Antiepileptic Hypersensitivity Syndrome: Clinicians Beware and Be Aware

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Antiepileptic hypersensitivity syndrome is a serious idiosyncratic, non–dose-related adverse reaction reported to occur with phenytoin, phenobarbital, carbamazepine, primidone, and lamotrigine. The reaction usually develops 1 to 12 weeks after initiation of therapy with one of the above agents and is recognized by the classic triad of fever, rash, and internal organ involvement. Immediate discontinuation of the suspected anticonvulsant is essential for good outcome. Patients usually are managed supportively with hydration, antihistamines, H_2-receptor blockers, and topical corticosteroids. In severe cases, the use of systemic corticosteroids may be necessary. The use of intravenous immune globulin should be limited to severe cases where Kawasaki disease or idiopathic thrombocytopenic purpura cannot be ruled out. Education of health care professionals and patients is imperative to improving outcomes and prevention of this reaction in the future.

Introduction

Adverse drug reactions (ADRs) are responsible for up to 20% of emergency department visits [1], are implicated as the fourth to sixth leading cause of death in the United States [2•], and are an important public health issue. Until recently, very little attention was focused on estimating and preventing ADRs in children, who are the most vulnerable group of patients because of the lack of controlled drug studies, leading to "off-label" prescribing practices in this patient population. Among the ADRs, allergic cutaneous reactions or drug eruptions occur in up to 8% of patients [3]. Most cutaneous drug reactions are relatively benign and resolve completely upon drug discontinuation, with a few leading to significant disability or death. Anticonvulsant medications are among the most common classes of drugs responsible for either isolated cutaneous reactions or cutaneous reactions as a component of antiepileptic hypersensitivity syndrome (AHS).

Antiepileptic hypersensitivity syndrome is a severe, dose-independent, idiosyncratic cutaneous reaction to aromatic anticonvulsants that may result in end organ damage and death. In the 1930s, AHS was referred to as "hydantoin hypersensitivity syndrome" or "phenytoin hypersensitivity syndrome" because the initial reports of hypersensitivity to antiepileptic drugs primarily involved phenytoin (diphenylhydantoin) [4]. Since then, there have been numerous case reports in the literature describing similar reactions to other antiepileptic drugs (AEDs), including phenobarbital, carbamazepine (CBZ), primidone, and lamotrigine. A common feature of the above-mentioned drugs is their aromatic ring structure (Fig. 1). Despite the inconsistency in the literature classifying lamotrigine as an aromatic anticonvulsant, it is our opinion that lamotrigine should be grouped with the classic aromatic AEDs as a potential cause of AHS due to the large number of case reports describing AHS with this agent [5–7].

Incidence

The majority of published reports quote the incidence of AHS as ranging between one in 1000 to one in 10,000 new exposures to aromatic anticonvulsants [8,9••,10]. The true incidence of AHS is unclear and probably largely underestimated because of the lack of consensus in the literature about its classification, variable presentation (which often mimicks other more common disease states), and the unfamiliarity with this syndrome in the medical community. The risk of AHS within the first 2 months of starting a new AED is estimated to be 2.3 to 4.5 per 10,000 phenytoin (PHT) users and one to 4.1 per 10,000 CBZ users [11]. Pediatric patients may be at an increased risk for the development of this syndrome because of the higher incidence of seizure disorder in the first decade of life [12,13]. There appears to be a genetic predisposition for abnormal metabolite detoxification of aromatic AEDs [14] Family members (particularly monozygotic twins) of patients with a history of anticonvulsant hypersensitivity may be at a particularly high risk for development of this syndrome.

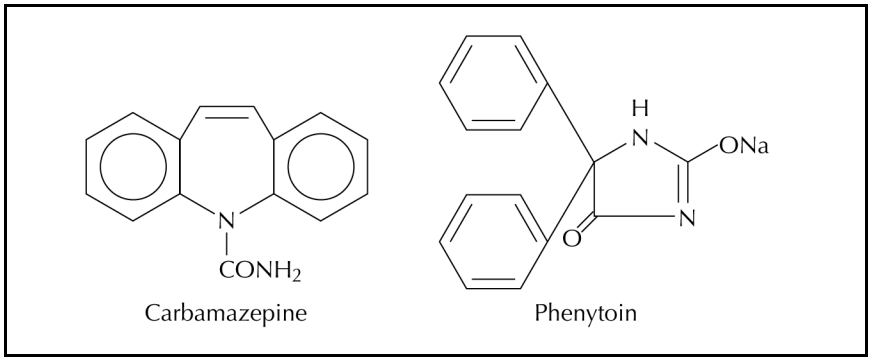

Figure 1. Structural formulas of carbamazepine and phenytoin.

