

Hypersensitivity syndrome due to 2 anticonvulsant drugs

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Drug-induced hypersensitivity syndrome is a multiorgan-system reaction characterized by fever, pleomorphic eruption, lymphadenopathy, eosinophilia, lymphocytosis and hepatitis. We report a drug hypersensitivity syndrome in a 6-year-old Tunisian child treated for epileptic absences with sodium valproate and ethosuximide. Imputability of these 2 drugs is probable because of the chronological and clinical features. Positive rechallenge with ethosuximide confirmed the toxicity of this drug. Sodium valproate was also responsible because patch testing was positive and followed by a generalized eruption. Human herpesvirus 6 (HHV6) antibody titers increased significantly within 15 days. There was a favourable outcome after discontinuation of the drugs and corticosteroid therapy. Our case is interesting because this drug hypersensitivity syndrome occurred with non-aromatic anticonvulsant drugs. It is the 1st case with ethosuximide and the 2nd with sodium valproate. We also observed a reactivation of HHV6 infection that may contribute to the development of this hypersensitivity syndrome.

Key words: adverse drug reaction; hypersensitivity syndrome; positive patch test; anticonvulsants; epilepsy; sodium valproate; ethosuximide; human herpesvirus 6. © Munksgaard, 1999.

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The onset of drug hypersensitivity syndrome usually occurs within 2 to 6 weeks of initiating treatment. It is a multiorgan-system drug-induced reaction characterized by fever, pleomorphic eruption, lymphadenopathy, eosinophilia, lymphocytosis and hepatitis. This adverse reaction was initially recorded with aromatic anticonvulsant drugs (1–3) but also with other drugs (4–6). Recently, some authors reported that reactivation of human herpesvirus 6 (HHV6) may contribute to the development of drug hypersensitivity syndrome (7–9). We report a case of hypersensitivity syndrome induced by sodium valproate and ethosuximide in which HHV6 antibodies titers rose.

Case report

On 8 June 1997, a 6-year-old Tunisian child presented with a diffuse pruritic morbiliform skin eruption with vesicular and target lesions. He also presented with oedema of the face, high fever (40°C) and enlarged lymph nodes but he had no mucosal involvement.

He had a history of epileptic absences and was treated with 600 mg/day of sodium valproate (De-

pakine®, Sanofi Winthrop, Gentilly, France) and 500 mg/day of ethosuximide (Zarontin®, Parke Davis, Courbevoie, France). The serum levels of sodium valproate (58 µg/ml) and ethosuximide (53 µg/ml) were in the therapeutic range ($50 < N < 100$ µg/ml). He received sodium valproate from 30 April to 10 June, though during this period, the drug was stopped for a few days because of gastrointestinal intolerance. He received ethosuximide between 8 May and 5 June; it was discontinued because it seemed ineffective (Fig. 1).

Laboratory studies showed a leucocytosis of $17.9 \times 10^9/l$ (normal range $4\text{--}12 \times 10^9/l$), an eosinophilia of $2 \times 10^9/l$ (normal $< 0.7 \times 10^9/l$), a lymphocytosis of $8.95 \times 10^9/l$ (normal range $2.5\text{--}5.5 \times 10^9/l$) and a monocytosis of $1.43 \times 10^9/l$ (normal $< 1 \times 10^9/l$), with the presence of stimulated lymphocytes. The platelet count was normal. The c-reactive protein was high at 57 mg/ml (normal < 5 mg/ml) and the liver function tests were abnormal: aspartate aminotransferase 70 U/l (normal range 10–35 U/l), gamma glutamyl transferase 50 U/l (normal range 5–30 U/l). The serum lactate dehydrogenase was elevated at 1020 U/l (normal range 270–530 U/l). Serum creatinine level, antinuclear antibodies,

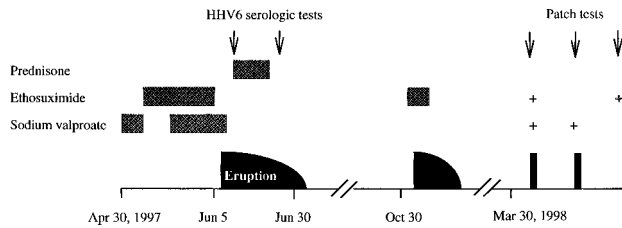


Fig. 1. History of the drug eruption.

blood and urine cultures, and chest X-ray were normal. Virological investigations for Epstein-Barr virus, human immunodeficiency virus, hepatitis A, B and C, *Mycoplasma pneumoniae*, cytomegalovirus, parvovirus B19 and herpes simplex virus were negative. 2 samples of the patient's serum were obtained and tested for HHV6 antibodies by indirect immunofluorescence (Fig. 1). The titers significantly increased within 15 days with values at 40 and 120, respectively (negative <20). Histologic examination showed a spongiotic epidermis with necrotic keratinocytes and a lymphocytic perivascular dermal infiltrate with a few hyperchromatic lymphocytes with irregular nuclei.

