CASE REPORT

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Anti-convulsant Hypersensitivity Syndrome – A Rare Life Threatening Adverse Effect of a Commonly Prescribed Drug

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Abstract

Anti-convulsant hypersensitivity syndrome is a delayed adverse drug reaction associated with the use of aromatic anti-convulsant drugs. It has been most commonly reported with the use of phenytoin, carbamazepine, and phenobarbital. Although its occurrence is rare, it is a serious adverse event often resulting in hospitalisation and even death. The clinical manifestations of anti-convulsant hypersensitivity syndrome include a triad of symptoms consisting of skin rashes, fever, and evidence of systemic organ involvement. Diagnosis is most frequently based on the recognition of this triad of symptoms and clinical judegment. The exact mechanism remains to be determined but is thought to have at least three components: deficiency or abnormality of the epoxide hydroxylase enzyme that detoxifies the metabolites of aromatic amine anticonvulsants, associated reactivation of herpes-type viruses, and ethnic predisposition with certain human leukocyte antigen subtypes. Management of anti-convulsant hypersensitivity syndrome primarily includes discontinuation of the associated anti-convulsant drug. Systemic corticosteroids are usually required for full recovery. An important issue regarding anti-convulsant hypersensitivity syndrome is the cross-sensitivity among aromatic anti-convulsant drugs, which has been reported to be 40 - 80%. This means that patients with a history of anticonvulsant hypersensitivity syndrome should avoid further use of any aromatic anti-convulsant drug.

Key words: Anti-convulsant, arene oxide, aromatic ring.

Case report

A 24-year-old male was admitted with complaints of fever, generalised pruritic rash all over the body, and swelling of both lips – all of 2 days duration. He had a history of head injury following a road traffic accident a month ago and had developed seizures. He was prescribed tab phenytoin 100 mg bd for the same. The patient took tab phenytoin regularly at the prescribed dose for 32 days, following which he developed fever, rash, and lip swelling for which he was admitted at our hospital.

On examination, he was conscious, oriented. Pulse rate of 102/minute, blood pressure - 110/80 mm of Hg, respiratory rate - 26/minute, oral temperature - 103° F. He was icteric, had tender cervical, axillary, and inguinal lymph nodes. The patient had periorbital oedema and marked labial oedema. He had a diffuse erythematous maculopapular rash all over the body. Examination of gastrointestinal, cardiovascular, respiratory, and nervous systems were within normal limits.

Investigations (day 1 of admission):

Complete blood count	
Total count	19,100 cells/mm^3
Differential count	Polymorphs - 69, lymphocytes - 6, eosinophils - 15
Erythocyte sedimentation rate	78 mm at 1 hour
Haemoglobin	11.8 g%
Platelets	1.90 lakhs
Red blood cell count	4.08 million/mm^3
Haematocrit	35

Renal function tests	
Glucose	77 mg/dl
Urea	52 mg/dl
Creatinine	1.8 mg/dl
Sodium	136 mmol/l
Potassium	5.0 mmol/l

Liver function tests	
Total bilirubin	15.7 mg/dl
Direct bilirubin	6.0 mg/dl
Alanine transaminase	515 IU/l
Aspartate transaminase	210 IU/l
Serum alkaline phosphatase	245 IU/l
Albumin	4.0 gm/dl
Total protein	6.4 gm/dl

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Peripheral smear – normocytic, normochromic red blood cells, leucocytosis with eosinophilia, atypical lymphocytes noted, platelets adequate.

Urine routine – No abnormalities detected

24 hour urine proteinuria – 200 mg protein/day

Absolute eosinophil count – 1,600 cell/mm^3

Ultrasound abdomen – Normal study

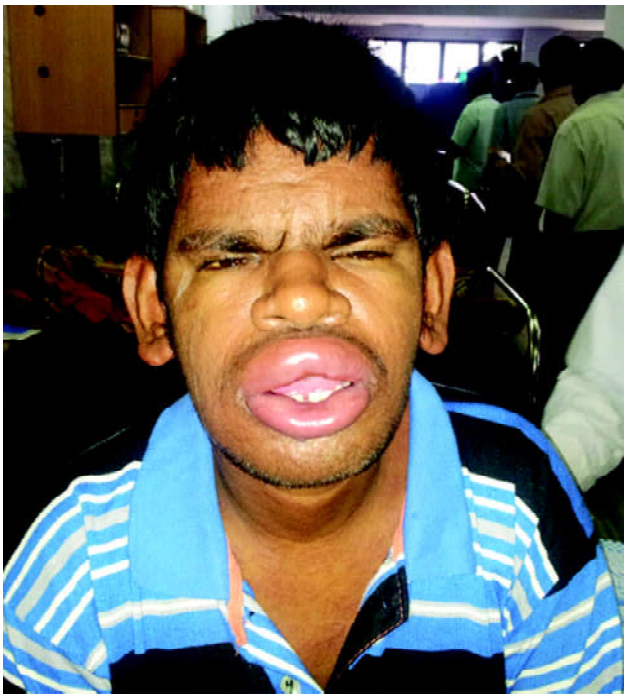
In view of the classical triad of rashes, fever, and organ damage occurring in the 5th week after starting phenytoin, a diagnosis of anti-convulsant hypersensitivity syndrome secondary to phenytoin with acute kidney injury and drug-induced liver disease was made. Tab phenytoin was stopped and the patient was treated with inj dexamethasone 4 mg IV bd for 3 days followed by tab prednisolone 60 mg OD and tapered off over 6 weeks. For the pruritic rash, topical calamine lotion was applied. Patient was put on tab valproate 200 mg BD for seizure control. Tab paracetamol 500 mg was given to control fever. Serial monitoring of blood investigations was done.

