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Case Report

A probable case of sodium valproate monotherapy induced drug reaction with eosinophilia and systemic symptoms syndrome: a case report in Indian population

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a drug-induced hypersensitivity syndrome most commonly caused by anti-epileptics like carbamazepine, phenytoin. It usually manifests as maculopapular rash, fever, eosinophilia, generalized lymphadenopathy, hepatitis, atypical lymphocytosis, and leucocytosis with the involvement of other organs. Valproate, a broad-spectrum antiepileptic, also used in bipolar disorders and migraine prophylaxis, is generally well tolerated. To date, very few cases of valproate monotherapy induced DRESS syndrome have been reported worldwide and here we are reporting one such rare case in a 72 years old Indian woman with a history of generalised tonic convulsions. The patient was classified as a 'probable' case of DRESS syndrome using the WHO-UMC criteria and Naranjo scale. Discontinuation of the offending medication and treatment with intravenous (IV) fluids, antihistamines, and steroids helped in recovery of the patient. Healthcare practitioners must be aware of valproate monotherapy induced DRESS syndrome and take effective measures to avoid severe side effects.

Keywords: Valproate, DRESS, Adverse drug reaction, Anti-epileptic drugs

INTRODUCTION

The syndrome of drug reaction with eosinophilia and systemic symptoms (DRESS) also known as drug-induced hypersensitivity syndrome (DIHS), is a potentially lethal type of severe cutaneous adverse reactions (SCARs) with an incidence of 1 in 1000 to 1 in 10,000 drug exposures and a mortality rate of around 10 to 20%.¹⁻⁴ It is characterized by generalized acute maculopapular eruptions with high-grade fever and multi-visceral involvement.¹ Generally, there is a late onset of symptoms (3 weeks to 3 months) after the start of the offending drug which may persist or worsen despite the

withdrawal of the offending drug.³ The most common offending drugs are anti-epileptic drugs (AEDs) (carbamazepine, phenytoin, phenobarbitone, lamotrigine, zonisamide, oxcarbazepine), allopurinol, sulphonamide, dapsone, minocycline, nevirapine.⁴ Non-aromatic AEDs such as valproate, gabapentin, vigabatrin, levetiracetam were traditionally thought to be safer.⁵ DRESS syndrome is diagnosed by RSCAR (the registry of severe cutaneous adverse drug reactions) criteria which encompass the following: an acute rash, lymphadenopathy at two sites, fever above 38°C, the involvement of at least one internal organ and abnormality of lymphocyte and eosinophil counts.⁶⁻⁸ Valproate which is one of the frontline antiseizure drug used in multiple types of seizures and the

side effects of valproate are many and well known which includes gastrointestinal upset, sedation, ataxia, and tremor.² However, serious adverse reactions such as DRESS, hepatotoxicity, encephalopathy, coagulation disorders, pancreatitis, and bone marrow suppression are rare.⁵ As there are few case reports in Indian literature to evaluate the causality of a rare case of valproate induced DRESS syndrome and hence the present report throws light on the importance of recognizing the possibility of SCARs associated with valproate.

CASE REPORT

Valproate induced DRESS syndrome was seen in a 72 years old female, who had a history of generalized tonic convulsion two months back and she was prescribed sodium valproate 500 mg twice a day. After one month she had developed a generalized skin rash, scaling of skin over the scalp, face, trunk, and both upper and lower limbs, crusting, facial edema, high-grade fever which was on and off, more in the night and associated with chills and rigor, for which she got admitted in a tertiary care hospital in Bangalore, after 3 days of illness. On general examination, the patient's vitals were stable, with blood pressure 100/70 mmHg and pulse rate 68 bpm. Laboratory findings were leucocytosis (11,070 cells/mm³), eosinophilia (E=43.4%, AEC=4800 cells), elevation of liver enzymes (SGOT=354 IU/l, SGPT=287 IU/l). Other investigations like dengue profile, malarial parasite, widal, platelet count, urine culture, random blood sugar, renal function tests were negative or within normal limits. Based on the RegiSCAR scoring system the patient had a score of 5 points, which indicated a probable case of valproate induced DRESS syndrome. The offending drug (valproate) was discontinued and levetiracetam 500 mg twice a day was substituted. Subsequently, the patient was managed with IV fluids, antihistamines, and parenteral betamethasone once daily for 5 days and it was replaced by tapering doses of oral prednisolone 10 mg, 5 mg once daily for two weeks. Symptoms resolved and laboratory parameters returned to normal levels after 8 days. No new episode of seizure was reported and she showed complete recovery at the time of discharge (10 days).

