

Case Report

Glucocorticoids for Treatment of Severe Pediatric Drug Hypersensitivity Syndrome

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ABSTRACT

Drug hypersensitivity syndrome (DHS) is a potentially life-threatening form of drug reaction that is particularly associated with anticonvulsants. The role of glucocorticoids (GC) for treatment of this condition is controversial. We describe a child with DHS including severe cutaneous and hepatic involvement, which improved during GC treatment, flared when GC were inadvertently withdrawn, and resolved once they were again given. Our experience suggests GC may be of benefit to children with severe DHS. (Pediatr Asthma Allergy Immunol 2005; 18[3]:156–160.)

INTRODUCTION

DRUG HYPERSENSITIVITY SYNDROME (DHS), also referred to as DRESS (drug rash with eosinophilia and systemic symptoms), is a potentially severe form of untoward drug reaction characterized by fever, rash, lymphadenopathy, hepatitis, and hematologic abnormalities. Involvement of other organ systems, manifesting as renal failure, carditis, pneumonitis, myositis, enteritis, meningoencephalitis, and/or thyroiditis may also occur.^{1–3}

There are several reports describing improvement in patients with DHS during treatment with systemic glucocorticoids (GC),^{4–7} but there are no controlled trials examining the efficacy of GC in this disorder.

In this report we describe a child who suffered from DHS with hepatic involvement caused by carbamazepine. His condition responded favorably to oral GC, but flared when therapy was abruptly interrupted. Resumption of GC treatment with subsequent gradual tapering resulted in resolution of his disease.

CASE REPORT

A 6-year-old boy presented in March 2003 with a severe rash. He had been seen by a neurologist 3 weeks previously for seizures of new onset. An electroencephalogram showed localized spike and wave activity in the left temporo-occipital region, and computerized tomography showed no structural brain abnormalities. After baseline hepatic enzymes and complete blood count were measured, therapy with oral carba-

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mazepine was begun. He received no other medications. An urticarial rash appeared after two weeks. Carbamazepine was withheld, prednisone 2 mg/kg/day was given with rapid improvement, and 5 days later carbamazepine was resumed. Within hours, the rash re-appeared accompanied by malaise, and he was referred for hospitalization.

Upon admission the child was ill appearing and complained of severe pruritis. Oral temperature was 38°C. A generalized urticarial rash was present, with no other abnormal physical findings. Carbamazepine was stopped, and H1 antihistamines were given. Over the next day the rash became morbilliform and more intense, and fever rose to 40°C. Jaundice appeared, and generalized lymphadenopathy, hepatomegaly, swelling of the face and distal extremities, red cracked lips, palatal petechiae, and non-purulent conjunctivitis were observed. Laboratory studies (Table 1) revealed eosinophilia; elevations in serum bilirubin and transaminases; and hypoalbuminemia. Serologic tests for Hepatitis A, B, and C viruses as well as Epstein-Barr and cytomegalovirus disclosed no evidence of acute infection. Therapy with oral Prednisone, 2 mg/kg/day was begun. Over the next 10 days the rash, signs of mucous membrane inflammation, lymphadenopathy, and hepatomegaly subsided completely, and laboratory abnormalities gradually improved. The patient was discharged home with instructions to continue prednisone therapy in tapering doses.

He returned to the Emergency Department at 36 h later because the rash had reappeared. His father reported that prednisone had not been given at home. A severe generalized rash, as well as fever, hepatomegaly, lymphadenopathy, signs of mucositis, and conjunctivitis were noted. Laboratory studies disclosed leucopenia, eosinophilia, marked elevations of hepatic transaminases, and hypoalbuminemia. Intravenous methylprednisolone, 2 mg/kg/day was given, with gradual improvement of physical findings and laboratory abnormalities over the next several days. After 1 week, treatment was switched to oral prednisone, which was tapered over the next month. Desquamation of the hands and feet occurred 2 weeks later, but otherwise the patient remained well, and laboratory results stayed within the normal range. Polymerase chain reaction-based tests detected no human herpes virus-6 DNA in sera obtained during either the first or second hospitalization.

DISCUSSION

In this report, we describe a child who developed a rash two weeks after commencement of carbamazepine treatment for newly diagnosed epilepsy. Upon continued exposure to the medication, the rash worsened, and subcutaneous edema, generalized lymphadenopathy, hepatomegaly with elevated transaminases, eosinophilia, and constitutional symptoms appeared. The differential diagnosis of DHS in children includes viral exanthems, toxic epidermal necrolysis, the hypereosinophilic syndrome, Kawasaki disease, and systemic onset systemic juvenile chronic arthritis.² However, the characteristic multi-organ system involvement of this patient's illness, the interval from initiation of carbamazepine treatment to appearance of rash, and negative viral serologies, are most consistent with the diagnosis of DHS.