The diagnosis of drug hypersensitivity syndrome

was proposed based on the clinical, histological and biological findings. Sodium valproate was discontinued. Ethosuximide had been stopped 2 days before the skin eruption. Because of severe clinical symptoms, oral prednisone was started at 1 mg/kg/day. The clinical and blood parameters returned to normal within 1 month. 4 months later, ethosuximide was rechallenged and the patient immediately experienced a maculopapular eruption with oedema of the face but without general symptoms. Ethosuximide was discontinued and the rash resolved spontaneously.

Patch tests were performed 9 months after total resolution. Both suspected anticonvulsant drugs were simultaneously and separately tested with 1 month between each test. To perform the patch tests, one gelified tablet of ethosuximide and one crushed tablet of sodium valproate were diluted 20% in water. Patch tests were performed with Finn Chambers on Scanpor (Epitest, Tuusula, Finland) and applied on the upper back. Patch tests were read 2 days later according to the International Contact Dermatitis Research Group guidelines (Fig. 2). Sodium valproate patch tests were positive (++), with associated reinduction of rash on the arms, legs and face.

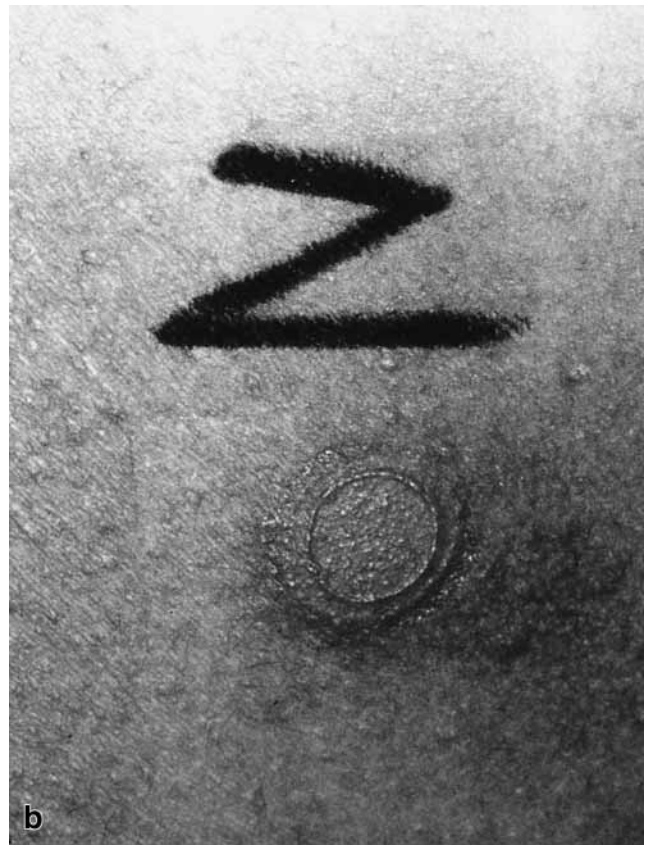


Fig. 2. (a) Positive patch test with sodium valproate (D: Depakine®). (b) Positive patch test with ethosuximide (Z: Zarontin®).

Histologic examination of the patch test showed an acute eczema. Ethosuximide patch tests were also positive (++). 25 control subjects had negative patch tests. 4 of them were on treatment with sodium valproate.

The patient did not have a relapse over the next year. Ethosuximide and sodium valproate had been discontinued. Other anticonvulsant drugs, diazepam, clonazepam and lamotrigine, were prescribed to treat the epilepsy.

Discussion

Drug hypersensitivity syndrome is a severe drug reaction that leads to death in 10% of cases. It appears 2 to 6 weeks after administration of the causal drug. Clinical signs include a maculopapular rash that often progresses to a pustular eruption or erythroderma, fever (88% of the patients), lymphadenopathy (78%). Liver dysfunction (74%), eosinophilia, atypical lymphocytes (88%), and elevated lactate dehydrogenase levels are frequently observed (1, 3). The prognosis depends on systemic involvement, which can cause severe hepatitis, nephritis, pneumonitis, cardiac failure and result in death. The symptoms are often progressive for several weeks after treatment with the causative drug is discontinued. The rôle of systemic corticosteroid therapy has not been studied, but it is used in severe multivisceral involvement (3).

