Scholars Journal of Medical Case Reports (SJMCR) **ISSN 2347-6559 (Online)**
Abbreviated Key Title: Sch. J. Med. Case Rep. **ISSN 2347-9507 (Print)**

A United of Scholars Academic and Scientific Society, India

Sodium Valproate: A Cause of Erythroderma

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Article History
Received: 02.10.2018
Accepted: 09.10.2018
Published:30.10.2018

DOI:
10.36347/sjmcr.2018.v06i10.014

Abstract: The antiseizure properties of the broad spectrum, non-aromatic sodium valproate are well known. It is being increasingly used in other conditions like bipolar disorders, acute mania, panic attacks and migraine. Non-aromatic antiepileptics are considered to be relatively safe and less likely to cause drug related cutaneous adverse reactions. Here, we report a case of a 20 year old female who was admitted to the dermatology ward with generalized erythema and exfoliation.. She had a history of focal seizures which first started in May, 2016. She was first treated with oxcarbazepine which was later changed to phenytoin due to recurrence after 18 months. Due to fever and itching after 2 months, she was switched over to sodium valproate along with the symptomatic treatment. Within 3-4 days, she developed erythema, first on the right upper limbs followed by left, then the lower limbs and gradually involved the whole body. She then came to the Dermatology OPD of RIMS where she was advised admission. On general examination, she had multiple hyperpigmented papules, some coalescing to form plaques, with edema of both hands. Generalised redness of the conjunctiva was seen along with oral candidiasis. Routine examinations of the blood and urine were done and were found to be normal. She was provisionally diagnosed with erythroderma due to valproate ingestion the drug was stopped. She was treated with iron, calcium, cetirizine and local application of vaseline. She recovered well and was discharged after seventeen days with healing of skin lesions with mild hyperpigmentation.
Keywords: Adverse drug reaction, sodium valproate, erythroderma, antiepileptic.

INTRODUCTION

Erythroderma (exfoliative dermatitis) is a cutaneous reaction pattern characterized by generalized erythema and scaling which can be seen in a wide range of cutaneous or systemic diseases and accounts for upto 1% of all dermatological admissions [1]. The erythema covers >90% of the total body surface area.

Adverse drug reaction is a major secondary cause of erythroderma in adulthood, the primary being eczema, psoriasis, phemphigoid and cutaneous T cell lymphoma [2]. Elderly male are most commonly affected.

Common clinical symptoms include fever, chills, malaise and pruritus along with peripheral edema, lymphadenopathy with secondary skin infections. It is a significant cause of morbidity and mortality. Hence, definitive diagnosis is essential for the correct treatment.

About 10% of patients receiving antiepileptic drug therapy develop skin allergy [3]. Various types of drug-related cutaneous eruptions include maculopapular rash, fixed drug eruption (FDE), erythema multiforme (EM), toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), urticaria, and erythroderma. The aromatic antiepileptics viz. phenytoin, carbamazepine, phenobarbitone and primidone can cause hypersensitivity reactions [4]. This pathogenesis of erythroderma seems to be related to arene-oxide metabolites of the aromatic anticonvulsants.

In such cases, the aromatic epileptics are discontinued and non-aromatic epileptics like sodium valproate or a benzodiazepine is given as an alternative therapy. Skin biopsy reveals acanthotic and focally parakeratotic epidermis with spongiosis and dermal edema. It may also present as a normal epidermis with scattered perivascular and peri-appendageal lymphohistiocytic infiltrate in the dermis.

Sodium valproate is a broad spectrum antiepileptic that has proven efficacy against all seizure types, which makes it a useful antiepileptic when exact seizure classification is unknown or multiple seizure type exists [4]. Hence,it is one of the most common first line antiepileptic therapy used all over. Apart from its antiepileptic properties, it is widely employed nowadays

as an antimaniac drug, for panic attacks and migraine as well.

Here, we present a case of erythroderma as an adverse drug reaction to this non aromatic antiseizure drug which is a rare occurrence. All the more, very little literature is available on erythroderma from this part of the country i.e. the Chhotanagpur plateau of Jharkhand state.

CASE REPORT

A twenty year old Hindu female came to the outpatient department of Dernatology. Leprosy and Venerology, RIMS, Ranchi with generalized erythema. Hypopigmented papules which coalesced to form plaques were present all over the body.

