Anticonvulsant Hypersensitivity Syndrome

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Background: Anticonvulsant hypersensitivity syndrome (AHS) is a serious but poorly understood and little known disease. It has been variously described in the literature since 1934. Fatalities are rare but have been reported.

__Methods:__ A MEDLINE search was undertaken from 1991 to present, using the keywords "anticonvulsant," "phenytoin," and "hypersensitivity." English language articles and their endnotes were reviewed, and neurologists, dermatologists, and specialists in hematology-oncology were consulted.

__Results:__ A case of AHS is described. Investigators have reported epidemiologic data and described the pathophysiology, diagnostic criteria, and management options.

__Conclusions:__ Family physicians should be aware of the AHS because of the high likelihood that patients with this syndrome will come first to their primary care physicians for care. Certain anticonvulsant medications have a high degree of cross-reactivity, the incidence of AHS is higher among first-degree relatives, and the disorder mimics systemic infection. If AHS is suspected, the antiepileptic drug should be discontinued. Supportive care should be directed to the appropriate organ systems, with particular attention to skin, eyes, and liver. Corticosteroid treatment might be effective in reversing the drug reactions, but it is not recommended in cases of suspected or actual infection because of the increased risk of immunocompromise, sepsis, and associated mortality. (J Am Board Fam Pract 2000;13: 364–70.)

Anticonvulsants have long been recognized as a cause of hypersensitivity reactions. Phenytoin use can be traced to 1916, when phenylethylhydantoin (phenytoin sodium), which was therapeutic for children with Sydenham chorea, was known to induce a hypersensitivity reaction. Phenytoin was then known as a "nerve sedative," and the hypersensitivity reaction, or "nirvanol sickness," resolved on discontinuation of the hydantoin.[1] The constellation of systemic manifestations was first described as the Dilantin sensitivity syndrome in 1950.[2] The syndrome was referred to as anticonvulsant hypersensitivity syndrome (AHS) in 1988, after its occurrence was found to be related to antiepileptic drugs other than phenytoin.[3] It remains a poorly understood malady consisting of a myriad of diagnostic features with which most physicians are unfamiliar.

Antiepileptic drugs have been implicated as etiologic agents for a variety of dermatologic eruptions, including the erythroderma associated with AHS, allergic or leukocytoclastic vasculitis, Stevens-Johnson syndrome (erythema multiforme major), and toxic epidermal necrolysis.[4,5] These dermatoses vary dramatically in description, severity, and systemic involvement, but all exhibit clear diagnostic features that differentiate them from AHS.

Methods

A literature search was conducted on MEDLINE from 1991 to present using the keywords "anticonvulsant," "phenytoin," and "hypersensitivity." The results of the search were limited to the English language, and the endnotes of these articles were also used. Neurology, dermatology, and hematology-oncology consultants helped to point out controversial areas.

Case Report

A 42-year-old woman was admitted to the family practice inpatient service of a tertiary-care medical center. Her medical history was notable for new nocturnal absence seizures degenerating to tonic-clonic seizures. She had been taking valproic acid for these seizures 9 months before admission; 6 weeks before admission her medication had been changed to phenytoin because of valproate-induced pancreatitis.

At admission she complained of 7 days of fever, pharyngitis, and the new appearance of a morbilliform rash. Her temperature was 102.2°F (39°C),

and her heart rate was 115 beats per minute. She had considerable facial edema and bilateral nonpurulent conjunctivitis, but no rhinorrhea or oral lesions. There was bilateral anterior and posterior cervical, as well as axillary, lymphadenopathy. Her lungs were clear, and findings on cardiac auscultation were normal. She had splenomegaly without petechiae.

Her family history was notable in that her 9-year-old daughter had a history of absence seizures, which degenerated to partial complex seizures, that had been treated 2 years previously with phenytoin. Shortly after starting phenytoin therapy, she developed a morbilliform exanthem, facial edema, and a mild elevation in hepatic transaminases. Her medication was changed from phenytoin to carbamazepine, and she was given 40 mg of oral prednisone for 7 days. The rash reappeared, and the carbamazepine was discontinued. Her seizures are now well-controlled with valproic acid, and there have been no side effects to date.

