Successful Treatment of Antiepileptic Drug Hypersensitivity Syndrome With Intravenous Immune Globulin

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ABSTRACT. Intravenous immune globulin (IVIG) has proved beneficial for severe immunologically related cutaneous adverse reactions. We report a child with severe antiepileptic drug hypersensitivity syndrome who was successfully treated with IVIG. IVIG should be considered in the pharmacologic armamentarium of severe antiepileptic drug hypersensitivity syndrome. Pediatrics 2001;107(1). URL: http://www.pediatrics.org/cgi/content/full/107/1/e14; antiepileptic drugs, hypersensitivity, immune globulin.

ABBREVIATIONS. AHS, antiepileptic drug hypersensitivity syndrome; SCAR, severe cutaneous adverse reaction; IVIG, intravenous immune globulin.

Antiepileptic drug hypersensitivity syndrome (AHS) is an adverse drug reaction associated with the aromatic antiepileptic drugs phenytoin, carbamazepine, phenobarbital, and primidone.1 The syndrome is defined by the triad of fever, rash, and symptomatic or asymptomatic internal organ involvement, including primarily hepatitis, nephritis, and lymphadenopathy. The rash may range from mild maculopapular exanthem to erythrodermia, pustular rash, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. AHS may be associated with severe morbidity and sometimes even mortality.1,2 In addition to early withdrawal of the offending drug, treatment is mostly symptomatic.3 The use of glucocorticosteroids, cyclophosphamide, and cyclosporine has been reported in patients with severe cutaneous adverse reaction (SCAR).4–6 Intravenous immune globulin (IVIG) proved beneficial in 3 acquired immunodeficiency syndrome patients with toxic epidermal necrolysis or SCAR7,8 and in 2 patients with Stevens-Johnson syndrome.9 Because of the severity of AHS and its potential mortality, we used IVIG to treat this condition and, herein, report its efficacy.

A 6-year-old boy was admitted with severe aseptic meningencephalitis. Because of persistent generalized and focal seizures, he was treated with phenytoin and phenobarbital. On the 18th day of treatment, a maculopapular rash developed on the trunk and face and soon turned into severe painful generalized erythroderma. The next day, his temperature rose to 38.5°C. Physical examination revealed massively swollen and fissured lips, significant cervico-occipital lymphadenopathy, severe allergic conjunctivitis with periorbital edema, and grayish-white ulcers on the buccal mucosa. An intention tremor was noted. The ankles were swollen and edematous, with no hepatosplenomegaly. Laboratory results were: total leukocytes (7.2 × 10⁹/L) with 17% eosinophils (absolute eosinophils, 1224 × 10⁶/L), erythrocyte sedimentation rate (101 mm/hour), and a mild elevation in liver enzymes (aspartate aminotransferase, 55 U/L). Urinalysis was normal. The clinical diagnosis was AHS.

The phenytoin was stopped, and the phenobarbitol dosage was tapered down. The patient was treated with oral corticosteroids (betamethasone, 0.4 mg/kg), H1 blocker (dimethindene maleate, fenistil), and paracetamol. However, 5 days later, he appeared severely ill and toxic. Temperature was 39°C and despite the withdrawal of the phenytoin, the rash, generalized edema, and involvement of his oral mucosa and conjunctiva had worsened, and he was bedridden. Considering his deteriorating condition, we decided on a trial of IVIG (1 g/kg/day for 2 days). Within 24 hours of the first IVIG dose, the patient showed dramatic improvement. Temperature dropped to 37.8°C and remained normal thereafter (Fig 1). The intensity of the rash decreased, and general-ized superficial exfoliation developed with new healthy skin appearing underneath. The exfoliation was very superficial without an secondary infection and with no scars. There was also rapid improvement of the mucosal involvement. No adverse effects of the IVIG were noted. On the eighth day after treatment with IVIG, the patient was discharged, after complete healing of skin. He was afebrile, and the conjunctivitis, oral ulcers, and edema had all disappeared. The lymphadenopathy slowly regressed. During 6 months of follow-up, the child felt well with no recurrence of symptoms. Laboratory abnormalities improved gradually. Total eosinophil count dropped to 575 × 10⁶/L 5 weeks after IVIG.

![Fig 1. Body temperature of a child with AHS before and after treatment with IVIG.](http://www.pediatrics.org/cgi/content/full/107/1/e14)
therapy, sedimentation rate and liver function tests were within normal range after a few weeks.

**DISCUSSION**

AHS is a severe and sometimes fatal adverse reaction to aromatic antiepileptic drugs. The course is long, even in mild cases, with normalization of the clinical (eg, rash and fever) and laboratory (eg, eosinophilia) abnormalities occurring gradually over several weeks. Management includes discontinuation of the offending drug as well as multifaceted treatment, focusing on systemic care, prevention of infection, skin care, management of the ocular disease, and treatment of ongoing seizures.

We describe a child with severe AHS who showed a dramatic response to IVIG within 24 to 48 hours, with an improvement in overall well-being and alleviation of symptoms of fever, rash, edema, conjunctivitis, and oral ulcers.

The pathogenesis of AHS is not yet fully understood, but there is considerable evidence that the immune system plays a major role. The issue of immune modulation in SCAR is controversial. A small prospective study of the use of intravenous methylprednisolone in children with Stevens-Johnson syndrome revealed significant improvement in both the duration of the fever and the skin eruption. In other series of Stevens-Johnson syndrome, patients treated with steroids had no mortality and no scarring. However, steroids themselves have been reported to cause SCAR. There are some safety considerations as well; in one study, patients treated with steroids for toxic epidermal necrolysis had higher mortality rates during sepsis. Some authors recommend the use of steroids only for Stevens-Johnson syndrome and not for toxic epidermal necrolysis. So far, reports on the use of IVIG for SCARs are anecdotal. Moudgil et al reported that IVIG improved the course of Stevens-Johnson syndrome caused by antibiotics, and there are 2 reports of patients with acquired immunodeficiency syndrome who were treated with IVIG for SCAR. Most recently, 10 patients with toxic epidermal necrolysis were treated with IVIG, with a rapid interruption of the progression of the skin disease (within 24–48 hours). In 1 of the 10 patients, the culprit agent was phenytoin, and in another, it was carbamazepine. Our patient showed a remarkable improvement in AHS after the addition of IVIG to steroids. The mechanism whereby IVIG led to improvement in SCAR is not fully understood. It has been shown that IVIG blocks CD95 (Fas), a cell-surface receptor on keratinocytes, which plays a role in triggering apoptosis. Antibodies present in IVIG blocked Fas-mediated keratinocyte death in vitro and in 10 patients with toxic epidermal necrolysis. We suggest that a similar mechanism may play a role in IVIG therapy for AHS.

**CONCLUSION**

The present report, taken together with earlier ones on the benefit of IVIG for SCAR, suggests that IVIG should be considered in the treatment of severe AHS. More cases and controlled studies are needed to evaluate the efficacy of IVIG for AHS.

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