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Valproate-related erythrodermia with reversible encephalopathy: a rare but serious adverse reaction, case report

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Abstract

Cutaneous adverse reactions to antiepileptic drugs (AEDs) are usually easily recognized in daily clinical practice when they manifest as a morbilliform or maculopapular rash within the first few weeks after introducing an AED. Valproate (VPA)-induced encephalopathy is a rare but serious complication, presenting with impaired consciousness, with or without hyperammonemia, normal liver enzymes, and normal serum level of VPA. A 2-year-old Caucasian boy with severe developmental disability and pharmacoresistant epilepsy presented with fever, generalized erythrodermia, and encephalopathy, which resolved after discontinuation of valproate. Sodium valproate (30 mg/kg/day) was introduced 5 months previously, as the third drug in combination with vigabatrin and levetiracetam, due to frequent daily seizures. The clinical condition of generalized erythrodermia and encephalopathy was recognized by the treating physician as a possible adverse reaction to VPA: with the Naranjo scale it was probably associated with VPA (six points) and possibly associated with vigabatrin and levetiracetam (three and two points, respectively). After valproate withdrawal, the patient recovered completely. This case is of interest because erythrodermia was a clue to the recognition of valproate-related adverse reaction with severe central nervous system involvement without hyperammonemia and with normal liver enzymes—a very rare occurrence.

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Introduction

Adverse reactions to antiepileptic drugs (AEDs) occur to a certain degree in almost 80% of patients and are a major concern for physicians (1, 2). Cutaneous adverse reactions to an AED are usually promptly recognized by the patient and clinicians because they typically manifest as a maculopapular rash within the first weeks after the introduction of a specific AED. Although skin rashes may occur with any AED, the risk is highest for phenytoin (10%), carbamazepine (8.7%), and lamotrigine (6.2%) (1, 3). Valproic acid, vigabatrine, levetiracetam, and benzodiazepines have lower risks (1). A recent retrospective study of 3,793 Chinese epilepsy patients showed skin side effects manifesting as any type of rash in 137 cases (3.6%) (4). The underlying mechanism of the drug-related maculopapular rash, which represents the most common allergic reaction to drugs and is observed in 2 to 3% of hospitalized patients (5), may be either immune-mediated hypersensitivity (6) or non-immune-mediated individual susceptibility as an idiosyncratic reaction (1, 3, 7).

Idiosyncratic reactions (IDR) are rare, accounting for only 6 to 10% of all adverse drug reactions in general, but they can be life-threatening (8). The most frequently occurring IDRs–Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)–are associated with the use of lamotrigine, carbamazepine, phenytoine, and phenobarbital (7, 9).

The term antiepileptic drug hypersensitivity syndrome (ADHS) or drug-related rash with eosinophilia and systemic reaction (DRESS) represents a rash that typically occurs during the first weeks of therapy with one of the following AEDs: phenytoin, lamotrigine, or carbamazepine. In addition to exanthema, there is also involvement of one or more internal organs, most frequently the liver, GI tract, kidneys, lungs, CNS, and hematopoietic system. In its most severe form, systemic ADHS or DRESS is associated with high fever, maculopapular exanthema, and multiple organ failure, mainly acute hepatopathy, and may be life-threatening (7).

Valproic acid (VPA), a broad-spectrum antiepileptic drug, has been used in therapy for epilepsy since 1967. VPA is a branched-chain fatty acid with anticonvulsive action due to the combined pharmacological effect of increased γ-amino-butyric acid (GABA) levels inhibiting N-methyl-d-aspartate (NMDA) receptors and a blockade of neuronal sodium channels. VPA also affects a variety of metabolic pathways. The side effects of VPA are many and well known; however, serious adverse reactions such as hepatotoxicity, encephalopathy, coagulation disorders, pancreatitis, and bone marrow suppression are rare (10).

The aim of this paper is to alert physicians and clinical pharmacists to a rare but serious encephalopathic manifestation of ADR, in which the cutaneous symptom was an important diagnostic clue.

Case report

A 2-year-old Caucasian boy had suffered severe B streptococcal meningoencephalitis at the age of 2 months, with resultant severe global developmental delay (DQ < 25), microcephaly, generalized hypotonia with tetraparesis, and pharmacoresistant epilepsy. Because of his frequent daily seizures, he was treated with many AEDs. Clinical improvement, with an important reduction in seizures, was achieved 5 months prior to admission, when sodium valproate (30 mg/kg/day) was added to the combination of vigabatrin (40 mg/kg/day) and levetiracetam (40 mg/kg/day). At a regular follow-up visit 2 months prior to admission, the normal therapeutic drug level of VPA was determined (597 μmol/L). His development started to improve; slowly, he became more alert and attentive in non-verbal communication, he achieved better head control and was able to sit with support, and he began to smile in response to his parents.

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Suddenly, on the 3rd day of an acute upper respiratory tract infection, he became somnolent, and then his condition deteriorated to lethargy and coma, with reaction only to painful stimuli. Laboratory tests ruled out sepsis (hemoculture was negative), CRP was 93 mg/L, and mild leukocytosis (15L), thrombocytopenia (49), and eosinophilia (7%), mildly elevated ALT (1.17 µkat/L) and normal AST (0.03 µkat/L), gamma-GT (0.50 µkat/L), and normal ammonia (42; 9 µmol/L) were found. Renal function and blood pressure were normal, and plasma therapeutic drug monitoring for sodium valproate was not performed. MRI showed gadolinium enhancement of meningeal coverings as in meningitis, and therefore he was treated with a third-generation cephalosporin and acyclovir, but his condition did not improve over the next few days. Lumbar puncture did not confirm any pathogenic organisms or inflammatory response within the CNS.

