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## Case Report

### CARBAMAZEPINE INDUCED HYPERSENSITIVITY SYNDROME- A CASE REPORT

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#### ABSTRACT

Anti-convulsant drugs elicited hypersensitivity syndrome could be a rare side effect of the primary line anticonvulsive medication like carbamazepine and alternative aromatic agents. We here mention a rare case of gastrointestinal and skin findings associated with carbamazepine administration that is incredibly uncommon and deserves to be reportable.

We report a study done on a 22-year woman with carbamazepine associated hypersensitivity syndrome, who developed diarrhea, fever and skin lesions. On withdrawal of carbamazepine and administration of methylprednisolone in the patient, all initial skin related symptoms, GIT symptoms were relieved and white blood corpuscle count normalized. Anticonvulsive drug hypersensitivity syndromes can present with a wide spectrum of unspecific symptoms, which the prescribing clinician should be aware of.

**KEYWORDS:** Anti convulsant drugs, Carbamazepine, Hypersensitivity.

#### INTRODUCTION

Carbamazepine (CBZ) is one among the routinely administered medication for the treatment of simple and complex epileptic seizures, neuralgia and alcohol withdrawal syndrome. The drug has anticonvulsive and anticholinergic properties by reducing excessive nerve signals within the brain and restoring the conventional balance of nerve activity. Side effects include diarrhea, inflammatory bowel disease, aplastic anemia and blood disease additionally different rare conditions like cardio toxicity.<sup>[1, 2]</sup>

Hypersensitivity reactions are basic unfavorable medication responses (ADR's) identified with hostile to anti epileptics<sup>[3]</sup>. Cutaneous unfavorable responses to medicine happen in up to eight percent of the world overall public and in 2-3% of hospitalized patients. Aromatic anticonvulsants (phenytoin, phenobarbitone and carbamazepine) are the pre-eminent regularly involved drugs for cutaneous ADR's. Cutaneous emissions happen in one third of

individuals who accept carbamazepine and it includes diffuse erythroderma, exanthematous rash, urticaria, purpuric petechiae, or a connective tissue syndrome any of which may happen from day eight to day sixteen when medicine has initiated<sup>[4]</sup>. Different medical science adverse effects of carbamazepine embrace drug hypersensitivity, exfoliative skin disease, erythema, and harmful dermal lysis. Development of rash is likewise partner in early cautioning of bone marrow toxicity. Abnormal liver perform and bone marrow suppression with deaths owing to anemia have in addition been reportable with carbamazepine<sup>[5]</sup>. Extraordinary responses of anti convulsant drugs incorporate myositis, lupus erythematosus-like syndrome, pustules, psoriasis, lichenoid responses and Anticonvulsant hypersensitivity syndrome (ACHS)<sup>[4]</sup>.

ACHS was initially portrayed in 1950 yet disarray still proliferates in regards to the syndrome. The triad of fever, rash and inside

organ association happening 1-8 weeks after introduction to anticonvulsant drugs heralds this rare (1 in 1,000 to 10,000 exposures) however a serious reaction<sup>[4]</sup>. Fever, in conjunction with discomfort and pharyngitis, is frequently the first sign. This is followed by a rash which may vary from easy eruption (mild form) to lethal epidermal necrolysis (severe form). Inward organ association generally includes the liver, albeit different organs, for example, the kidney, CNS or lungs may also be involved <sup>[4]</sup>.

We report an interesting case of ACHS-drug hypersensitivity reaction affected via carbamazepine given to female patient with epilepsy. The notable characteristics of the presentation, judgment and administration of this condition are talked about beneath.

#### CASE STUDY

- 22 years, old female, was admitted into tertiary care centre unit with history of seizures.

**Presenting complaints:** Mrs.GD had been complaining of black color rashes all over the body since 10 days. She complained that ten days after intake of anti epileptic medicines, she developed a reddish maculo-papulous rash with pruritus affecting her entire body simultaneously she developed fever and watery diarrhea. She also developed mild lesions in oral mucosa which spread to the face, upper extremities, trunk and ultimately all over the body.

