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Case Report

Drug-induced hypersensitivity syndrome caused by valproic acid as a monotherapy for epilepsy: First case report in Asian population

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ABSTRACT

Valproic acid (VPA) is a broad-spectrum antiseizure drug used for a variety of clinical conditions, such as epilepsy and mood disorders. Drug-induced hypersensitivity syndrome (DRESS) accompanied by hyponatremia, thrombocytopenia, hypoalbuminemia and elevated aminotransferase has never been reported as an adverse effect of VPA monotherapy during titration for epilepsy in Asian population. Hereby, we present the case of a 73-year-old Chinese male who suffered from DRESS and other complications two weeks after initiating VPA treatment for epilepsy. Understanding the risk associated with VPA-induced DRESS, and taking effective measures to avoid the severe side effects are necessary.

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1. Introduction

Valproate acid (VPA), one of first-line traditional antiseizure drugs (ASDs), effectively controls many types of seizure. As reported, VPA-induced hyponatremia could happen in patients with epilepsy, especially in elderly people [1]. VPA-induced drug-induced hypersensitivity syndrome (DRESS) is rare in patients with epilepsy-related seizures. DRESS is a type of severe cutaneous adverse drug reactions (SCARs), characterized by generalized acute maculopapular eruptions, accompanying high fever and internal organ involvement. It is a rare, but potentially fatal adverse event with a mortality range from 10%–40% [2]. It's most often caused by first-line aromatic ASDs. The risk is highest for phenytoin (PHT) of 5%–7%, carbamazepine (CBZ) of 5%–17%, and lamotrigine (LTG) of 5%–10%. SCARs with internal organ dysfunction such as DRESS are approximated between 1/1000 and 1/ 10,000 exposures [3]. It seldom happens with patients taking non-aromatic antiseizure drugs such as valproic acid (VPA), vigabatrin (VGB), levetiracetam (LEV), and benzodiazepines. Moreover, SCARs accompanying with hyponatremia, thrombocytopenia, hypoalbuminemia and high aminotransferase are rare in patient under VPA treatment. Given the rarity of this severe case, it is important to recognize the possibility of SCARs associated with VPA.

2. Case report

A 73-year-old male taking VPA monotherapy for epilepsy, was admitted to the dermatology department of West China Hospital of Sichuan University, because of generalized ruptured skin erythema followed by high fever, hyponatremia, thrombocytopenia and high aminotransferase for 2 weeks.

The patient had seizures and diagnosed with epilepsy in a local hospital 8 months ago without treatment. Almost 1 month ago, he was prescribed VPA (500 mg/d, increased to 1000 mg/d one week later) for epilepsy in the local hospital because of his recurrent seizures. Two weeks after VPA exposure, he suffered from erythematous maculopapular eruptions without mucous membrane involving a large area of his face, back, bilateral shoulders and both lower limbs (Fig. 1). He didn't have feelings of pain, itch, or burning, etc. His symptoms worsened gradually by the disease processing, presenting with a fever of 39.5 °C, fused maculopapular rash, oval erythema and ruptured blisters over his whole body, with face and lower limbs edema (+/4, ++/4 separately). This patient's other vital signs were stable.

This patient suffered from and had atrial fibrillation beginning one year ago. He persistently took warfarin as anticoagulation treatment afterwards without routine monitoring. He used to smoke for more than

Abbreviations: VPA, valproic acid; DRESS, drug-induced hypersensitivity syndrome; ASDs, antiseizure drugs; SCARs, severe cutaneous adverse drug reactions; PHT, phenytoin; CBZ, carbamazepine; LTG, lamotrigine; VGB, vigabatrine; LEV, levetiracetam; ECG, electrocardiogram; AHS, acute hypersensitivity syndrome; MDH, multiple drug hypersensitivity; HLA, human leukocyte antigen; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