DISCUSSION

DRESS syndrome is a hypersensitivity reaction to drugs, with a delayed onset. In our case it was one month after taking the offending drug, similar to other reports and it also produces fatal organ failures (especially liver and lungs) leading to a higher rate of mortality.^{1,2} Aromatic anticonvulsants like carbamazepine, phenytoin, and lamotrigine have been the culprit drugs.^{1,2} Though non-aromatic AEDs like valproate were thought to be safer; there is 70% cross-reactivity between aromatic AEDs and non-aromatic AEDs.⁹

Various mechanisms postulated include the presence of circulating antibodies or toxic metabolites and

reactivation of HHV 6 infection.⁴ It is suggested that aromatic AEDs produce DRESS since they are metabolized by CYP450 to an arene oxide metabolite which is detoxified by epoxide hydrolase enzyme, which may be deficient/mutated genetically in some individuals.⁴ In our case, the safer, non-aromatic AED, valproate (branched-chain fatty acid) is mainly metabolized by oxidation (CYP2C9, 2C19) and by hepatic glucuronidation has initiated DRESS and the exact mechanism is unclear, though genetic predisposition may play a role in this SCAR.¹⁻⁵

Criteria for the diagnosis have been given by the Japanese study group of severe cutaneous adverse reactions to drugs (SCAR-J) and the European group, RegiSCAR.⁶⁻⁸ In our case, probable features of valproate induced DRESS were present (score of 5 on RegiSCAR) (Table 1).⁶⁻⁸ Valproate was stopped and levetiracetam, systemic steroids were prescribed. Though systemic corticosteroids are warranted only in the severe form of DRESS, most physicians prescribe it even in mild forms of DRESS, because of the higher propensity of relapse, similar to a study done by Brentano et al.¹⁰ Identical to our case, a 73 years old male with valproate induced DRESS, was managed by the withdrawal of the offending drug and replacing it with levetiracetam and successfully treated with pulse methylprednisolone followed by oral prednisone.¹ Similar line of management was also followed in a 12 years old boy with valproate induced DRESS.¹¹ Even intravenous immunoglobulin, cyclosporine has been tried in severe cases.^{1,2}

Table 1: RegiSCAR scoring*.

Clinical and laboratory criteria	RegiSCAR scoring
Fever >38.5° C	0 (yes)
Enlarged lymph nodes	0
Eosinophilia	2
Atypical lymphocytes	0
Skin rash >50% of BSA	1
Skin rash suggesting DRESS	1
Biopsy suggesting DRESS	0 (unknown)
Organ involvement	1 (liver)
Resolution >15 days	0
ANA, blood culture, serology for HAV/HBV/HCV, chlamydia, mycoplasma	0 (No)
Total	5
RSCAR	Probable

*BSA: body surface area, ANA: anti-nuclear antibody, HAV: hepatitis A virus, HBV: hepatitis B virus, HCV: hepatitis C virus, Final score <2- no case, 2-3- possible case, 4-5- probable case, and >5- definite case.

