Anticonvulsant Hypersensitivity Syndrome: Report of 2 Cases from Kuwait

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Abstract
Objective: To illustrate the clinical features, laboratory findings, and management of anticonvulsant hypersensitivity syndrome (AHS), emphasizing the importance of recognizing its multiple clinical components and raising awareness of the cross-sensitivity among different antiepileptics. Clinical Presentation and Intervention: Two cases of AHS due to carbamazepine and a combination of sodium valproate and lamotrigine are reported. Both patients presented within the first month of starting the new antiepileptic medication with fever, skin rashes, hematological abnormalities, and hepatitis. The offending antiepileptic drugs were immediately stopped in both cases. Skin rashes responded to intravenous immunoglobulin in case 1 and to intravenous hydrocortisone in case 2. Conclusion: AHS is a serious, life-threatening condition. This report demonstrates that the most important steps in the management of AHS are to recognize the disorder, discontinue the offending antiepileptic drug, and provide supportive care in an inpatient setting and treat with benzodiazepines if seizures occur.

Introduction
Phenytoin has long been recognized as a cause of hypersensitivity reaction, originally reported as fever, rash and lymphadenopathy [1]. The systemic manifestations (including primarily hepatitis and nephritis) were first described in 1950 as the Dilantin sensitivity syndrome [2]. Later it was observed that the syndrome was also caused by other aromatic antiepileptic drugs (carbamazepine, phenobarbital and primidone) and was therefore referred to as anticonvulsant hypersensitivity syndrome (AHS) in 1988 [3]. Recently, other antiepileptics such as lamotrigine have been reported to cause AHS, especially when used in combination with sodium valproate [4]. AHS remains a poorly understood problem consisting of countless diagnostic features with which most physicians are unfamiliar. In this report, we describe 2 cases of AHS due to carbamazepine and a combination of sodium valproate and lamotrigine.

Case Reports

Case 1
A 7-year-old Kuwaiti girl was well until the age of 5 years when she had three attacks of simple partial seizures in the form of mouth twitches. Two years later she developed generalized tonic clonic convulsions. The patient was given carbamazepine and after 1 month of treatment, she was admitted to the hospital with fever and general-
ized pruritic skin rash. She was toxic and febrile (40 °C). She had severely congested throat with significantly enlarged strawberry tongue and tender cervical lymphadenopathy. The rash was maculopapular and erythematous involving the trunk and extremities. After 3 days the rash became more confluent with severe itching and could peel easily. She developed icteric sclera with swollen face and bilateral periocular edema. There was tenderness over the right hypochondrium with a massively enlarged liver, 7 cm below the right costal margin. The carbamazepine was withdrawn immediately and the patient was placed on oral and local antihistamine. Investigations as given in table 1 revealed: leukocytosis with eosinophilia and normal erythrocyte sedimentation rate. Liver function tests showed elevated liver enzymes and a high bilirubin level. Urinalysis and renal function tests were normal. Throat and blood cultures were sterile. Monospot test was negative, nti-streptolysin O titer (ASOT) >200, and virology study for Epstein-Barr virus and cytomegalovirus infection was negative. Because the general condition of the patient did not improve she was given intravenous immunoglobulin in a dose of 2 g/kg) in 24 h. After 36 h, the patient became afebrile with improved general condition and liver function. She continued to have skin rash for another 7 weeks. Currently, she is doing well on sodium valproate only.

**Case 2**

Another 7-year-old Kuwaiti girl had an uneventful medical history until the age of 3 years when she had the first attack of febrile seizures. Two years later, she developed frequent absence seizures degenerating to complex partial seizures (staring, loss of consciousness and incontinence of urine) for about 1–2 min, 10 times per day. She was on incrementally adjusted doses of sodium valproate, initially 5 mg/kg/day and subsequently increased up to 40 mg/kg/day for a better control of the seizures. Two weeks before admission lamotrigene was added to her medication (in step-up doses of 1–5 mg/kg/ day) because of sodium valproate-induced persistent thrombocytopenia. On admission she had tremors, fever, cervical lymphadenopathy, and pruritic pleomorphic skin rash. Blood investigations (table 1) revealed pancytopenia, eosinophilia, with atypical lymphocytes and mildly elevated liver enzymes. Virology screen ruled out Epstein-Barr virus infection. Both sodium valproate and lamotrigene were stopped within 2 days and were replaced with clonazepam. Her blood investigations reverted to almost normal levels. She continued to have skin rashes for another 3 weeks that responded to intravenous hydrocortisone. The patient continues to be on clonazepam and the seizures are under control.