A blood analysis showed the patient's phenytoin level to be 12.7 μg/mL (normal = 10–20 μg/mL), white blood cell count $6 \times 10^3/\mu$L, hemoglobin 12.1 g/dL, platelets $183 \times 10^3/\mu$L, aspartate aminotransferase 41 U/L, alanine aminotransferase 60 U/L, and lactate dehydrogenase 759 U/L. Phenytoin was discontinued after consultation with a neurologist. The patient did not have a seizure. The exanthem progressed to erythroderma, exfoliating without bullae (Figure 1). A dermatologist was consulted, and a skin biopsy showed a superficial and deep dermal perivascular lymphocytic dermatitis with scale crust and numerous eosinophils (Figure 2). The white blood cell count, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase continued to climb to $20.3 \times 10^3/\mu$L, 123 U/L, 151 U/L, and 1,793 U/L, respectively. A hematologist-oncologist was consulted, and a peripheral blood smear showed atypical cleft lymphocytes (Figure 3). Bone marrow biopsy was remarkable for reactive hypercellularity (50%–60%) with marked eosinophilia and lobulated, cleft, atypical lymphocytes (pseudo-Sézary cells) (Figure 4). The patient was given 100 mg of intravenous methylprednisolone, then 60 mg of daily oral prednisone, until the rash began to resolve 12 days later. The white blood cell count peaked at $58.3 \times 10^3/\mu$L 5 days after corticosteroid therapy had begun. The patient subsequently suffered from an iatrogenic percutaneous line infection, but it resolved with intravenous antibiotic

Figure 1. Patient with facial edema and erythroderma, exfoliating without bullae.

therapy despite the previous addition of corticosteroids. Gabapentin was therapeutic for further seizure prophylaxis.

Discussion

AHS is uncommon, occurring in 1 in 1,000 to 1 in 10,000 patients, and is more frequently observed in African-Americans.[5,6] Some investigators suspect that the incidence is underestimated as a result of quantification based on using a denominator combining all antiepileptic drug users rather than new users only. These investigators report that among new users of antiepileptic drugs, there was an incidence of greater than 4 in 10,000 for patients taking phenytoin and carbamazepine, and no reactions among 1,504 patients taking valproic acid.[7]

The addition or substitution of antiepileptic drugs should be influenced by the 80% cross-sensitivity between phenytoin, phenobarbital, and carbamazepine; these drugs should not be combined or substituted.[6] First-degree familial association of AHS has been documented.[5] Immediate family

**Figure 2. Skin biopsy showing superficial and deep dermal perivascular lymphocytic dermatitis with scale crust and numerous eosinophils (hematoxylin and eosin, 100×).**

members of an affected patient should be prescribed antiepileptic medications only after specific counseling and precautions have been given.

Pathophysiology

The mechanism by which the antiepileptic drugs induce AHS is not well understood. Most data have
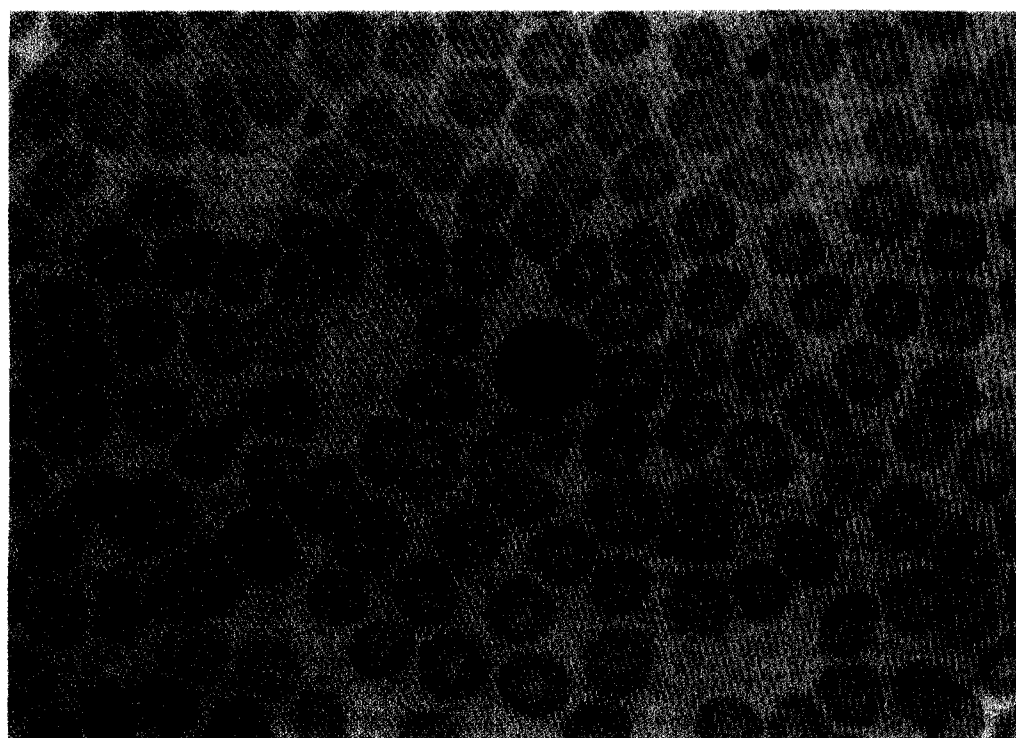
Figure 3. Peripheral blood smear showing a representative atypical cleft lymphocyte (Wright-Giemsa, 200×).