On the 2nd day after admission, his skin became diffusely red and edematous, including facial edema (Figure 1). All common infectious causes were excluded. Recalling a similar patient with high fever, diffuse erythrodermia, and irritability, but no lethargy, probably related to VPA (unpublished), the treating physician considered the possibility of an adverse reaction to an AED and decided to stop sodium valproate immediately. The child continued to receive vigabatrin and levetiracetam and he also received intravenous antihistamines. The second day after cessation of VPA the erythrodermia became less intense and the patient's level of consciousness started to improve, and after 5 days his mental state slowly returned to the previous baseline. According to the Naranjo ADR probability scale, the total score for sodium valproate in this case was six points and ADR was assigned as probable, in comparison to vigabatrin (three points) and levetiracetam (two points).

Figure 1 | Facial edema with erythrodermia.

Discussion

The clinical recognition of an adverse drug reaction (ADR) is very important because drug withdrawal may be the necessary therapeutic procedure or another drug should be administered (2, 3, 11). Maculopapular exanthema, as the most frequent ADR to antiepileptic drugs such as carbamazepine or lamotrigine, is well recognized among physicians, especially severe cutaneous reactions such as SJS or TEN (3, 4, 7). However, rashes are not common adverse reactions to VPA. Valproate-induced vasculitis as an ADR has been reported, with an incidence of less than 1/1000 (12). Although rare, a clinician should be aware of cutaneous eruptions as a possible adverse event related to VPA (13).

Erythrodermia, on the other hand, is a very rare symptom and not as well known as a possible drug-associated adverse reaction. A maculopapular or generalized erythematous rash associated with facial edema is usually a predictor of DRESS syndrome (14). In our patient, along with erythrodermia, diffuse edema was present, but due to CNS involvement and fever at admission, along with MRI findings, a diagnosis of meningoencephalitis was initially suspected and antibiotic treatment started. Only after 2 days, when no clinical improvement was observed, with negative results of CSF and other tests for infection, and because of progressive deterioration of the child's condition, was the possibility of systemic drug-induced hypersensitivity syndrome considered. Eosinophilia and thrombocytopenia, in addition to CNS involvement in our patient, were sufficient evidence for the diagnosis of DRESS syndrome, which includes fever, rash, hematological abnormalities, lymphadenopathy, and single or multiple internal organ involvement (7).

In addition, according to the Naranjo ADR probability scale (2) used as an assessment tool, the adverse event was probably related to sodium valproate (six points). After discontinuation of this drug, the patient's clinical condition returned to the previous level and all symptoms of the adverse event resolved.

The causal relationship between the clinical picture in our patient and the other two AEDs–vigabatrin and levetiracetam–was graded with three and two points on the Naranjo scale, indicating the only possible relationship (2). Both drugs have more favorable pharmacokinetics and do not bind significantly to plasma proteins or influence hepatic metabolism, and no clinically significant adverse effects of vigabatrin and levetiracetam in combination with sodium valproate have been reported (2, 3, 7, 10).

Encephalopathy with normal ammonia during VPA treatment was reported in 13 of 19 patients in a German study, but no patient had erythrodermia. The mechanism of a direct toxic effect of VPA on neurotransmitters was postulated for encephalopathy (15). All patients recovered after VPA withdrawal, as was the case in our patient. The same toxic mechanism might be responsible for erythrodermia.

Patients with brain damage and intellectual disability may be at a higher risk of VPA-induced encephalopathy without hyperammonemia or elevated valproate levels (16). Our patient had a pronounced developmental delay after severe meningoencephalitis early in life; therefore he was at higher risk of VPA-induced encephalopathy. The VPA levels were not monitored.

Three forms of encephalopathy have been described in children and adults treated with VPA: encephalopathy due to the direct toxic effect of VPA with high serum levels of VPA and normal ammonia, hyperammonemic encephalopathy, and encephalopathy with impaired liver function (15–17). However, none of these forms include erythrodermia. We presume that our patient clinically belongs to the early phases of DRESS syndrome. This report highlights the increased potential for adverse reactions when prescribing antiepileptics as polytherapy, and therefore cooperation

between clinical pharmacists and clinicians is important. This occurs in many hospitals in Slovenia (18, 19), but was absent in this case.

In the field of serious cutaneous ADRs such as Stevens–Johnson syndrome or DRESS syndrome, there was some hope of finding biochemical markers or genetic predictors, but at present it is impossible to assess the risk of these severe reactions in each patient.

The role of genetic factors involved in idiosyncratic drug reactions is so far limited to the presence of human leukocyte antigen HLA-B*1502 allele as a risk factor for skin hypersensitivity. For carbamazepine-induced SJS/TEN, a strong association has been found with the HLA-B*1502 allele in southeast Asian patients, but not in Caucasian and Japanese patients. Future research may help reveal additional genetic predictors of susceptibility to severe adverse reactions to antiepileptic drugs.

Conclusion

Drug-induced hypersensitivity reactions are of major medical concern because they are associated with high morbidity and high mortality. Antiepileptics are known to be quite well tolerated and safe, but physicians and clinical pharmacists should constantly be aware of the risk of adverse effects. From a clinical point of view, cutaneous manifestations may represent an important diagnostic clue to severe ADR and should always be kept in mind.

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