

## Case report

# Severe hypersensitivity syndrome to lamotrigine confirmed by lymphocyte stimulation *in vitro*

**Background:** The anticonvulsant lamotrigine has been associated with severe adverse events such as the hypersensitivity syndrome and severe bullous reactions. So far, specific immunologic tests have rarely been performed to demonstrate specific sensitization.

**Methods:** A 36-year-old man suffering from epilepsy was concomitantly treated with high doses of sodium valproate and lamotrigine. About 1 month later, a severe hypersensitivity syndrome occurred affecting skin, lymph nodes, and liver. Three months later, skin tests and lymphocyte stimulation tests with anticonvulsants were performed.

**Results:** Skin tests were negative with all drugs; lymphocyte stimulation tests were twice positive with lamotrigine. Later re-exposure to sodium valproate was tolerated.

**Conclusions:** Lamotrigine may elicit a severe hypersensitivity syndrome. Particularly high initial doses and concomitant treatment with sodium valproate increase the risk of cutaneous reactions. The lymphocyte stimulation test was used to identify the culprit drug. Lymphocyte sensitization to the drug or a metabolite may be involved in the pathogenesis.

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Lamotrigine, like other anticonvulsant drugs (e.g., carbamazepine, phenytoin, and phenobarbital), may cause a potentially life-threatening adverse drug reaction, also known as the anticonvulsant hypersensitivity syndrome (1, 2). Clinically, in its complete form, this syndrome includes severe maculopapular exanthema, fever, lymphadenopathy, and internal organ involvement. Organ involvement can be asymptomatic or symptomatic, and usually involves the liver, although hematologic, renal, or pulmonary impairment may occur, too. In addition, eosinophilia may be present (1, 3). We report the occurrence of a hypersensitivity syndrome in a 36-year-old man who was concomitantly treated with high doses of lamotrigine and sodium valproate.

## Case report

In October 1996, a 36-year-old man suffered an epileptic seizure and was later admitted to hospital because the established therapy with phenytoin was insufficient. In 1982, generalized epilepsy had first been diagnosed. In the beginning, the patient had received sodium valproate and phenobarbital, but for almost 10

years he had taken no medication, except for short-term therapy with sodium valproate (1200 mg/day) in 1995.

A few days after admission, on 23 October, phenytoin was replaced with sodium valproate 1500 mg daily. Because of inadequate seizure control, lamotrigine 300 mg daily was added on 4 November. On 15 November, sodium valproate was decreased to 1000 mg daily, and a few days later, lamotrigine was decreased to 200 mg daily. On 21 November, about 1 month after beginning treatment, the patient developed febrile maculopapular exanthema and later desquamation of the face. On 26 November, the patient was again admitted to hospital, lamotrigine was discontinued, and treatment with oral corticosteroids and antihistaminic drugs was begun. The exanthema resolved, but reappeared after the corticosteroids and antihistaminics were tapered. Therefore, sodium valproate was discontinued, too. The epilepsy was then treated with phenobarbital (300 mg/day) and barbitone (300 mg/day) (Fig. 1). On 4 December, physical examination revealed generalized maculopapular exanthema with edema of the face and desquamation of the distal extremities. Generalized lymphadenopathy and hepatomegaly were present. The patient was febrile.

Laboratory studies showed mild anemia, eosinophilia of 10% (normal  $\leq 5\%$ ), and elevated liver-function tests.

Treatment with oral corticosteroids and antihistaminics resulted in a complete resolution of the pathologic findings. Weeks later, he developed transient diffuse alopecia and transverse onychodystrophy of all nails. He was referred for an allergologic workup 3 months after the incident.

#### Allergologic Investigations

The patient had no history of atopic diseases or previous adverse drug reactions. Prick tests with common respiratory allergens were negative. Patch tests with phenytoin, phenobarbital, carbamazepine, lamotrigine, and sodium valproate were twice negative, and skin prick and intracutaneous tests with sodium valproate were negative. Lymphocyte transformation tests (LTT) were performed twice, 3 and 4 months after the incident. Briefly, peripheral lymphocytes were separated as previously described (4). Lamotrigine, phenytoin, phenobarbital, carbamazepine, and sodium valproate were incubated in four concentrations (100, 10, 1, and 0.1  $\mu\text{g/ml}$ ) in triplicates with  $2 \times 10^5$  cells for 5 days. As baseline control, the mean value of six wells without allergen incubation was used; as positive control, tetanus toxoid and phytohemagglutinin (10  $\mu\text{g/ml}$ ) were used. The cells of two normal individuals served as controls. Lamotrigine only twice gave positive results (stimulation index = 7.4, and 2.9 at concentrations of 100  $\mu\text{g/ml}$ ); the other drugs and the LTT in the controls were all negative.