Other proposed potential predisposing factors are a history of allergic reactions to other medications and viral infections (Epstein-Barr virus, human herpesvirus-6, cytomegalovirus) [15].

Pathogenesis

The proposed cause of AHS is an immune reaction mediated by the toxic metabolites of the aromatic anticonvulsants leading to cell death, mutations, and tumors. The cytochrome P-450 (CYP 450) enzyme system is responsible for metabolizing the aromatic anticonvulsant agents to arene oxide, and the epoxide hydrolase enzyme system is responsible for detoxifying these metabolites. Susceptible individuals may have a diminished activity of epoxide hydrolase. There is some evidence to suggest that the diminished activity or a relative deficiency of epoxide hydrolase is related to an autosomal codominant inheritance at the cellular level. Since a sensitization period is required for AHS to develop, it usually occurs 7 to 10 days after the first exposure; however, it may develop much sooner after a repeated exposure.

The toxic metabolites (arene oxides) may alter the human CYP 450 3A enzyme to resemble the rat CYP 450 3A, which differs by only one amino acid. These neoantigens can initiate an autoimmune attack on organs that produce the CYP 450 enzymes, *ie,* the stomach, liver, intestines, and lungs [16] Evidence that the metabolites, not the parent compounds, are the culprits for AHS is proven by experimental assays in which lymphocytes (which contain epoxide hydrolase) are incubated with mouse CYP 450 and phenytoin. The lymphocyte death rates are higher than controls from patients who have a clinical diagnosis of AHS; furthermore, lymphocytes that were not incubated with CYP 450 had the same cell death rates as controls. The role of the epoxide hydrolase enzyme system in AHS is demonstrated with the addition of 1,1,1-trichloro-2-propene oxide (TCPO) (a noncompetitive inhibitor of epoxide hydrolase) in the same assay setup, and it is observed that the lymphocyte cell death rates were similar as those observed in assays with lymphocytes derived from patients with AHS. The substitution of carbamazepine and phenobarbital in these experiments for phenytoin yielded the same results [17].

Manifestations

Appropriate identification of AHS represents a diagnostic and therapeutic challenge. This syndrome often may be mistaken for a variety of infectious, immunologic, and neoplastic conditions because of its delayed onset in relation to initiation of the antiepileptic therapy (Table 1).

The constellation of symptoms associated with AHS is reported in Table 2 and includes a classic triad of fever, rash, and lymphadenopathy or internal organ involvement. These manifestations may occur as soon as 7 days to up to 3 months after initiation of therapy with one of the associated antiepileptic agents, with the majority of cases reported within 2 to 8 weeks.

The onset of fever usually precedes the appearance of a rash by a couple of days. Patients may initially present with nonspecific, flu-like symptoms of fever, malaise, and pharyngitis. Skin involvement is most commonly described as erythematous, maculopapular, pruritic, blanchable, or confluent rash and usually involves the entire body. In severe cases, the rash may progress to the development of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or erythema multiforme. The relative risk (RR) of development of SJS/TEN in new users of AEDs is the highest within the first 8 weeks of therapy, with the individual RR of 57 for phenobarbital, 91 for PHT, 120 for CBZ, and 25 for lamotrigine [18]. Improvement in skin manifestations of AHS may take days to weeks after discontinuation of the aromatic anticonvulsant.

Another common finding is lymphadenopathy, which may display a spectrum of histopathologic changes ranging from benign lymphoid hyperplasia or "pseudolymphoma" to focal necrosis suggestive of lymphoma. The anticonvulsant-induced pseudolymphoma often is difficult to distinguish from a true lymphoma and may result in unnecessary treatment with chemotherapy.