Figure 4. Bone marrow biopsy, remarkable for reactive hypercellularity (50%–60%), marked eosinophilia, and lobulated, cleft atypical lymphocytes (pseudo-Sézary cells) (hematoxylin and eosin, 200×).

been obtained for the antiepileptic drugs whose chemical structure is based on an aromatic ring (carbamazepine, phenobarbital, phenytoin, and primidone). Oxidation renders these compounds to nontoxic hydroxylated metabolites. The arene-oxide intermediate of this reaction might be responsible for toxic interactions with the cytochrome P-450 system.[3,6-8]

The cytochrome P-450 mixed-function oxidase system has been implicated in many drug reactions and interactions. Carbamazepine, phenobarbital, and phenytoin induce cytochrome P-450 3A (CYP3A), a subfamily of the cytochrome P-450 system.[9,10] Using rat liver microsome-derived cytochrome P-450, it has been shown that the serum of antiepileptic drug-exposed patients contains predominantly anti-rat CYP3A antibodies. The amino acid sequence of rat CYP3A differs from homologous human CYP3A by only one amino acid. Site-directed mutagenesis in vitro has confirmed that alteration of the rat cytochrome sequence to that of the human cytochrome sequence renders the rat cytochrome nonantigenic. Arene-oxide metabolites of antiepileptic drugs might alter these homologues to more closely resemble rat CYP3A, initiating an autoimmune attack on the target organs where these cytochromes are produced: stomach, liver, intestine, and lung. Predisposed patients might be unable to detoxify these metabolites adequately.[3,9,11-13]

It has also been proposed that AHS is virally mediated in association with human herpesvirus 6 in a fashion similar to the viral association of Epstein-Barr virus and ampicillin or the proposed association of sulfa hypersensitivity in HIV disease. Each of these three viral associations invokes an immunocompromised state that effectively disables detoxification pathways.[12] Other investigators have shown in vitro and in vivo evidence that carbamazepine and phenytoin mimic viral infection by activating CD4+ and CD8+ T cells, with the concomitant production of interleukin 5, the main maturation factor for eosinophils. These findings are similar to other superantigenic processes, eg, toxic epidermal necrolysis,[14] and contribute to our understanding of the exanthems associated with AHS.

The newer antiepileptic drugs, eg, lamotrigine and felbamate, might work in similar fashion;[10] lamotrigine has been implicated with the cutaneous manifestations of Stevens-Johnson syndrome and toxic epidermal necrolysis almost exclusively when used in combination with valproic acid.[15]

Diagnosis
The original description of AHS reported fever, rash, leukopenia, and eosinophilia.[1] Among investigators there is confusion with respect to diagnos-

Table 1. Diagnostic Criteria for Anticonvulsant Hypersensitivity Syndrome.

Finding	Incidence (%)
Fever	90–100
Rash	87–90
Lymphadenopathy	70
Hepatitis	50–60
Hematologic abnormalities*	23–50
Periorbital orofacial edema	25
Myalgia, arthralgia	20
Nephritis	11
Pharyngitis	10
Pulmonary manifestations	9

*Manifestations might include hemolytic anemia, thrombocytopenia, agranulocytosis, eosinophilia, leukocytosis, and lymphocytosis.

Table 2. List of Commonly Prescribed Anticonvulsants.

Aromatic Anticonvulsants*	Other Anticonvulsants
Carbamazepine	Felbamate
Phenobarbital	Gabapentin
Phenytoin	Lamotrigine†
Primidone	Valproic acid

*These anticonvulsants should not be combined or substituted because of the 80% cross-reactivity risk for the anticonvulsant hypersensitivity syndrome.
†Possible increased risk of serious adverse cutaneous reaction, eg, Stevens-Johnson syndrome or toxic epidermal necrolysis, if combined with valproic acid.

tic criteria for AHS in terms of clinical and laboratory data, resemblance of other disease processes, and a lack of consistent terminology.[16] The current diagnostic criteria are listed in Table 1.[3,16]