#### Discussion

Lamotrigine, a relatively new, aromatic anticonvulsant agent, is thought to act by an effect on voltage-dependent sodium channels and, at higher concentrations, calcium channels. This results in stabilization of neuronal membranes and inhibition of glutamate release (5, 6). Lamotrigine was initially licensed as add-on therapy for seizures inadequately controlled by other drugs and is therefore usually prescribed for patients already being treated with other agents (7).

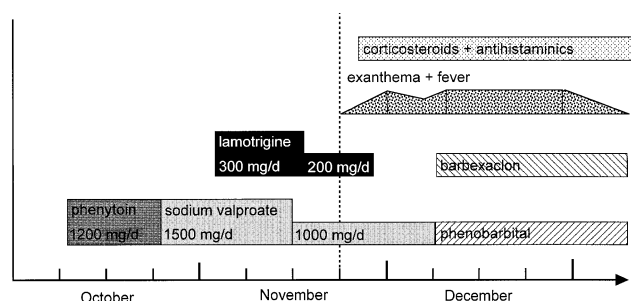


Figure 1. Temporal relation of drug intake and onset of symptoms. d: day.

However, increased clinical experience has seen its use extended to other indications (8). The most common adverse events associated with lamotrigine include primarily neurologic, gastrointestinal, and cutaneous symptoms (5). Exanthema, occasionally severe, occurs typically within the first 4 weeks of treatment in about 10% of patients and is the most common cause of treatment withdrawal (5, 7, 8). It has been estimated that the incidence of potentially life-threatening skin reactions such as the hypersensitivity syndrome may occur in up to one in 1000 adults treated with lamotrigine and in one in 50–100 children (8). This led to the addition of a black box warning on the package label of the potential for severe, life-threatening exanthema (1). In addition to age, the risk of exanthema is also strongly associated with high initial doses of lamotrigine (9). This risk can be reduced through adoption of a slow dosage titration schedule on initiating therapy (5). Concomitant use of sodium valproate is another risk factor for adverse skin reactions (5–9). It increases the incidence of rashes to 21% in adults and 34% in children (9). By administration of sodium valproate, total clearance of lamotrigine is reduced and plasma elimination half-life increased, probably by impairment of glucuronidation (10).

The patient not only received high initial doses of lamotrigine (300 mg/day instead of the recommended 25 mg every other day), but was also given sodium valproate, thus being exposed to two out of the three risk factors for severe skin reactions. Although patch testing was negative, the LTT twice confirmed lymphocyte reactivity to lamotrigine or possibly a metabolite. The LTT is an *in vitro* test which can be used to demonstrate sensitization to a certain drug. It can reveal sensitization of T cells by an enhanced proliferative response of peripheral blood mononuclear cells to a given drug (11). The negative patch test in our patient may have been due to the drug's inability to pass the skin barrier, or to the absence of the generation of a responsible metabolite in the skin.

In a study to validate the test, the sensitivity of the LTT was shown to be significantly higher than that of commonly used skin tests. Patients with penicillin allergy had a positive LTT in 74%, whereas the skin tests were positive in only 62% of cases (11). In another case of lamotrigine-induced Stevens-Johnson syndrome, a positive LTT was found as well. As no patch tests were performed, the negative results in our patient remain difficult to interpret (12). In two children with maculopapular exanthema to lamotrigine, an increase of activated helper and suppressor T cells and of total IgE was found, indicating an immunologically mediated process (13). A 6-year-old child with a hypersensitivity syndrome to lamotrigine and circumstances very similar to our patient has also been reported (14). Several other case reports of lamotrigine-associated skin reactions have been described, mostly in children, but often there

was no direct experimental evidence that the exanthema was due to lamotrigine (15). Sodium valproate may rarely elicit a hypersensitivity syndrome, as has recently been proven by positive patch tests (16).

By using the LTT, we were able to prove that our patient suffered from lamotrigine-associated hypersensitivity syndrome. A systematic review of 26 cases found that the characteristics of the syndrome associated with lamotrigine are comparable to the hypersensitivity syndrome induced by older aromatic anticonvulsants (17).

Initially, our patient was treated with barbitone (300 mg daily) and vigabatrin (2500 mg daily), but was still suffering from epileptic seizures. Later sodium valproate was added in full doses, which he tolerated without adverse reaction, but he was not rechallenged with lamotrigine. Some authors suggest that successful rechallenge is possible after a hypersensitivity syndrome (15), but others observed a prompt recurrence (17, 18). Due to the severity of symptoms in our patient, we believe a rechallenge would have been dangerous and unethical.

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