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CASE REPORT

ANTI-CONVULSANT HYPERSENSITIVITY SYNDROME -A RARE LIFE THREATENING ADVERSE EFFECT OF A COMMONLY PRESCRIBED DRUG

Dr. Rajesh Kumar Meena MBBS, MD, Institute of Internal Medicine Lady Harding Medical College New Delhi

Dr. Meena Rinoo Banwarilal MBBS MD Senior Resident department of skin ,ESIC Hospital Mumbai

Dr. Nidhi Garg MBBS MD Senior Resident Department of Obs & Gynecology Dr. Ram manohar lohia hospital new Delhi

ABSTRACT

Anticonvulsant hypersensitivity syndrome is a delayed adverse drug reaction associated with the use of aromatic anticonvulsant 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 hospitalization and even death. The clinical manifestations of anticonvulsant 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 judgment. 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 anticonvulsant hypersensitivity syndrome primarily includes discontinuation of the associated anticonvulsant drug. Systemic corticosteroids are usually required for full recovery. An important issue regarding anticonvulsant hypersensitivity syndrome is the cross-sensitivity among aromatic anticonvulsant 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 anticonvulsant drug.

KEY WORDS : Anti convulsant,arene oxide,aromatic ring

CASE REPORT

A 24 year old male was admitted with complaints of fever,generalized pruritic rash with all over body and swelling of both lips of 2 days duration.He had a history of head injury following a road traffic accident 1 month ago and 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 degree farenheit.He was icteric,had tender cervical, axillary,and inguinal lymph nodes.The patient had,periorbital edema and marked labial edema.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	19100 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/mm3
Haematocrit	35

Renal Function Tests

Glucose	77 mg%
urea	**52**
creatinine	**1.8**
sodium	136
potassium	5.0

Liver Function Tests

Total bilirubin	15.7 mg/dl
Direct bilirubin	6.0mg/dl
Alanine transaminase	515 IU
Aspartate transaminase	210 IU
Serum alkaline phosphatase	245 IU
albumin	4.0 gm/dl
Total protein	6.4 gm/dl

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-1600 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 Anticonvulsant 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.mg Tab Paracetamol 500 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	18800 cells/mm^3	13400 cells/mm^3	8900 cells/mm^3

Article History	Received	Accepted	Published
	06/02/2017	30/04/2017	20/05/2017

***Corresponding Author** Dr. Rajesh Kumar Meena
MBBS, MD, Institute of Internal Medicine Lady Harding Medical College New Delhi, rajesh.marga@gmail.com

Differential count	Polymorphs-47,lymphocytes-36,eosinophils-17	Polymorphs-70,lymphocytes-20,eosinophils-10	Polymorphs-90,lymphocytes-8,eosinophils-2
Erythocyte sedimentation rate	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 clood 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%	127 mg%	98 mg%
urea	60	40	28
creatinine	1.7	1.0	0.6
sodium	132	135	140
Potassium	3.7	3.8	4.9

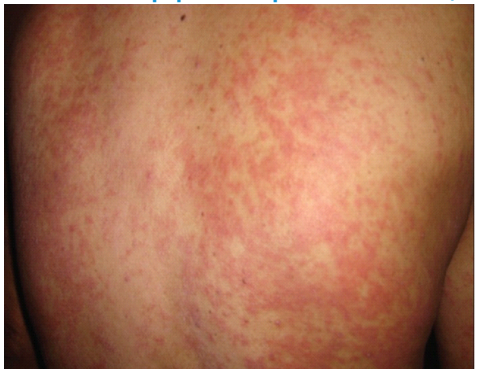
Liver function tests	DAY 3	DAY 7	DAY 12(at discharge)
Total bilirubin	10.3 mg/dl	8.7 mg/dl	8.5 mg/dl
Direct bilirubin	5.7mg/dl	4.2mg/dl	3.8.0mg/dl
Alanine transaminase	439 IU	218 IU	98IU
Aspartate transaminase	208 IU	112 IU	103 IU
Serum alkaline phosphatase	212 IU	227 IU	280 IU
albumin	4.0 gm/dl	3.4 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.

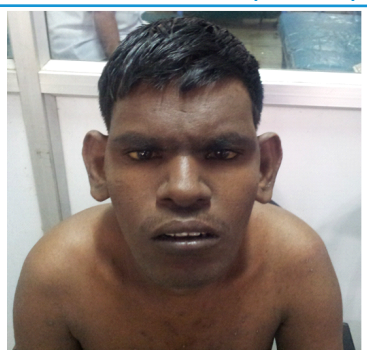
Blood culture,widal,IgM dengue,peripheral smear for malarial parasite,HbsAg,Anti HCV,IgM anti HAV, IgM anti HEV were negative Patients facial and labial edema settled in 3 days,fever subsided in 5 days,patient was discharged 12 days after admission with advice to avoid Tab Phenytoin henceforth in the future He was prescribed Tab Prednisolone 30 mg OD to be tapered over weekly visits.

Patient on day 1 of admission. (note the labial edema)

Erythematous maculopapular rash present over trunk (day 2)



Patient during discharge (12th day of admission)



DISCUSSION

We present a 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 anticonvulsant hypersensitivity syndrome.

Anticonvulsant hypersensitivity syndrome is a rare adverse effect which typically develops within 3 weeks to three months after initiation of treatment with anticonvulsants. 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 10000 patients on carbamazepine and 2-6 per 10,000 patients on phenobarbitone .The exact mechanism of anticonvulsant 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 anticonvulsants 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 anticonvulsant hypersensitivity syndrome varies, however the most frequent finding are fever,skin rashes and lymphadenopathy. A generalized macular papular eruption with follicles and pustules on the face and upper trunk is characteristic However generalized erythroderma, patchy erythema, and less commonly, erythema multiforme and toxic epidermolysis have been reported Hepatitis occurs in about 75% of the patients, and is characterized 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 hemolytic anemia and interstitial pulmonary infiltrates . Rhabdomyolysis and acute renal failure have also.Other complications which may be seen include interstitial pneumonitis, hypersensitive myocarditis,encephalitis or aseptic meningitis. Laboratory evaluation has usually reveals leukocytosis with eosinophilia and atypical lymphocytosis, and a mild Coomb-negative hemolytic anemia.

Summary of the clinical findings seen in anticonvulsant hypersensitivity syndrome

CLINICAL FEATURES	INCIDENCE (%)
Fever*	90-100
Rash*	87-90
Lymphadenopathy*	70
Hepatitis*	50-60
Haematological abnormalities*	23-50
Periorbital,orofacial edema*	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 anticonvulsant 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 anticonvulsant hypersensitivity syndrome other than immediate discontinuation of the offending anticonvulsant 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 anticonvulsant drug is necessary, all aromatic anticonvulsant drugs should be avoided Valproic acid appears safe, as do the benzodiazepines. Alternatively, one of the other nonaromatic anticonvulsant drugs may be used: ethosuximide, gabapentin, levetiracetam, tiagabine and topiramate.

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