CASE REPORT

Combination of Steven-Johnson syndrome and neuroleptic malignant syndrome following carbamazepine therapy: a rare occurrence

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SUMMARY

Stevens–Johnson syndrome (SJS) is a severe, episodic, acute mucocutaneous reaction that is most often elicited by drugs and occasionally by infections. The drugs commonly implicated as the cause of SJS are anticonvulsants, sulfonamides, non-steroidal anti-inflammatory drugs and antibiotics. Carbamazepine (CBZ) has been commonly implicated in SJS. Neuroleptic malignant syndrome (NMS) is a rare, life-threatening but potentially treatable condition. Among the neuroleptics, haloperidol (parenteral) is implicated as a most common drug for NMS. Though rare, association of NMS with CBZ and association of NMS with toxic epidermal necrolysis (TEN) in a single patient after administration of neuroleptics has been reported in the literature before. However, a combination of NMS and SJS in a single patient after administration of CBZ has not been reported so far. We present a patient with seizure who developed SJS and NMS following administration of CBZ.

BACKGROUND

Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TENS) and neuroleptic malignant syndrome (NMS) are rare yet life-threatening conditions and often occurs as reactions to drugs. Carbamazepine (CBZ) and other anticonvulsants, sulfonamides been commonly implicated for SJS and neuroleptics for NMS. But both conditions though rare can occur in a single patient following administration of these common drugs either alone or in combination. Knowledge of this rare occurrence will help clinician to identify this serious yet potentially treatable condition.

CASE PRESENTATION

A 15-year-old boy presented to us following two episodes of generalised tonic-clonic seizures. He had history of infrequent seizures for 5 years with seizure frequency of 2–3 per year and was not on any antiepileptic drugs (AEDs). At the time of presentation the patient was conscious, oriented, without fever with stable vitals. There were no focal neurological deficits on clinical examination and meningeal signs were absent. His CT head and EEG was normal.

Oral CBZ was started at the dose of 100 mg twice daily and escalated over next 3 days at the rate of 100 mg/day. There were no seizures during hospital stay. Within 3 days after initiation of CBZ, the patient developed fever, oral ulcerations and

maculopapular rashes all over the body. Within next 12 h he developed altered sensorium, profuse sweating and fluctuation in his blood pressure and heart rate. On examination he had nuchal rigidity as well as rigidity in all the four limbs (figure 1). Over next 8–10 h there was peeling of skin over chest and forearm (figure 2). Possibility of CBZ-induced SJS was considered and later confirmed by dermatological opinion.

INVESTIGATIONS

His blood haemogram showed leucocytosis, and serum biochemistry showed hypocalcaemia. His creatine kinase (CK) was elevated (6000 IU/L), C reactive protein was positive and serum iron was low. In view of fever, autonomic instability, encephalopathy and rigidity with elevated CK, diagnosis of NMS was made as per Caroff and Manns criteria. His MRI brain with contrast as well as cerebrospinal fluid (CSF) analysis was normal.

DIFFERENTIAL DIAGNOSIS

1. Meningitis/encephalitis: prodromal viral illnesses, headaches, seizures, meningeal signs, focal neurological deficits, CSF studies and neuroimaging may suggest an infectious aetiology.
2. Heat stroke: history of exposure to heat and signs of dehydration will be present.
3. Lethal catatonia:
 - ▶ Evidence of preexisting psychosis (bipolar disorder) and schizophrenia.
 - ▶ Rigidity, diaphoresis, delirium with alternating excitement and stupor.

Figure 1 Rigid lower limbs showing erythematous maculopapular rashes.

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Figure 2 Peeling of skin over chest suggestive of Steven-Johnson syndrome.