The fever can precede other manifestations by several days and can be low-grade, but it is generally high, spiking to 100°F to 104°F (38°C to 40°C). The rash occurs 3 weeks to 3 months after the antiepileptic drug is initiated and might or might not be pruritic.[5,8] Clinical cases of AHS have the classic morbilliform or erythrodermal exanthem, with subsequent desquamation. Severe cutaneous adverse reactions, eg, Stevens-Johnson syndrome or toxic epidermal necrolysis, can be associated with antiepileptic drug use,[3,7,8,15] but these cutaneous manifestations are not consistent with a diagnosis of AHS.[4,13] Lymphadenopathy can be local or generalized. Hepatic involvement ranges from a transient rise in transaminases to liver necrosis with fulminant failure. Coombs-negative hemolytic anemia, thrombocytopenia, agranulocytosis, eosinophilia, or lymphocytosis might be observed.[5,6] Profound leukocytosis can manifest with white blood cell counts previously reported as high as $43 \times 10^3/\mu L$.[16] Pulmonary findings are less common but can manifest with such serious outcomes as bronchiolitis obliterans with organizing pneumonia.[17]

The most disturbing hematologic finding is that of atypical lymphocytes consistent with lymphomatous transformation. In 1959, histologic lymph node findings among all 7 patients with AHS were consistent with a lymphoma-like pattern.[18] This finding is now commonly referred to as "pseudolymphoma," "pseudo-Sézary syndrome," or "pseudolymphoma syndrome," consistent with the findings of cytologic or histologic lymphoma-like cells.[18,19] Some investigators suggest that there are actually two separate hypersensitivity syndromes mimicking lymphoma. The first is the hypersensitivity syndrome described above; the second is more insidious, the initial manifestation being cutaneous nodule and plaque formation months after an antiepileptic drug is initiated. These latter cutaneous manifestations reveal histologic pseudolymphoma, which resolves with discontinuation of the antiepileptic drug but increases the likelihood of lymphomatous transformation later in life. These investigators propose a formal name of "drug rash with eosinophilia and systemic symptoms" for the former condition, currently known as AHS.[18] Perhaps AHS is an appropriate name for the former, and the latter entity should be identified as "cutaneous pseudolymphoma," or "mycosis fungoides-like lesions," as described in 1991.[20]

Treatment

The most important step in management of AHS is to recognize the disorder and to discontinue the offending antiepileptic drug. An inpatient care setting is prudent for seizure prophylaxis and treatment. Interim anticonvulsant therapy, as previously discussed, should be guided by avoiding similar or interactive antiepileptic drugs (Table 2). Benzodiazepines may be used for short-term control. Severe cutaneous adverse reactions should be treated in consultation with a dermatologist or burn team depending on the extent of involvement. Continued enteral nutrition, intravenous fluid augmentation, pain relief, and ocular care in consultation

with an ophthalmologist are essential.[21] Silver sulfadiazine and prophylactic antibiotics are not routinely recommended. The use of systemic corticosteroids has not been substantiated in randomized study[13,16,18] but has been considered the standard of care.[6] The preponderance of literature supports corticosteroid use in extensive cases, or cases with involvement of internal organs,[4,18] although there are contrary data to suggest that only cutaneous manifestations are reversed.[16] When used, the most common dose is greater than 0.5 mg/kg/d,[13] or 60 mg of intravenous methylprednisolone every 6 hours.[22] Other immunomodulation (eg, plasmapheresis, cyclophosphamide, cyclosporine, and intravenous immune globulin) has had anecdotal success.[23-26]

The prognosis of AHS varies widely in the literature. Mortality from AHS with associated hepatitis has been reported to range between 18% to 40%.[16] A recent review of hypersensitivity syndrome in general states that it is drug-induced in 90% percent of cases, with an overall mortality of 10%.[13] In one case series of 38 patients with AHS, there were no deaths reported.[27] In another case series of 44 patients taking phenytoin for epilepsy, 34 patients had to discontinue treatment because of side effects; no deaths were reported. The same case series reviewed earlier studies, which showed several deaths resulting from status epilepticus or bronchopneumonia in the absence of AHS-like manifestations.[28]

Conclusion

The anticonvulsant hypersensitivity syndrome is an uncommon but serious disorder that should be recognized by family physicians, who are very likely to be the first providers to encounter the initial manifestations of this disease. It is associated mainly with the aromatic anticonvulsants (phenobarbital, phenytoin, carbamazepine) but can be observed with the newer anticonvulsants. The incidence of AHS is 1 to 4 in 10,000, and more common in the African-American population. The incidence among first-degree relatives is higher. Molecular and cellular studies implicate the immune system as a contributing factor. Diagnostic criteria are primarily fever, rash, and lymphadenopathy, but the gastrointestinal tract, lungs, and blood can be affected. Management emphasizes discontinuing the offending drug, supportive care in the inpatient

setting because of the risk of seizure, and prudent consultation for specialty care. Corticosteroids should be considered in definitive drug eruptions only after infectious causes have been ruled out.

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