TABLE 1. LABORATORY RESULTS

<i>Laboratory result</i>	<i>2/4/03, Daily GC dose begun 2 mg/kg</i>	<i>10/4/03, 8 days of treatment completed</i>	<i>13/4/04, withheld 48 h</i>	<i>20/4/03, resumed 2 mg/kg</i>	<i>11/5/03, after taper</i>
WBC/ μ L	17,000	18,200	16,500	22,000	18,700
Eosinophils/ μ L	2500	1400	1300	300	170
Albumin (g/L)	27	37	33	36	45
Bilirubin (μ mol/L)	26	14	50	9	6
AST (IU/L)	210	176	1694	44	23
ALT (IU/L)	200	341	1402	299	33
LDH (IU/L)	2176	1025	5176	880	482

The disease exacerbation which occurred after drug was continued despite the appearance of a rash emphasizes the importance of prevention: DHS should be suspected in patients who develop a rash beginning 1–8 weeks after beginning chronic drug therapy. If the diagnosis is confirmed, further use of the suspected drug is permanently contraindicated.

Carbamazepine, the cause of this child's disease, is an aromatic anticonvulsant that is chemically related to phenytoin and phenobarbital. Collectively, these three drugs are by far the most common cause of DHS, affecting as many as 0.1% of patients who receive them. *In vitro* studies show up to 80% cross-sensitivity between them,⁸ and 40–60% clinical cross-sensitivity has been described,⁹ which significantly limits anti-epileptic treatment options for a child who has experienced this form of reaction. Lamotrigine, another aromatic anticonvulsant, may cause DHS but does not appear to exhibit cross-sensitivity to the above medications.¹⁰ Valproic acid is believed to be a less common cause of DHS, and is generally considered a safe alternative for patients who have experienced reactions to aromatic anticonvulsants. However, there is a report of a patient with apparent cross-sensitivity to carbamazepine and valproic acid.¹¹ Other relatively frequent causes of DHS in childhood include minocycline and sulfonamides,² but a wide variety of other drugs have also been implicated.

The pathogenesis of DHS is complex and incompletely understood. Risk may be as high as 25% for individuals with a first degree relative who experienced DHS,¹² implicating genetically determined factors. In addition, metabolic factors,⁸ drug dose,¹³ and concomitant administration of other drugs¹⁴ may also confer increased risk.

Immune-mediated mechanisms also appear to be an important pathogenic factor. With respect to cell-mediated immunity, *in vitro* studies of lymphocyte transformation have demonstrated drug-specific T-cell reactivity in patients recovered from DHS.^{15,16}

A possible role for eosinophils in DHS is suggested by increased numbers of these cells in the peripheral blood, and by reports of eosinophilic and lymphocytic infiltration of the papillary dermis and internal organs.^{6,17} Furthermore, increased concentrations of interleukin-5, a cytokine associated with eosinophilia, have been found in the plasma of patients with active disease.¹⁸ Insofar as GC have been shown to be efficacious for treatment of other human diseases associated with activated cellular immunity and/or eosinophilia, these observations provide theoretic support for the use of GC in DHS.

This waxing and waning of both clinical and laboratory abnormalities according to whether or not GC were given strongly suggests that treatment affected the activity of this patient's disease. Hepatic failure occurs in up to 10% of cases of DHS, and is the most common cause of mortality.¹ In this regard, the apparent GC dependence of the activity of his hepatitis, evaluated by liver size and degree of transaminase elevation, is of special interest. In the absence of controlled trials, current knowledge regarding the efficacy of GC in DHS is limited to case reports mainly from the adult literature, including a description of phenytoin-induced DHS whose activity varied according to GC dose in a manner similar to that observed in this patient.⁵ There are also small pediatric series describing patients with DHS, some of whom were treated with GC.² The use of other immunomodulatory agents for DHS, including immune serum globulin¹⁹ and cyclosporine A,²⁰ has also recently been described. In our opinion, the present report provides important evidence that childhood DHS, and DHS-associated hepatitis in particular, are GC-responsive conditions.

Several recent studies have found evidence for reactivation of herpesvirus-6 in patients with DHS, sometimes in association with hypogammaglobulinemia.²¹ These reports suggest that HHV-6 may be a co-factor in the pathogenesis of DHS, and have raised concern that immunosuppressive treatment might prolong the disease by facilitating viral replication.^{22,23} However, HHV-6 infection is nearly ubiquitous in humans after infancy,^{24,25} and evidence for its reactivation has been observed in a variety of conditions associated with altered immune regulation including common febrile illnesses of infancy and childhood.^{26,27} There are no case controlled studies examining the prevalence of HHV-6 activation in patients with DHS as compared to in other forms of systemic illness. Thus, at present it is unclear whether HHV-6 represents a co-factor in the pathogenesis of DHS, or rather a non-specific consequence of generalized immune activation. Additional studies will be necessary to further clarify this issue.

In summary, pediatric allergists should have a high index of suspicion for DHS in children who present with fever and rash after having received medications, in particular anticonvulsants, during the preceding

two months. Mild cases of DHS may be managed with supportive therapy and/or topical corticosteroids. The favorable response of this patient's disease to systemic GC treatment supports their use in children with DHS when hepatic other potentially life-threatening complications are present.

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