- ▶ Withdrawal of offending agents and electroconvulsive therapy is a safe and effective treatment.
- 4. Anticholinergic toxicity: hot, dry skin, pupillary dilatation, tachycardia, urinary retention, confusion and hallucinations.
- 5. Malignant hyperthermia:
 - ▶ Rapid onset, severe muscular rigidity, ischaemia, hypotension.
 - ▶ Elevated CK, potassium, magnesium; disseminated intravascular coagulation; acidosis; rhabdomyolysis.
 - ▶ Dantrolene sodium is used as an antidote for the treatment.
- 6. Serotonin syndrome:
 - ▶ Typically rapid onset with hyper-reflexia, tremors, myoclonus, diaphoresis, confusion, agitation or shivering.
 - ▶ Removal of the offending agents and supportive therapy are the main stay, though cyproheptadine is considered as possible therapy.

TREATMENT

He was shifted to intensive care unit. The offending agent, CBZ was withdrawn immediately. He was treated with supportive measures and adequate hydration with intravenous fluids.

Specific treatment like bromocriptine was started at the dose of 2.5 mg every 6 h. CBZ was replaced with levetiracetam for seizure management. Antihistaminics and topical steroids were used in the treatment of SJS, along with intravenous antibiotics. However, systemic steroids were not used. The patient gradually improved over the next week. He recovered without any further episodes of fever and his CK returned to normal.

OUTCOME AND FOLLOW-UP

The patient recovered completely and discharged in stable condition. The patient was seizure free 3 months after the follow-up.

DISCUSSION

SJS is a clinical syndrome presumed to be a hypersensitivity reaction manifested by prodromal symptoms of fever, malaise and a sore throat followed by acute polymorphous dermatological syndrome manifested as erythematous, maculo-papular lesions.¹ SJS has long been considered to resemble erythema multiforme (EM) with mucosal involvement, but is now thought to form a single-disease entity with TEN. Although SJS is less severe, aetiology, genetic susceptibility and pathomechanism are the same for Stevens-Johnson syndrome/toxic epidermal necrolysis.²

TEN/SJS are a group of severe life-threatening drug reactions that are most often elicited by drugs and occasionally by infections and now considered to be differing only in the extent of body surface area involved.³ The drugs commonly implicated as the cause of SJS/TEN are anticonvulsants, sulfonamides, non-steroidal anti-inflammatory drugs and antibiotics.⁴ In a study performed by Devi *et al*,⁵ the commonest drug implicated as the cause of SJS/TEN was CBZ. The mechanism of SJS disease is not completely understood, but immunological mechanisms, cytotoxic reactions and delayed hypersensitivity been proposed.⁶ Direct interaction between human leukocyte antigen (HLA)-B and CBZ activates T cells in patients with SJS.⁷

A strong genetic association between HLA-B*1502 and CBZ-induced SJS and TEN has been shown in Asian populations. Independent studies from different countries confirmed that patients carrying the HLA-B*1502 are at high risk of SJS/TEN when exposed to CBZ. HLA-B*1502 is a risk allele for SJS/TEN caused by other aromatic automated external defibrillator AEDs with a similar structure to CBZ. Screening for HLA-B*1502 allele before starting treatment with CBZ is justified in patients from high-risk populations.⁸ However, genetic test for HLA-B*1502 was not performed in our patient prior to the initiation of CBZ due to the lack of resources. Management of SJS includes removal of offending agent and supportive measures including wound care, antihistaminics and topical steroids. Specific therapy includes systemic steroids and immunoglobulins though debatable.⁹

Whereas NMS is recognised as a hypodopaminergic state characterised by muscle rigidity, hyperthermia, altered sensorium, autonomic instability and elevated serum CK levels. It is a serious and potentially fatal adverse effect of neuroleptic medications and considered as idiosyncratic reaction to drugs.^{10 11} Though dopamine receptor blockade been postulated as mechanism responsible for NMS features owing to antidopaminergic drugs till date,¹² Anglin *et al*¹³ proposed a neuroimmunological hypothesis for NMS. NMS is associated with a profound and precipitous decrease in serum iron levels, which is a key feature of the immunological cascade known as the acute phase response.^{13 14} Mechanisms for the induction of the acute phase response in NMS include autoantibody production, virus-drug interaction, heat stress, muscle breakdown and psychological stress.¹³ There is strong evidence that iron is essential for the normal functioning of the dopamine D₂ receptor.¹⁵ Hence, the reduction in serum iron levels that occurs in the acute phase response may result in a decreased number of functional dopamine D₂ receptors in the brain.¹³ One should be aware of clinical conditions that can mimic NMS, and are listed in the section of differential diagnosis.^{10 11 16–19}

