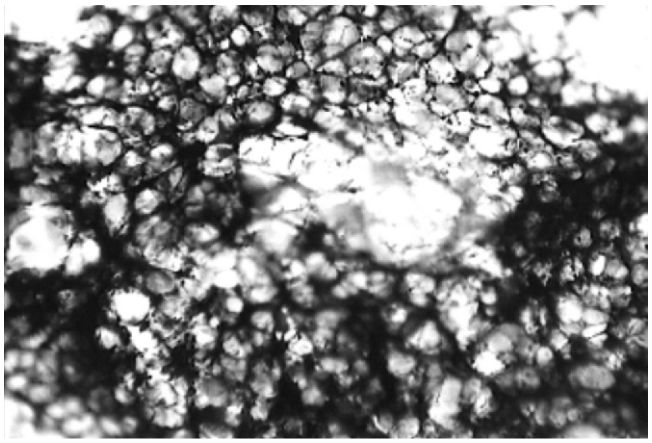

Figure 1 - Bone Marrow Aspirate: Hypocellular marrow with increased fat density, erythroid cells are markedly reduced.

A follow up complete blood count was done after 10 days of stopping carbamazepine- haemoglobin- 10.3 g/dL, packed cell volume- 29.6%, total red cell count- 3,98,000/mm^3, total leucocyte count- 6900/mm^3 (neutrophil 32%, lymphocyte 62%, monocyte 1.5%, eosinophil 3.2%, basophil 1.2%), platelet count- 3,45,000/mm^3, mean corpuscular volume- 88.6 μ^3, mean corpuscular haemoglobin- 30.9 pg, mean corpuscular haemoglobin concentration- 34.9%, red cell distribution width- 19.8 and the corrected reticulocyte count was 3.5%. At 1 month, haemoglobin was 10.9 g/dL.

Discussion

Pure red cell aplasia (PRCA) is the name given to a group of conditions wherein there is an isolated depression of erythropoiesis. This condition may appear as an acquired defect of either acute or chronic type, or a congenital form (Josephs-Diamond-Blackfan syndrome). Acquired pure red-cell aplasia is usually transient in nature in contrast to the congenital variety. The former has been associated with malnutrition and a variety of drugs, toxins and infectious agents or it may result from unknown causes. The various causes are enlisted in table 1. Although, haematological complications like aplastic anemia due to carbamazepine therapy are well known but pure red cell aplasia is exceedingly rare. A slow progressive normocytic-normochromic anemia and reticulocytopenia, without leukopenia and thrombocytopenia in a patient who, except pallor, does not generally show abnormal findings on physical examination, should arouse the suspicion of PRCA [1]. In this case, Naranjo probability scale [2] suggests carbamazepine as the probable causal association for isolated red cell production failure in our case.

Carbamazepine is known for its neurological side-effects, however even forty years earlier aplastic anemia was reported and regular haemoglobin monitoring was recommended [3]. Leucopenia and thrombocytopenia were reported in 2% of patients [4], while aplastic anemia in 0.8% [3]. Four cases have been reported to have developed PRCA following carbamazepine in published literature to date [5-7]. The aplasia may be associated with splenomegaly [5] or Coomb's positivity [6]. In a series of 16 patients with PRCA [7], 14 patients had Diamond-Blackfan syndrome and of the remaining two- one had transient erythroblastopenia and the other had PRCA secondary to carbamazepine.

This patient developed isolated failure of red cell production on carbamazepine therapy, and the child improved rapidly after discontinuation of the drug, responding with an increase in the reticulocyte and erythrocyte counts. Isolated bone marrow failure of the red cell line after anticonvulsive therapy may be delayed. Appearance of clinical anemia 3½ months after initiation of carbamazepine therapy reflects delayed involvement of isolated bone marrow failure of the red cell line after anticonvulsive therapy. It is not morally or ethically justifiable to rechallenge a patient with the drug suspected of causing the haematological abnormality in order to confirm the diagnosis. For this reason, the patient was not re-exposed to carbamazepine after recovery.

The exact mechanism of drug induced PRCA in most cases is unknown. The possible mechanism suggested includes- (i) toxic interference by drugs with the metabolism of nucleated red cells, (ii) immunologically mediated reaction with antibody formation against red cell precursors and (iii) specific inhibitory effect on DNA synthesis probably

Table 1- Causes of PRCA

Acquired Acute self-limited Red Cell Aplasia	1. Viral Infections: Respiratory infections, primary atypical pneumonia, gastroenteritis, infectious mononucleosis, mumps and viral hepatitis 2. Parvovirus B19 3. Antiepileptic medications (eg, phenytoin, carbamazepine, sodium dipropylacetate), Azathioprine, Chloramphenicol and thiamphenicol, Sulfonamides, Isoniazid, Procainamide. 4. Possible coincidental associations include Nonsteroidal anti-inflammatory agents, Allopurinol, Halothane, D-penicillamine, Dapsone/pyrimethamine, Quinidine and quinacrine, Gold, Benzene, Pesticides.
Acquired Chronic (Sustained)	1. Thymoma 2. Chronic Lymphocytic Leukemia (B-Cell Type) 3. Autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, autoimmune haemolytic anemia, chronic active hepatitis, collagen-vascular diseases, and chronic lymphocytic leukemia. 4. In patients who are immunocompromised, pure red cell aplasia may be due to persistent parvovirus B19 infections.
Congenital Chronic form of Red Cell Aplasia	Diamond-Blackfan syndrome- Possible cause is in-utero damage to erythroid stem cells.

at the step of deoxyribonucleotide formation. Drug-induced PRCA is usually reversible after discontinuation of the offending drug. The clinician must be aware of these events as failure to recognise and discontinue the responsible drug in time may cause permanent morbidity and mortality due to generalized marrow hypoplasia.

The haematologic side-effects of carbamazepine, although not common, should nevertheless be borne in mind due to the serious, prolonged and sometimes even fatal consequences. It may be pertinent to explain the neurologic, haematologic, hypersensitivity or dermatologic side-effects of carbamazepine, at the time of initiation of therapy; and advise patients for regular monitoring of blood counts. The symptomatology of early toxic effects viz. fever, sore throat, rash, oral ulcers, easy bruising, lymphadenopathy, petechial or purpuric rash; should prompt the patient to report to the treating physician immediately. Haematological dyscrasias are important because they can be rapidly fatal if progressive. It is recommended that a full blood count be performed before beginning therapy with carbamazepine, weekly for the first month and then monthly for the duration of therapy.

Carbamazepine should be promptly discontinued if leucocyte counts fall below 3000/mm^3, absolute neutrophil count (ANC) < 1500/ mm^3, or platelet count < 100,000/mm^3. Carbamazepine is a commonly prescribed drug in today's scenario and it is important to be aware about its common and uncommon side-effects.

Key Points

- Common as well as uncommon side-effects of commonly used drugs in clinical practice should be borne in mind.
- Carbamazepine is known to cause neurological, haematological, dermatologic and hypersensitivity reactions/side-effects.
- It is important to educate patients about the need to identify early toxic symptoms of a potential drug-related side-effect. Treating physicians also should be able to anticipate and recognize drug-related side-effects early and advise for regular monitoring.
- Carbamazepine is known to cause aplastic anemia and agranulocytosis. Pure red cell aplasia is a rare complication which has been noticed with carbamazepine, and is reversible with cessation of therapy.

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