Patient had a history of focal seizures since May, 2016 for which she was prescribed oxcarbazine. This treatment continued for one and a half years after which there was a recurrence. The patient was then prescribed phenytoin, first as 100mg BD which was increased to 150 mgs BD after a month. She developed fever and itching after two months. She was given symptomatic treatment for the above and she was switched over to sodium valproate.

Within 3-4 days, she developed generalized erythema with hypopigmentation. She visited the RIMS OPD after a week of this development. Here; she was admitted to the ward for treatment. On examination, she was febrile with a pulse of 110 and BP 110/70.

Cutaneous examination showed diffuse, white scaling on the scalp, face and neck. Generalised erythema with exfoliation and tiny hyperpigmented papules scattered over the entire face, more on upper than on the lower side. Hyperpigmented papules coalesced to form large plaques on the dorsal aspect of neck. Periorbital edema and diffuse hyperpigmentation of the lips were also seen. Similar findings were seen on the chest, back and abdomen, more on the upper than on the lower part.

Generalised erythema with multiple papules coalesced to form larger plaques over the cubital fossa bilaterally. The entire upper and lower limb presented with erythema and exfoliation on both the dorsal and the ventral surfaces. Hands were edematous. Palms showed irregular, ill-defined patches of reddish brown colour. Changes in the nails could not be appreciated because of nail painting.

There was generalized conjunctival redness. Multiple papules spread over the whole tongue and the angle of mouth. Thick, ulcerative patches were suggestive of candidiasis. Similar ulcers with a clear base were seen on the soft palate.

Genitalia showed poor hygiene with erythematous spread. Routine blood and urine examinations were normal. Serum electrolytes were normal. On the basis of history and clinical examinations, a provisional diagnosis of drug induced erythroderma was made.

Sodium valproate was immediately stopped and she was referred to the medicine department for further treatment of epilepsy. She was treated with antihistaminics, flouroquinolones, iron capsules, protein and calcium supplements and H2 blockers. Vaseline was given for local application. No rechallenge with sodium valproate was attempted.

She recovered slowly but steadily. She was discharged after full recovery after seventeen days. Total score >9 showed the probability of the adverse reaction due to the drug to be ‘definite’ on Naranjo’s scale. Scorten scale assessment was 2 which means that risk of dying was approximately >12%.

Fig-1: is Exfoliation from palms at the time of admission

Fig-2: Is Post inflammatory hyperpigmentation after treatment

DISCUSSION

Improvement in the symptoms of the patient after removal of the suspected offending agent indicates a causal relationship between the drug and the disease. A 'definite' score on Naranjo's scale further strengthens this association. Since the fever and itching started after phenytoin administration itself, a cross reactivity with phenytoin also can be possible.

Antiepileptics are well known to cause cutaneous adverse reactions. In India, they account for 4.5 to 9.25% of all drug reactions, whereas in the Western world, it accounts for almost 20% [5]. Erythroderma and other cutaneous drug reactions are mainly attributed to the non-aromatic group of antiepileptics like phenytoin and carbamazepine where sodium valproate is alternatively used. But the implication of valproate in causing erythroderma cannot be ruled out and other safer alternatives have to be searched for, keeping in mind the long term of treatment of this disease and the morbidity and mortality rate associated with this drug reaction.

Erythroderma is increasing in the third world countries with the use of many herbal and non-herbal medications. Late admission to the hospitals adds to this problem.

Gehgal and Srivastava performed a large prospective study in the Indian subcontinent, where they determined the incidence to be 35 per 100,000 dermatologic outpatients. In general, studies have shown a male predominance, with the male-to-female ratio ranging from 2:1 to 4:1, and the mean age between 40 and 60 years [6].

Personal clinical history, family history and laboratory investigations are helpful apart from the biopsy of the lesion. .But, sadly many investigational facilities are not available in many hospital set ups.

Complications can be related to infection, nutrient deficiencies, dehydration and heart failure, leading to death. They have to be taken care of while treating the patient.

CONCLUSION

The knowledge of the drugs that may induce, trigger, or exacerbate erythroderma, is of importance in clinical practice. The drugs with greatest erythroderma inducing potential are carbamazepine, phenytoin, phenobarbital, cimetidine, lithium salts and gold salts [7]. To this list we should add valproate and valproate should be used with caution by physicians while prescribing alternative drugs in case of hypersensitivity reaction to the aromatic antiepileptics.

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