Treatment involves cessation of antipsychotic medications and supportive care, including rehydration, cooling, antipyretics and benzodiazepines.¹³ Regarding specific treatment dantrolene sodium and bromocriptine and in refractory cases—electroconvulsive therapy have been tried, in addition to withdrawal of the offending drug. Emphasis should also be laid on avoiding dehydration.¹⁰ Patients with a history of NMS are likely to require future antipsychotic treatment. If alternatives are poor and the benefit outweighs the risk, antipsychotics should be restarted after a 4-week gap following the resolution of the episode. Beginning with a low dose, advancement should be slow towards the target dose and atypical or a low potency agents with lower D₂ affinity (risperidone, clozapine, olanzapine, quetiapine), should be preferred.¹⁶

NMS cases associated with drugs been reported usually following exposure to typical antipsychotic medications

particularly phenothiazines and butyrophenones.^{10 11 17} However, atypical neuroleptics (eg, clozapine and risperidone), antiemetics (metaclopramide, promethazine) as well as other drugs like lithium, amitriptyline have also been reported to be associated with NMS.^{18 20} Association of NMS with CBZ is rare. Thomas *et al*²¹ rather reported two cases where NMS dramatically improved with CBZ.

Woo Benjamin *et al*²² reported a atypical case of NMS caused by olanzapine and CBZ. Nisijima *et al*²³ reported a case of NMS occurring after addition of CBZ to long-term neuroleptics. Bruce Janati *et al*¹⁹ reported a case of NMS while receiving CBZ with amitriptyline (TCA) and it was postulated that CBZ is a potentially dopaminergic drug and addition of TCA to CBZ decreased the serum level of CBZ presumably through cytochrome 3A4 induction, resulting in a state of relative dopamine deficiency. Dalkin and Lee *et al*²⁴ reported a case of forme fruste NMS after taking overdose of trifluoperazine with CBZ and postulated that CBZ might modify the presentation of NMS. But all the above cases of NMS with CBZ had association with other drugs. Pure case of NMS with CBZ alone is extremely rare. O'Griofa *et al*²⁵ reported a case of NMS after treatment with CBZ, where symptoms resolved after CBZ therapy was stopped. Similarly our patient also had all the features of NMS after CBZ therapy without association of any other offending drugs like neuroleptics.

Simultaneous occurrence of SJS and NMS has not been reported; however, TEN which can be considered as spectrum of SJS has been reported with NMS in a single patient. Muhammed *et al*²⁶ reported a case of 18-year-old presenting with simultaneous appearance of TEN and NMS following antipsychotic drugs given for bipolar mood disorder with recovery. Even our patient had simultaneous occurrence of SJS and NMS but following CBZ therapy, which has not been reported so far in the literature to the best of our knowledge.

To conclude SJS following CBZ therapy is common but NMS after CBZ therapy is very rare and often reported with combination therapy; however, NMS following CBZ alone is extremely rare. SJS with NMS following CBZ treatment alone in our case further adds to its rarity. Immune hypothesis has been postulated in SJS as well as NMS, and acute phase reactants with autoantibody production in NMS. So we like to hypothesise that CBZ may have triggered immune reaction as well as acute phase reactants which mediated both SJS and NMS.

Learning points

- Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TENS) and neuroleptic malignant syndrome (NMS) both are medical emergency with high mortality and one should withdraw the offending agent at the earliest.
- SJS/TENS after carbamazepine (CBZ) therapy is common but, NMS after CBZ therapy is very rare and often reported with combination therapy.
- One should have a high index of suspicion when the patient develops NMS following CBZ therapy either alone or in combination, particularly with neuroleptics.
- CBZ may trigger immune reaction as well as acute phase reactants which mediates both SJS and NMS.

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