The liver is the most common internal organ involved, with hepatotoxicity reported in up to 64% of patients [19••]. Transaminase elevations may be greater than 25 times the upper limit of normal at presentation and may take weeks to resolve. Mortality from AHS is directly correlated with the degree of hepatic involvement. Furthermore, the coadministration of other hepatotoxic medications (*ie,* acetaminophen on an around-the-clock basis to treat fever associated with AHS) may potentially worsen

Table 1. Differential diagnosis of antiepileptic hypersensitivity syndrome

Infectious diseases
Bacterial septic shock
Staphylococcal toxic shock
Infectious mononucleosis
Atypical measles
Viral hepatitis
Collagen vascular disorders
Kawasaki disease
Systemic lupus erythematosus
Polyarteritis
Polymyositis
Hematologic/oncologic conditions
Idiopathic thrombocytopenic purpura
Lymphoma
Mycosis fungoides

Table 2. Clinical features of antiepileptic hypersensitivity syndrome

Manifestation	Frequency* (%)
Fever	100
Skin rash	100
Lymphocytosis	71
Lymphadenopathy	70
Hepatic involvement	64
Atypical lymphocytes	50
Eosinophilia	42
Coagulopathy	42
Renal involvement	11
Pneumonitis	9

*Based on highest reported value in the literature.

the outcome (authors' own precaution). Up to 43% of patients also may develop coagulopathy associated with severe hepatic dysfunction and need to be monitored for any signs of bleeding [19••]. Administration of vitamin K may be necessary in these cases. Pathologic findings on liver biopsies in severe cases often reveal periportal inflammation, fatty infiltration, or even diffuse hepatic necrosis [20].

Other nonspecific clinical features of this syndrome are hepato- or splenomegaly, decreased appetite, facial or lower extremity edema, desquamation of the skin, fatigue, malaise, nausea, vomiting, scleral icterus, myositis, pneumonitis, and renal failure [19••,21]. A complete blood count should be drawn on every patient in whom a diagnosis of AHS is entertained. Laboratory findings that may be helpful in making a presumptive diagnosis of AHS include the presence of atypical lymphocytes or lymphocytosis, leukocytosis or leukopenia, thrombocytopenia, and eosinophilia. A nonspecific laboratory finding may be an elevated erythrocyte sedimentation rate (ESR).

Diagnostic Tests

Antiepileptic hypersensitivity syndrome is a clinical diagnosis of exclusion; however, there are some assays that may be performed to implicate a drug as a causative agent. Although not widely available, two of such in vitro tests are the lymphocyte toxicity assay and lymphocyte transformation (proliferation) test. These assays use lymphocytes isolated from heparinized blood and incubate them with the suspected anticonvulsant, and a positive diagnosis of AHS is based on the presence of toxic metabolites or demonstration of lymphocyte proliferation [22,23•]. These assays, however, are being used only in research centers and may not be readily available in the clinical setting since they are expensive and cumbersome to perform.

Review of Clinical Studies

Because of the relative rarity of AHS and difficulty in diagnosis, the majority of published literature about this syndrome is represented by case reports and small case series. The drugs implicated in causing AHS in two of the largest case series (Haruda, 1979 [21] and Bessmertny *et al.*, 2001 [19••]) were phenytoin, carbamazepine, and phenobarbital. Patients' age ranged from 1 month to 72 years in these reports. Approximately 15 patients were 20 years of age or younger in Haruda's series [21], but further specifics of clinical and laboratory results were not separated by age. Rash and fever were the most common manifestations in these two studies, followed by elevated liver enzymes, lymphadenopathy, eosinophilia, blood dyscrasias (leukopenia or leukocytosis, atypical lymphocytes, anemia), and coagulopathy (INR > 1.3). In the pediatric case series by Bessmertny *et al.* [19••], one patient each developed TEN, SJS, and erythema multiforme, compared with seven patients in Haruda's report [21] who developed erythema multiforme or SJS. The duration of therapy prior to initial manifestations of symptoms ranged from 9 to 90 days in the study by Bessmertny *et al.* [19••]. Since only 12 patients in the report by Haruda [21] had both fever and rash, the other 26 cases are likely to represent phenytoin allergy rather than true hypersensitivity reactions. The onset of symptoms in this report occurred 1 to 35 days from the start of therapy, although three patients were reported to have symptoms that occurred from 18 months to several years later. Only one death caused by severe liver injury occurred in the series by Bessmertny *et al.* [19••]. There was a strong correlation between the duration of therapy with the offending AED after onset of AHS symptoms and the severity of clinical symptoms or laboratory data change. It is interesting to note that in the pediatric case series, four patients were switched to another aromatic anticonvulsant after the reaction occurred. One patient died and two experienced rash and/or fever again, thus underscoring the importance of educating clinicians of the