Complete blood count	**Day 3**	**Day 7**	**Day 12 (at discharge)**
Total count	18,800 cells/mm^3	13,400 cells/mm^3	8,900 cells/mm^3
Differential count	Polymorphs - 47, Lymphocytes - 36, Eosinophils - 17	Polymorphs-70, Lymphocytes - 20, Eosinophils - 10	Polymorphs-90, Lymphocytes - 8, Eosinophils - 2
Erythocyte sedimentation rate (ESR)	40 mm at 1 hour	28 mm at 1 hour	35 mm at 1 hour
Haemoglobin	11.6 g, %	10.9 g, %	11.0 g, %
Platelets	2.90 lakhs	1.66 lakhs	1.60 lakhs
Red blood cell count	4.24 million/mm^3	3.70 million/mm^3	3.60 million/mm^3
Haematocrit	37	434	33
Renal function tests	**Day 3**	**Day 7**	**Day 12 (at discharge)**
Glucose	111 mg/dl	127 mg/dl	98 mg/dl
Urea	60 mg/dl	40 mg/dl	28 mg/dl
Creatinine	1.7 mg/dl	1.0 mg/dl	0.6 mg/dl
Sodium	132 mmol/l	135 mmol/l	140 mmol/l
Potassium	3.7 mmol/l	3.8 mmol/l	4.9 mmol/l
Liver function tests	**Day 3**	**Day 7**	**Day 12 (at discharge)**
Total bilirubin	10.3 mg/dl	8.7 mg/dl	8.5 mg/dl
Direct bilirubin	5.7 mg/dl	4.2 mg/dl	3.8.0 mg/dl
Alanine transaminase	439 IU/L	218 IU/L	98 IU/L
Aspartate transaminase	208 IU/L	112 IU/L	103 IU/L
Serum alkaline phosphatase	212 IU/L	227 IU/L	280 IU/L
albumin	4.0 gm/dl	3.4 gm/dl	3.9 gm/dl
Total protein	6.2 gm/dl	6.2 gm/dl	6.9 gm/dl

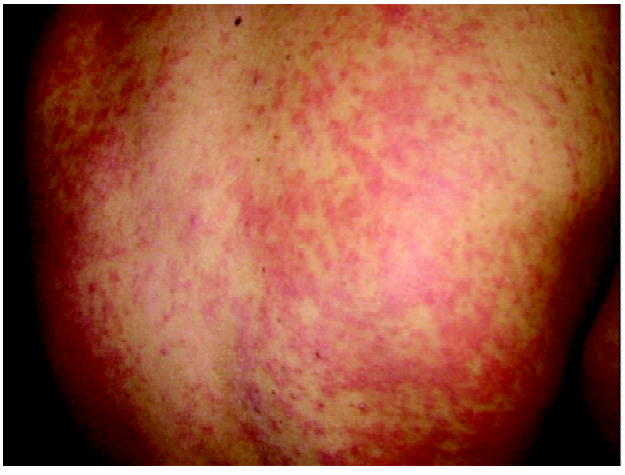
Skin biopsy showed superficial and deep dermal perivascular lymphocytic dermatitis with abundant eosinophils.

Blood culture, Widal, IgM Dengue, peripheral smear for malarial parasite, HbsAg, anti HCV, IgM anti HAV, IgM anti HEV were negative.

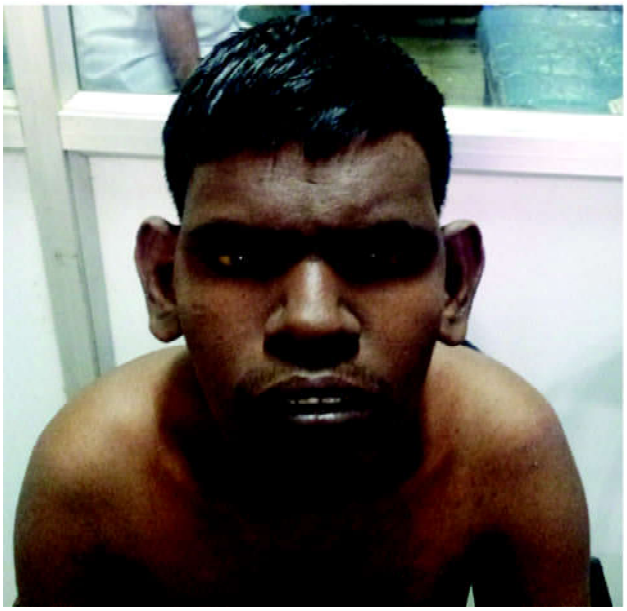
The patient's facial and labial oedema settled in 3 days; fever subsided in 5 days; patient was discharged 12 days after admission with advice to avoid tab phenytoin henceforth in future. He was prescribed tab prednisolone 30 mg OD to be tapered over weekly visits.