**Previous medical history:** Mrs. GD's medical history included epilepsy. She was operated for brain tumor in year 2007. Brain tumor was diagnosed when she experienced seizure in 2007. She was experiencing tremors and jerks from past one month before hospital admission. The patient had two uncomplicated vaginal deliveries, no smoking history and alcohol consumption. Her family history was clear.

**Drug history:** Mrs. GD was taking: tab. sodium valproate 200mg twice daily, tab. carbamazepine 200mg twice daily from one month for jerks that she was experiencing from one month.

#### Physical examination

**O/E:** She was moderately built. She was conscious and coherent. Mrs. GD was found to be an epileptic individual with a pulse rate of 35 to 50

beats per minute. Neurological workup included EEG, CT scan of the brain, MRT but no intracranial pathology could be demonstrated. Her EEG showed abnormality indicative of seizures. Blood and CSF chemistry were unremarkable and serum as well as CSF tested negative for bacterial, viral, fungal or parasitic pathogens.

#### Other results were

**On General examination:** Slight pedal edema was seen in-patient with Pallor positive.

#### Vital signs

- Blood pressure: 110/70mmHg
- Respiratory rate: 14 breaths per minute
- Pulse rate: 90 beats/minute
- CNS examination: plantar ↓↓

Laboratory findings showed an increased white blood cell count with relative eosinophilia (8% of total leukocytes), increased neutrophils (78%), decreased RBC count (3.25m/cmm), decreased hemoglobin (9 gm/dl), decreased serum albumin (3.7%) and elevated transaminases (AST of 40 U/L, ALT of 39 U/L). C-reactive protein (CRP) level was 2.2 mg/dL. Serum creatinine and serum potassium level was found to be normal. Pus cells, blood cells and urine albumin 4+ were seen on urine examination. Chest x-ray and abdomen ultrasound was unremarkable. Stool cultures were negative for enteric pathogens and no occult blood could be detected.

#### DIAGNOSIS

It was suspected that the patient suffered from epilepsy and abdominal pain was thought to represent an epigastria aura. Rashes on her body were confirmed as exfoliative eczema that was suspected as drug iatrogenic. Severity of the lesion was more additional toward drug hypersensitivity. The condition of the patient worsened after 2 days and was referred to dermatology department in a tertiary care hospital. On body covering examination, multiple hyper-pigmented lesions and a few target lesions were found everywhere on the body and her oral tissue layer was found to be with mild lesions (Fig 1 and Fig 2). She was diagnosed as having maculopapular eruptions owing to carbamazepine. The amount of SGPT was borderline high suggesting of liver involvement.

Albumin, blood cells, pus cells were indicative of Kidney involvement.

### Treatment plan

The decision was to stop offending medication immediately and administered following medications.

- Methyl Prednisolone- 10mg TID PO,
- Tab. Mizolastine-BT
- Tab. Pheniramine-25mg BD
- Tab. Ascorbic acid-500mg OD
- Injection Ranitidine i.v. Two times a day
- Tab. Phenobarbital-30mg (mrg) + 60mg (nyt) BD
- Calamine + aloe vera gel + liquid paraffinlotion BT
- Petro gel-for local application in the morning.

The Pharmacist was contacted to discuss about hypersensitivity induced by anticonvulsant drugs. Later CBZ was replaced with phenobarbitone and sodium valproate.

Following withdrawal of CBZ and provision of corticosteroids i.v. (methylprednisolone at a dose of 10 mg every day for one week) and antihistamines, the patient condition quickly improved, loose bowels halted. After 4 days of treatment, sores subsided without any sequelae and liver enzymes returned to normal.

### DISCUSSION

ACHS can exhibit with a wide range of manifestations, for example, skin sores, fever, and lymphadenopathy in combination with pathologic laboratory findings like leucocytosis/leucopenia and elevated liver enzymes. It has been depicted after introduction to, aromatic drugs such as CBZ, phenytoin and Phenobarbital<sup>[6]</sup>.