In our case, the presence of a compatible induction period, the clinical features, the presence of eosinophilia, atypical lymphocytes, high levels of lactate dehydrogenase and the failure to demonstrate another etiology strongly support the diagnosis of drug hypersensitivity syndrome. Systemic involvement was mild and probably explains the favourable outcome. However, we started systemic corticosteroid therapy because the cutaneous eruption was extensive and occurred in a 6-year-old child.

Drug hypersensitivity syndrome was described for aromatic anticonvulsants, such as phenytoin, carbamazepine, and phenobarbital. We report drug hypersensitivity syndrome induced by 2 unusual anticonvulsant drugs, sodium valproate and ethosuximide. These 2 anticonvulsant drugs are used in the treatment of absence seizures of epilepsy.

Sodium valproate is metabolized in the liver by several pathways: glucuronic acid conjugation, β and ω -oxidation. It does not induce liver enzyme activity but inappropriate biotransformation by cytochrome P-450 can lead to the generation of toxic metabolites. Cutaneous adverse reactions are rare (10, 11). The frequency is higher when it is combined with lamotrigine (12). Our child did not

receive this combination. Only 1 case of drug hypersensitivity syndrome from sodium valproate has been reported (13). Apart from cutaneous adverse reactions, hepatotoxicity was reported. This is due to the 2-n-propyl-4-pentenoic acid metabolite of valproate that inhibits cytochrome P-450 and fatty acid β -oxidation. The risk of hepatic dysfunction is more severe when patients receive valproate along with aromatic anticonvulsant drugs, which are enzyme inducers (14). Ethosuximide is metabolized in the liver and is not an enzyme inducer. It may cause systemic lupus erythematosus, erythema multiforme, abdominal discomfort and bone-marrow depression. Drug hypersensitivity syndrome has not been reported.

The pathogenesis of hypersensitivity reaction to anticonvulsant drugs is not elucidated. Phenytoin, carbamazepine and phenobarbital are metabolized by cytochrome P-450 via arene oxide intermediates. Cross-reactions between these 3 aromatic anti-epileptic drugs are probably due to a deficiency of detoxication of these intermediates (1, 2). Ethosuximide and sodium valproate are neither aromatic anticonvulsant drugs nor enzyme inducers; a common metabolite between these drugs has not been discovered. Thus, the risk of cross-reactivity between these drugs is probably low. However, sodium valproate is able to decrease ethosuximide clearance, with concomitant increase in the serum levels (15). In our case, as the serum levels of each anticonvulsant were in the normal range, we eliminated a toxic overdosage.

Imputability of the 2 drugs was probable because of the chronological and clinical features. Rechallenge with ethosuximide was positive and confirmed the causal nature of the drug. Sodium valproate was also responsible for the hypersensitivity syndrome because patch testing was positive and elicited a generalized eruption, although less severe than the original adverse reaction. Therefore, it was a double sensitization to 2 anticonvulsants, not previously reported in the literature. It was probably an immunoallergic reaction because it needed sensitization and patch tests were positive. It is the 1st case of drug hypersensitivity syndrome to ethosuximide and the 2nd one to sodium valproate (13). Our case illustrates that patch testing is worthwhile for detection of the drug responsible for a hypersensitivity syndrome. Such patch tests are well documented for drug hypersensitivity syndrome due to carbamazepine (16, 17). It is helpful to perform these tests in drug hypersensitivity syndrome, even though they may induce a generalized eruption following topical application (18).

Recent publications strongly suggest that viral infections contribute to the pathogenesis of drug

hypersensitivity syndrome. HHV6, which is the agent of exanthema subitum, may be implicated. In our case, HHV6 antibody titers increased significantly between the 2 samples. The increase in the antibodies is probably due to reactivation of the viral infection. The relation between HHV6 infection and drug hypersensitivity syndrome is not established. Is it a reactivation of HHV6 contemporary to the lymphocyte stimulation induced by the drug? Does HHV6 impair the enzymatic function of detoxification? Is it a co-factor? In the literature, it is suggested that this infection should be treated with antiviral drugs (9).

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