Day One of admission: Labial oedema.



Day 2: Erythematous maculopapular rash present over trunk.



On day of discharge (12th day of admission).

Discussion

We present this case report of a patient with characteristic features of the anticonvulsant hypersensitivity syndrome (PHS), who developed multi-system organ failure after treatment with phenytoin. In addition to the clinical picture, the time of onset of symptoms, and the absence of a septic focus, the probable response to corticosteroid therapy is compatible with the diagnosis of anti-convulsant hypersensitivity syndrome.

Anti-convulsant hypersensitivity syndrome is a rare adverse effect which typically develops within 3 weeks to three months after initiation of treatment with anti-convulsants. There is no age or sex predilection. However, the black population appears to be at increased risk for developing this syndrome. First-order relatives of patients who have experienced this reaction have also been reported to have an increased risk.

The exact incidence is unknown; however, it is estimated to occur in 2.3 - 4.5 per 10,000 patients on phenytoin, 1 - 4 per 10,000 patients on carbamazepine, and 2 - 6 per 10,000 patients on phenobarbitone. The exact mechanism of anti-convulsant hypersensitivity syndrome is not known. However, several observations suggests that it is a result of a Gell and Coombs delayed type IV hypersensitivity reaction. Aromatic anti-convulsants may act directly as antigen or indirectly as a hapten to trigger antibody production. In some patients, circulatory IgG antibodies to phenytoin have been detected. It has also been suggested that some individuals may lack the enzyme epoxide hydrolase which is needed to detoxify arene oxides. These oxides, which are very highly reactive and potentially cytotoxic, are formed as a result of oxidative metabolism of the aromatic chain. Phenobarbital and carbamazapine share the same metabolic pathway as phenytoin and consequently cross-sensitivity to these drugs is found in most patients. Studies have also shown reactivation of human herpes virus - 5, 6 and 7 to play a role. It is also thought that HLA- B1502 may also play a role.

The clinical presentation of anti-convulsant hypersensitivity syndrome varies; however, the most frequent findings are fever, skin rashes, and lymphadenopathy. A generalised macular papular eruption with follicles and pustules on the face and upper trunk is characteristic. However, generalised erythroderma, patchy erythema, and less commonly, erythema multiforme and toxic epidermolysis have been reported. Hepatitis occurs in about 75% of the patients, and is characterised by hepatomegaly and a marked increase in serum aminotransferase values. Severe hepatitis is associated with a prolonged hospital stay and a mortality of up to 50%. Additional findings that have been reported in some cases include interstitial nephritis, myopathy, Coomb's negative haemolytic anaemia, and interstitial pulmonary infiltrates. Rhabdomyolysis and acute renal failure have also been seen. Other complications which may be seen include interstitial pneumonitis, hypersensitive myocarditis, encephalitis or aseptic meningitis. Laboratory evaluation usually reveals leukocytosis with eosinophilia and atypical lymphocytosis, and a mild Coomb-negative haemolytic anaemia.

Summary of the clinical findings seen in anti-convulsant hypersensitivity syndrome.

Clinical features	Incidence (%)
Fever*	90 - 100
Rash*	87 - 90
Lymphadenopathy*	70
Hepatitis*	50 - 60
Haematological abnormalities*	23 - 50
Periorbital, orofacial oedema*	25
Myalgia, arthralgia	20
Acute kidney injury*	11
Pharyngitis	10
Pulmonary manifestations	9

**Clinical features present in our patient.*

There is no definite criteria for the diagnosis of anti-convulsant hypersensitivity syndrome. The characteristic triad of fever, rash and visceral organ involvement which occurs between 2 weeks to 8 weeks after starting the

offending drug is useful in making the diagnosis.

There is no specific therapy for anti-convulsant hypersensitivity syndrome other than immediate discontinuation of the offending anti-convulsant and supportive care. Systemic corticosteroids are required in most cases. Most case reports suggest a positive response to steroids when initiated early in the course of the disease. Of practical importance is the fact that re-exposure to the drug, or exposure to phenobarbital or carbamazepine, will result in reactivation of the syndrome with a potentially fatal outcome. If further use of an anti-convulsant drug is necessary, all aromatic anti-convulsant drugs should be avoided. Valproic acid appears safe, as do the benzodiazepines. Alternatively, one of the other nonaromatic anti-convulsant drugs may be used: ethosuximide, gabapentin, levetiracetam, tiagabine, and topiramate.

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