Our patient presented with classic symptoms of ACHS which included black color rash all over the body, fever and diarrhea and elevated liver enzymes ten days after initiation of CBZ therapy. Symptoms of patient worsened and required hospitalization. She had no history of medication related reactions, gastrointestinal, dermatological or cardiovascular issue and no obvious intense disease making ACDHS a possible conclusion. In our study, patient had liver and kidney involvement suggested by elevated SGPT and proteinuria.

Onset of ACHS might develop one week to a few months after CBZ administration<sup>[7]</sup>, the term "drug rash with symptom and general symptoms" (DRESS) has been awhile ago utilized. The precise mechanism of ACHS remains to be determined however is thought to be connected with enzymatic insufficiency or variation in the metabolism of anticonvulsants, and ethnic inclination with certain human leukocyte antigen subtypes<sup>[6]</sup>.

The aromatic anticonvulsants (phenytoin, phenobarbital, and carbamazepine) are metabolized to hydroxylated aromatic compounds for example, arene oxides. If detoxification of this dangerous metabolite is deficient; the poisonous metabolite may tie to cell macromolecules bringing on cell necrosis or an auxiliary immunological reaction. Cross-reactivity among the aromatic anticonvulsants may be as high as 75%. Moreover, there is a familial propensity to hypersensitivity to anticonvulsants. Inside organ association influencing liver, lungs, lymphatic framework and kidneys may prompt confusion of the side effects<sup>[4]</sup>.

CBZ is well known to cause neutropenia and pancytopenia. Up to 1-2 cases for every year for every 100,000 subjects may create agranulocytosis as the most noticeably awful inconvenience complication<sup>[8]</sup>. People with "moderate liver metabolism" may be at exaggerated risk to develop "drug elicited hypersensitivity syndrome" because of the processing of harmful metabolites in the liver considerably even after CBZ has been totally cleared; CBZ hypersensitivity syndrome has additionally been coupled to acute liver failure.

Enterocolitis may be brought about by different antiepileptic drugs. Diagnosis of enteric indication of ACHS is focused around a nearby transient relationship between medication exposure and development of loose bowels and additionally improvement once withdrawal of the inflicting drug like in our case.<sup>[9,10]</sup>

Advancement of a rash throughout medication warrants withdrawal of the drug and if no option exists, desensitization might be considered<sup>[11]</sup>. Our patient started response within 7-10 days of initiating carbamazepine medication and which subsided within 5 days of cessation of medicine. Other medication that

generally can be included in ACHS are antihistamines (H1-receptor blockers), epinephrine, glucocorticoids, anabolic steroids and airway management depending upon the seriousness of the condition [12].

In our case, patient received steroids and antihistamines and she was improved with given antihistamine and steroid medicine. Methylprednisolone was used in this patient that resulted in associate improvement of initial symptoms and standardization of the previously elevated white blood cell count.

The role of glucocorticoids in the medicine of ACHS has been dubiously talked about [13]. Glucocorticoids diminish the levels of IL-5, which that is one in all the key growth factors for eosinophilic granulocytes (particularly in Eosinophilic conditions)[6].

We likewise found comparable case reports of angioedema and maculopapular eruptions connected with carbamazepine by Elias *et al.*, [11] a case of drug iatrogenic hypersensitivity syndrome because of carbamazepine by Morimoto *et al.*[14]. The vicinity of the HLA-A\*3101 allele was connected with carbamazepine-induced hypersensitivity responses among subjects of Northern European lineage. The vicinity of the allele redoubled the danger of hypersensitivity reactions from 5.0% to 26.0%[15]. Because of absence of pharmacogenetic research facility setup, we couldn't genotype our patient for the HLA-A\*3101.

In our case, because of promptly consideration of the patient in the hospital, culpable drug was ceased and patient was kept from going into the extreme phase of the response with internal organ involvement. As maculopapular rash is a first indication of bone marrow depression seen with aromatic anticonvulsants, doctors ought to must be vigilant in regards to this sort of response happening.

#### CONSENT

Written consent was obtained from the patient for publication of this case report and related pictures.

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**PHOTOGRAPHS**



**Fig 1: Exfoliative dermatitis on legs seen in the patient after administration of Carbamazepine**



**Fig 2: Rashes on hands of the patient after administration of Carbamazepine**