high degree of cross-sensitivity from one aromatic anticonvulsant to another.

Lamotrigine is an antiepileptic agent indicated for refractory partial and generalized seizures and is administered as either monotherapy or add-on therapy. Schlienger *et al.* [7] identified 26 cases of lamotrigine-associated adverse drug reactions that had features consistent with AHS. Nine cases were reports published in the literature, and 17 cases were unpublished information obtained from the database of the World Health Organization Uppsala Monitoring Center through a search using terms that are consistent with descriptions of allergic reactions. Features that are consistent with AHS include the presence of a fever in all patients (37.5° to 41.5° C), exanthematous rashes in 77% (in 19% of cases, the cutaneous reactions progressed to SJS and TEN), eosinophilia in 69%, and liver enzyme abnormalities in 65%. Overall, in 46% of the cases, two or more organ systems other than skin were involved. In 40% of these patients, an aromatic anticonvulsant was given in conjunction with lamotrigine, and in 58%, valproic acid was the concomitant agent. Previous allergic or hypersensitivity reactions to another anticonvulsant agent were not reported in any of the published cases.

A recent panel of pediatric and adult epileptologists and dermatologists with expertise in cutaneous drug reactions analyzed published and unpublished data to determine the possible factors that may increase the risk of severe cutaneous reactions in children and adults who are prescribed lamotrigine. From this review, recommendations were made to physicians prescribing lamotrigine [24]. Factors that may increase the risk of lamotrigine rashes are excessive dose or rate of titration, the combination of lamotrigine with valproic acid, and possibly a history of skin or allergic reaction to another anticonvulsant drug. Thus, it is recommended for prescribers to not exceed manufacturer's dosing guidelines when prescribing lamotrigine, and physicians should be aware that dosing varies according to whether lamotrigine is added to valproic acid, an enzyme inducing agent, or used in monotherapy [24].

Treatment

Early recognition of AHS and discontinuation of aromatic anticonvulsants are essential in improving patient outcome. The onset of fever, rash, lymphadenopathy, or abnormalities in hepatic enzymes in a patient started on one of the above-mentioned antiepileptics within the last 3 months should serve as a presumptive evidence of AHS (pending results of diagnostic work-up) and warrants immediate discontinuation of suspected agents. A stepwise approach to a patient with suspected AHS is given in Table 3.

The therapy of AHS consists mainly of supportive care. The first step in the management of AHS should be the discontinuation of any aromatic anticonvulsant agent. Most patients are managed with antihistamines for pruritus (hydroxyzine being more potent than diphenhydramine) and topical corticosteroids. The use of H_2-receptor blockers or proton pump inhibitors is especially pertinent in patients with evidence of mucosal sloughing and suspected SJS/TEN to prevent the risk of gastrointestinal bleeding or ulcerations. Patients with SJS/TEN should be approached as burn patients, and intense fluid management may be required. Benzodiazepines, valproic acid, or gabapentin have been used safely for seizure control. However, due to its inherent risk of hepatotoxicity, especially in children less than 2 years of age, valproic acid therapy may not be a viable option during the first several weeks of AHS in patients with elevated hepatic enzymes. Tiagabine, topiramate, levetiracetam, and zonisamide, the newest anticonvulsant agents with chemical structures different from aromatic AEDs, may represent another alternative; however, the relatively slow speed of dose titration recommended for their administration may limit their usefulness in an actively seizing patient. The administration of acetaminophen, especially around the clock, or other hepatotoxic drugs should be avoided in patients with hepatic involvement.

