LETTER TO EDITOR (VIEWER'S CHOICE)

CARBAMAZEPINE INDUCED PURE RED CELL APLASIA IN A YOUNG GIRL

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A 7 yrs old Hindu female child, first born to a non-consanguineous marriage, presented with increasing pallor first noticed 6-7 days previously, intermittent fever with chills and rigor for 4 days. There was no history of prolonged or profuse bleeding after cuts or injury, bleeding from sites other than nose, petechiae, ecchymoses, bruising. No family history suggestive of any bleeding disorder. Child was on Carbamazepine at a daily dose of 11mg/kg for the last three and half months for generalized tonic clonic seizure due to multiple Neurocysticercosis (NCC) (left frontal and right parietal region). Child received full course of steroids and Albendazole as per protocol. At presentation, liver was 1.5cms below coastal margin, soft and non tender, spleen was palpable by 2 cms in its axis below coastal margin. Rest of the systemic examination was unremarkable. Her initial hemogram is depicted in Table 1. Peripheral blood smear showed anisocytosis, poikilocytosis, polychromasia and leukocytosis. . Patient was started on Injection Artesunate (4mg/kg/day for 3 days) started keeping a possibility of malaria and transfused with packed cells. But tests for malarial parasite were negative. Injection Ceftriaxone (75mg/kg/day) was also added keeping possibility of sepsis and completed a course for seven days though the sepsis screen was negative. Post blood transfusion hemogram is depicted in Table 1. Since the total leucocyte count was low, so a repeat hemogram was done, which revealed a total leucocyte count- 5700 (neutrophil 28, lymphocyte 62, monocyte 5, eosinophil 5); other parameters were same as that of the previous hemogram. Liver function test was normal. Stool occult blood- negative; no ova, cyst. Serum iron studies done, which revealed iron- 152, Total iron binding capacity- 306, ferritin- 454.7 (iron overload state). A possibility of Carbamazepine induced pure red cell aplasia was kept in mind and carbamazepine stopped on day 3 of hospitalization. Computed tomography scan of head showed complete disappearance of NCC. Electroencephalography showed generalized epileptogenic activity. The child was started on Sodium Valproate and discharged from hospital. A follow up Complete blood count was done after 10 days of stoppage of Carbamazepine and is depicted in Table 1. Smear showed anisocytosis, lymphocytosis.

Pure red cell aplasia (PRCA) is a relatively rare disease although multiple factors are implied in the pathogenesis of its development. 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 arise the suspicion that he has PRCA. (1) 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. Carbamazepine is one of the drugs known to cause pure red-cell aplasia. The aplasia may be associated with splenomegaly (2). The patient described developed isolated failure of red cell production. A bone marrow examination would have

Table 1: Serial hemograms of the patient

	On presentation	Post blood transfusion	After 10 days after stopping carbamazepine	After one month after stopping carbamazepine
Hemoglobin (gm/dL)	3.8	8.5	10.3	10.9
WBC count (cells/cumm)	15900	4400	6900	
Polymorphs (%)	62	45	32	
Lymphocytes (%)	34	45	62	
Platelets (cells/cumm)	3,51,000	2,03,000	3,45,000	
RBC (cells/cumm)	2,10,000		3,98,000	
Packed cell volume	11.7%	21.7%	29.6%	32%
MCV	84.9	88.1	88.6	88.6
MCH	27.8	34.4	30.9	32.9
MCHC	32.7	39	34.9	36.9
RDW	16.6	16.9	19.8	15.8
Reticulocyte count	5% (corrected - 1.3%)		3.5% (corrected)	

MCV = Mean corpuscular volume, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, RDW = red cell distribution width

helped, but parents did not agree to the procedure. Isolated marrow failure for red cell production most probably resulted from carbamazepine intake, since she 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. This could have happened in this case, where clinical anaemia developed 31/2 months after initiation of carbamazepine therapy.

The "Naranjo probability scale" for estimating the probability of adverse drug reactions suggests that carbamazepine was the probable cause for isolated failure of red cell production. (3) According to Pisciotta, 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 (4). 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 antibodies formation against red cell precursors and (iii) specific inhibitory effect on DNA synthesis probably at the step of deoxyribotide formation. Drug induced PRCA is usually reversible after discontinuation of the offending drug. The clinician must be aware of these events as failure to recognize and discontinue the responsible drug in time may cause permanent morbidity and mortality due to generalized marrow hypoplasia (5)

The hematologic side-effects of carbamazepine, although not common, should nevertheless be borne in mind due to the serious, prolonged and sometimes even fatal consequences. The manufacturers recommend that a full blood count should be done before starting therapy, weekly thereafter for the first 4 weeks and then monthly. This should be continued for the duration of the therapy. (3)

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