**Discussion**

AHS is a rare syndrome that is characterized by the triad of fever, skin rash, and internal organ involvement [3]. More commonly, patients on antiepileptic medications develop an isolated skin eruption without fever or internal organ involvement [5]. The exanthem often subsides with reduction of dosage despite continued anticonvulsants in some patients. The incidence of severe skin reactions (Stevens-Johnson syndrome, or toxic epidermal necrolysis) as part of AHS was found to be as high as 9% among 53 patients with AHS induced by phenytoin, or carbamazepine, or phenobarbital [3]. As in our 2 cases, the diagnosis of AHS is difficult because this syndrome can have a variable spectrum of clinical and laboratory findings, and may mimic infectious, neoplastic, and collagen disorders. Currently, diagnostic criteria include the following: fever, rash, lymphadenopathy, hepatitis, hematologic abnormalities (hemolytic anemia, thrombocytopenia, agranulocytosis, eosinophilia, leukocytosis, and lymphocytosis), periocular/orofacial edema, myalgia/arthralgia, nephritis, pharyngitis, and pulmonary manifestations [6]. These manifestations usually appear within the first 2–8 weeks after initiation of anticonvulsant therapy and resolve on its discontinuation [7] as observed in these 2
cases that had similar clinical presentations and laboratory findings in spite of the use of different anticonvulsants. Recently AHS has been described in children due to carbamazepine as in case 1 [8] and due to adding lamotrigine to sodium valproate as in case 2 [4]. The pathogenesis of this syndrome is still poorly understood. It is thought that predisposed patients might be unable to detoxify areneoxide metabolites of antiepileptic drugs adequately, initiating an autoimmune attack on the target organs where the cytochrome P-450 system is produced. It has also been proposed that the antiepileptic drug mimics viral infection by activating CD4+ and CD8+ T cells, with the concomitant production of interleukin-5, the main maturation factor for eosinophils [9].

AHS is a serious, life-threatening condition; rare fatalities have been reported [10]. It should be promptly recognized and managed. In this study the offending antiepileptic drugs were immediately stopped in both cases and replaced with intravenous immunoglobulin in case 1 and intravenous hydrocortisone in case 2. It has been reported that intravenous immunoglobulin can shorten and ameliorate the clinical course of the anticonvulsant hypersensitivity disease [11] as exemplified in case 1. As such it is recommended that all patients suspected to have this syndrome should be immediately admitted to hospital; the offending antiepileptic drug should be discontinued with minimal risk of status epilepticus [12]. Benzodiazepines may be used for short-term control and continuous intravenous infusion of diazepam is a reasonable therapeutic choice for the management of status epilepticus in a patient with AHS [13]. Aromatic antiepileptics (carbamazepine, phenobarbital, phenytoin, and primidone) and some other anticonvulsants (lamotrigine, and gabapentin) should be avoided because cross-reactivity among these drugs is as high as 70–80% [14]. Supportive and symptomatic treatment, focusing on nutritional care, prevention of infection, skin care, and management of ocular disease, is essential [12]. Intravenous corticosteroid (0.5 mg/kg/day) has been considered the standard of care in cases with extensive skin rash, or in cases with involvement of internal organs (as in our 2 cases).

First-order relatives of patients who have experienced AHS have been reported to have an increased risk [15]. It has been suggested that the AHS may be inherited as an autosomal codominant pattern [3]. Therefore, both the patient and his family should be counseled. Lymphocyte toxicity assay and patch testing [16] can be used to confirm the diagnosis of AHS. If positive, in vitro testing of alternative antiepileptic drugs can be helpful in guiding the patient’s future therapy. Patient’s relatives can be screened by lymphocyte toxicity assay and should be informed about the increased risk for AHS.

**Conclusion**

AHS is a serious, life-threatening condition. This report demonstrates that the most important steps in the management of AHS are to recognize the disorder, discontinue the offending antiepileptic drug, and provide supportive care in an inpatient setting and treat with benzodiazepines if seizures occur. Intravenous immunoglobulin and systemic corticosteroids should be considered especially in cases with severe skin rashes.

**References**