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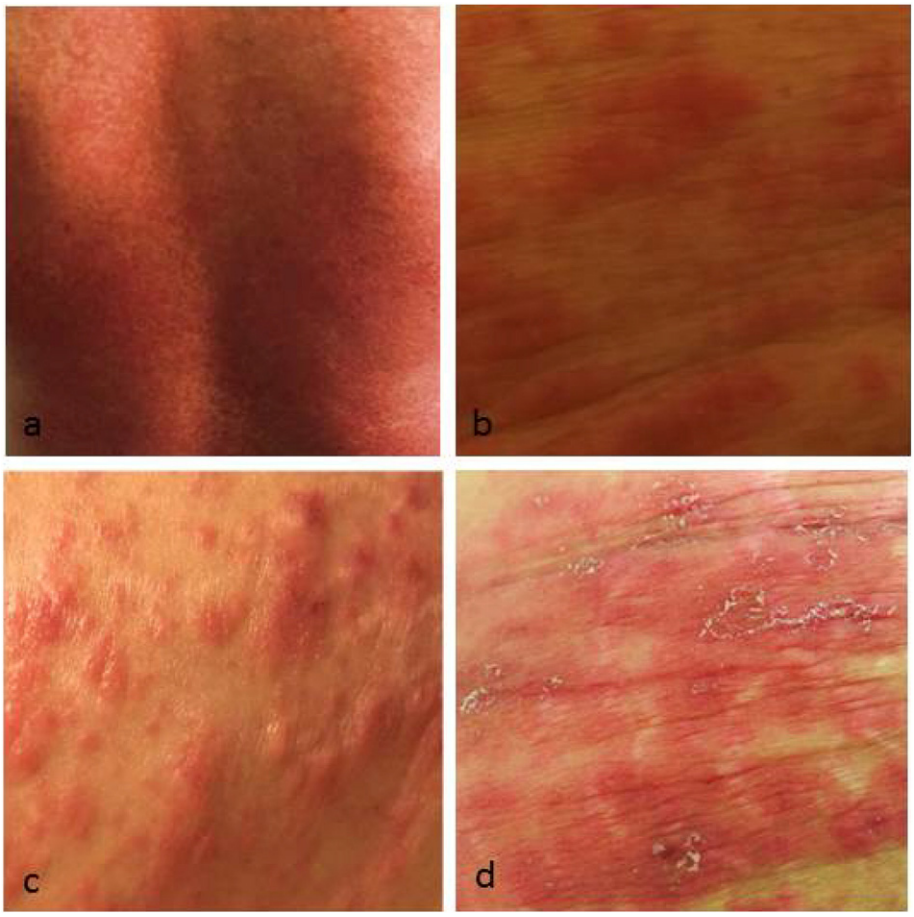

Fig. 1. a— Maculopapular eruptions on his back; b— oval erythema on his abdomen; c— oval erythema and blisters; d— ruptured blister with desquamation.

40 years and quitted for one year. He had no history of drug allergies previously.

After the hospitalization, laboratory tests showed normocytic and normochromic anemia (HGB 119 g/L), hyponatremia (Na+: 127.1 mmol/L), thrombocytopenia (PLT: $79 * 10^9$/L), hypoalbuminemia (TP: 51.3 g/L, ALB 29.4 g/L), elevated levels of hypersensitive C reactive protein (HsCRP: 6.81 mg/L), transaminases (ALT: 219 IU/L, AST: 128 IU/L), and gamma-glutamyl transpeptidase (GGT: 243 IU/L). A HLA-B*1502 test was negative. Serology for human immunodeficiency virus, syphilis test and hepatitis B were negative. Chest radiography revealed chronic inflammatory changes in bilateral lungs without acute infections, while abdominal ultrasound showed no significant changes. Electrocardiogram (ECG) confirmed the atrial fibrillation. Echocardiography showed enlarged atrias with normal left ventricular systolic function. Head CT demonstrated an old infarction in right temporal lobe.

Infusion of methylprednisolone for 5 days (40 mg/d) followed by prednisone tablets (40 mg/d), human serum albumin, gamma globulin, intravenous calcium gluconate, cyclosporine (100 mg/d) and other symptomatic treatments were used to treat this patient, besides replacing VPA with LEV for epilepsy. Two months after admission and several treatment cycles, this patient became better was discharged from the hospital.

3. Discussion

Drug-induced hypersensitivity syndrome (DRESS) is a rare but a potentially fatal reaction to ASDs. Several researches reported the incidence and manifestations of ASDs-induced DRESS. It is well known that aromatic ASDs, including PB, PHT, CBZ, LTG and OXC are common causative drugs, however, typically does not include non-aromatic ASDs such as VPA, TPM, LEV, GBP, VGB and benzodiazepines.

In our case, the patient had DRESS and hyponatremia, thrombocytopenia, hypoalbuminemia and high aminotransferase two weeks after VPA for his epilepsy. The exact mechanism is still not known yet. As previous studies note, human leukocyte antigen (HLA) alleles are the genetic factors involved in DRESS [1,2] which was confirmed by several studies that HLA-B*1502 has the strong association with CBZ-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) [3]. These linkages can be explained by an off-target activity of a particular drug to a certain HLA protein [4]. Although, no specific HLA allele is identified as a biomarker of VPA-related DRESS so far, a genetic predisposition and related immunologic reactions could be the potential explanation.