The most controversial issue with regard to the management of AHS is the use of systemic corticosteroids and intravenous immune globulin (IVIG). Several case reports described success with the use of systemic corticosteroids or IVIG in severe cases of AHS [25–28].

The risk of systemic corticosteroids may outweigh the benefit in patients with infectious processes or disrupted skin barrier (*ie,* SJS or TEN). In fact, corticosteroids should not be used in patients with AHS who progress to TEN because of the increased mortality from sepsis [29]. If the choice to administer corticosteroids is made, prednisone or methylprednisolone intravenously have been used at doses of 1 to 2 mg/kg/d for 10 to 14 days. It is important to taper steroid doses slowly when patients show improvement because of increased risk of AHS recurrence when these agents are discontinued abruptly. Two case reports described successful use of IVIG (0.5 mg/kg/d for 4 days or 1 mg/kg/d for 2 days) in patients with suspected AHS [27,28]. Systemic corticosteroids were used in combination with IVIG in both cases. The contribution of IVIG to improvement in these patients' symptoms is hard to assess; therefore, routine use of IVIG in severe cases cannot be recommended at this point. One exception to this may be patients in whom it is difficult to distinguish between AHS and other life-threatening conditions (*eg*, idiopathic thrombocytopenic purpura or Kawasaki disease) in which the use of IVIG is indicated.

Considering that there is a 40% to 80% incidence of cross-sensitivity between the different aromatic anticonvulsants [30], both patients and health care providers should be informed about the dangers of rechallenging patients with one of these agents after an AHS has

Table 3. Suggested management of a patient with antiepileptic hypersensitivity syndrome

1. Stop suspected anticonvulsant immediately
2. Patients receiving AEDs for seizure control may be switched to topiramate, gabapentin, lorazepam, tiagabine, zonisamide, levetiracetam, or valproic acid
3. Obtain a complete blood count with differential, hepatic enzymes panel, and basic metabolic panel
4. Examine the patient for the presence of lymphadenopathy or hepato- or splenomegaly; perform a thorough skin examination
5. Provide supportive care with hydration, antihistamines, H_2-receptor antagonists (especially in patients with mucositis), and topical corticosteroids
6. Consider systemic corticosteroids for patients with life-threatening disease or severe end-organ involvement (eg, transaminases >5 times upper limit of normal and rising)
7. If desquamation or mucous membrane involvement is present, consider obtaining dermatology consult
8. Consider skin biopsy in patient with pustules or blisters
9. Avoid cross-reacting AEDs (PHT, CBZ, oxcarbazepine, phenobarbital, primidone, lamotrigine) and educate patients and family about the risk of cross-reactivity
10. Counsel family members about increased risk of this syndrome in first-degree relatives
11. Label the patient's chart with allergy to PHT, CBZ, phenobarbital, primidone, and lamotrigine

AED—antiepileptic drugs; CBZ—carbamazepine; PHT—phenytoin.

occurred. The reaction may develop as soon as one day after re-exposure to an aromatic AED and potentially may progress more rapidly than during the initial exposure. After a patient has experienced a confirmed AHS reaction, the importance of documenting that the patient is allergic to all aromatic AEDs cannot be overemphasized and is illustrated by numerous examples in the literature of the high risk of morbidity and mortality that may occur as a consequence [19••,31].

Conclusions

Antiepileptic hypersensitivity syndrome is a serious, potentially fatal adverse drug reaction that requires prompt diagnosis and management. Health care professionals need to be educated about heralding signs and symptoms and management of this syndrome. Significant incidence of cross-reactivity between aromatic AEDs needs to be taken into account when choosing an alternative anticonvulsant agent. Patients with a history of AHS should be labeled as being allergic to PHT, phenobarbital, primidone, CBZ, oxcarbazepine, and lamotrigine to prevent occurrence of this reaction in the future. Discontinuation of the culprit anticonvulsant is essential to avoid dire outcomes. Supportive care is the mainstay of therapy as no one agent has been shown to improve AHS outcomes. Systemic corticosteroids should be avoided in the case of TEN, but may be considered in patients with severe AHS. Educating the patient and family members is necessary to prevent this reaction from occurring or reoccurring.

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