The causality assessment for the adverse drug reaction (ADR) according to the Naranjo scale which is a 10 items questionnaire, the score was 5, and so it was classified as a 'probable' case of valproate induced DRESS, so also

based on WHO-UMC criteria.^{12,13} Severity assessment as per modified Hartwig and Siegel scale, where ADRs are classified into seven levels based on the severity and our case falls into level 4b- moderate severity.¹⁴ As per modified Schumock and Thornton scale, (9 items questionnaire) it was 'probably preventable' (Table 2).¹⁵

Table 2: ADR assessment.

Scales	ADR assessment
WHO-UMC causality	Probable
Naranjo's probability	Probable
Modified Hartwig and Siegel severity	Moderate
Modified Schumock Thornton preventability	Probably preventable

There are few case reports of DRESS with multiorgan dysfunction due to the combination of valproate with lamotrigine or carbamazepine, not as valproate monotherapy. DRESS syndrome due to concomitant administration of valproate and lamotrigine/carbamazepine was described by Nakhi et al and Lorido et al respectively.^{16,17} The possible explanation could be multiple drug hypersensitivity as proposed by Pichler et al due to substitution therapy of valproate (as a second drug) with other aromatic AEDs causing activation of the immune system, thereby leading on to DRESS.¹⁸ This fact is endorsed by a case of a 25 years old woman with bipolar disorder who experienced valproate induced DRESS one month after lamotrigine withdrawal due to nonspecific rash.¹

A small number of cases of DRESS syndrome were reported, when valproate was combined with other drugs apart from AEDs and in the presence of other comorbidities. According to an Indian study, DRESS syndrome was encountered in a 39 years old male diagnosed with a recurrent depressive disorder who was under treatment with escitalopram and sodium valproate.³ Another case of DRESS was reported in a 20 years old Brazilian female who took valproate and haloperidol.¹⁹ An adolescent with symptoms of mania, developed DRESS syndrome when valproate was combined with olanzapine.²⁰ A 60 years old Iranian male developed DRESS syndrome with prophylactic valproate (1000 mg/day) therapy, after subarachnoid haemorrhage and concomitant insulin therapy for diabetes.² A 19 years old female, a case of brucellosis, who was under treatment with valproate (chorea), doxycycline capsules and streptomycin as polytherapy developed DRESS.²¹ In this case probably the leading cause might be brucellosis, though not known. A 73 years old Chinese male, a case of atrial fibrillation, on treatment with warfarin suffered DRESS with other complications like hyponatremia, thrombocytopenia, hypoalbuminemia, high aminotransferase when he was put on 1000 mg/day valproate for seizures.¹ DRESS with acute liver failure was reported in a 26 years old man with valproate, clemastine, baclofen, and acetaminophen.²² Though our report was a

rare case of valproate monotherapy induced DRESS syndrome without any precipitating/concomitant factors/drug combinations in an adult female, future studies should direct towards identifying the risk factors for DRESS, which may be due to valproate monotherapy or polytherapy or existing comorbidities.

Therefore, it was a probable case of valproate monotherapy induced DRESS syndrome with moderate severity and probably preventable. The health care professionals (HCPs) need to keep in mind about the risk of DRESS syndrome even with non-aromatic AED like valproate as a monotherapy, (no concomitant illness/multidrug) as well as the cross-reactivity between aromatic anticonvulsants and valproate. Switching the patient to different safer drugs like levetiracetam and treating with systemic corticosteroids may prove to be useful, similar to our case.

CONCLUSION

To the best of our knowledge, very few cases of valproate monotherapy induced DRESS was reported in Indian population. Valproate being the frontline AED, proper subject/public instructions, by the HCPs regarding the offending drugs that cause hypersensitivity reactions like DRESS, prompt early reporting, and recognition of this cutaneous ADRs with timely initiation of therapy could prevent or minimize the involvement of other organs/mortality and also aid in pharmacovigilance activities, so as to propose future guidelines for safer prescribing. Though aromatic AEDs are proposed to be safer, based on our report, still there is an unmet need to explore the mechanisms involved in valproate monotherapy induced DRESS syndrome. A vigilant attitude towards multidrug hypersensitivity with valproate substitution therapy is pivotal.

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