Furthermore, our patient increased the dosage of VPA from 500 mg/d to 1000 mg/d in one week. The titration of VPA was fast. Previous studies found that age ≤ 13 years, female, higher starting dose, rapid titration, and concomitant use of VPA are risk factors for patients suffering from LTG-induced SCARs, but not the VPA-monotherapy-induced DRESS [5,6]. Although slower titration rate is commonly recommended to reduce the risk of severe rash, ASDs-induced SCARs are generally considered idiosyncratic, unpredictable and non-dose dependent [7]. More studies focusing on this point should be done in the future.

There are a few reports concerning VPA in combination with LTG causing acute hypersensitivity syndrome (AHS) with multiple organ dysfunction [8–11], but all these patients had a concomitant use of LTG and VPA, not VPA alone. That's why LTG rather than VPA is probably the causal drug, or VPA enhanced the adverse reaction. Moreover, Arevalo-Lorido et al. described a 36-year-old man with AHS caused by VPA two weeks after initial CBZ, which was discontinued because of

severe skin rash [12]. Bota et al. discussed the case of a 25-year-old woman with bipolar disorder who experienced DRESS caused by valproic acid one month after withdrawal of LTG because of a nonspecific skin rash [13]. Replacement treatment of VPA with other aromatic ASDs may cause DRESS. It might be former aromatic ASDs activated the immunologic mechanism, which would be considered as multiple drug hypersensitivity (MDH), a novel syndrome re-proposed by Pichler WJ and his colleagues recently [14]. The T-cell activations in MDH are not due to cross-reactivity [14]. Prior drug exposure initiates severe T-cell reactions, which appear to have a long-lasting effect on the patient's immune system. VAP as the second drug stimulates the activated immune system, and then causes DRESS.

There are also some reports of VPA combination with other drugs besides for ASDs. A 19-year-old female patient diagnosed as DRESS with positive Brucella Coombs test and Rose Bengal test undergoing VPA for his chorea as well as streptomycin and tetradox capsules as polytherapy for the brucellosis [15]. In this case, whether the brucellosis might be the dominant cause for DRESS was unknown. One case presented a 26-year-old man with DRESS and acute liver failure after an intracerebral bleed for 5 months and epileptic seizure for 1.5 months, taking VPA, baclofen, clemastine and acetaminophen daily [16]. One case reported a 60-year-old Iranian man who had been treated with oral VPA (1000 mg/d) to prevent seizures after subarachnoid hemorrhage and developed DRESS. This patient had insulin at the same time for his diabetes [17]. Another case reported a 20-year-old Brazilian female with DRESS after a treatment with VAP and haloperidol [18]. Our patient took warfarin for his previous ischemic stroke and atrial fibrillation for a long time, while he took VPA for epilepsy. So, many patients suffered from DRESS when they had at least two kinds of drugs because of comorbidities. Therefore, a question is proposed for further studies: which drug or which type of drug combinations or potential risk from comorbidities could be a possible cause of DRESS?

What's more, Yang et al. concluded that most of the patients tolerated nonaromatic ASDs, especially VPA, after their SCARs episodes caused by aromatic ASDs [19]. Considering VPA has a potential risk of DRESS which could be accompanied by certain complications, especially, the patients with previous drug-allergic symptoms, when using VPA as a replacement therapy, doctors should be aware of possible MDH, meanwhile, closely monitoring the clinical features and laboratory results with is quite important and necessary.

4. Conclusion

This is the first case report of VPA monotherapy in epilepsy accompanied by hyponatremia, thrombocytopenia, hypoalbuminemia and high aminotransferase in the Asian population. Understanding the potential risk associated with VPA-induced DRESS and taking effective measures to avoid the severe side effects are necessary. When skin rash occurs in a patient taking VPA, the possibility of an adverse effect to this drug should be considered, and switching the patient to a different drug may be a good option. Moreover, laboratory tests should be done for detecting other side effects, such as hyponatremia, thrombocytopenia, hypoalbuminemia and high aminotransferase, in order to intervene before the patient suffers severe adverse effects. Furthermore, when using VPA as a replacement therapy, doctors should be aware of possible MDH. Finally, if VPA is considered for patients, especially those with co-morbidity or under polytherapy for other diseases, the clinical and laboratory observations of these patients should be closely monitored. Additional studies should be done in order to find out the potential mechanisms of VPA-induced DRESS in the future.

Ethical statement

Informed consent was obtained from the patient.

Conflict of interest

The authors have no conflicts of interest to report.

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Declaration

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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