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BRIEF COMMUNICATION

Anticonvulsant hypersensitivity syndrome: Is there a role for immunomodulation?

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Summary

The anticonvulsant hypersensitivity syndrome (AHS) is an idiosyncratic immunologic reaction to certain anticonvulsant medications, in which internal organ involvement may lead to fatal multisystemic failure. This syndrome has been associated with the use of aromatic ring-containing agents such as phenytoin, carbamazepine, or phenobarbitone. Clinically, this condition presents with the classic triad of fever, rash, and lymphadenopathy. We review the existing literature on AHS pathogenesis and illustrate a case complicated by liver dysfunction where the use of N-acetylcysteine (N-AC) and intravenous immunoglobulin (IVIG) may have altered the course of the disease. The rationale of suggesting N-AC and IVIG for the treatment of this syndrome relies on the theoretical synergistic effects of the two agents. Although treatment for this syndrome remains controversial and relies heavily on anecdotal evidence, the progression of hepatic injury may be prevented by the addition of N-AC. The scavenging properties of N-AC may palliate and possibly prevent free radical-mediated liver damage. In addition, IVIG may effectively modulate the overreactive immune system in AHS. We discuss the possible role of using immunomodulating agents for the treatment of this syndrome and suggest that alternative regimens should be given special consideration especially in those critical clinical situations where supportive measures appear to be unsuccessful.

KEY WORDS: Anticonvulsant hypersensitivity syndrome, N-acetylcysteine, Intravenous immunoglobulin, Immunomodulation, Drug reaction, Liver injury.

Anticonvulsant hypersensitivity syndrome (AHS) is one of the less known side effects of antiepileptic medications. It is described as an idiosyncratic immunologic reaction against certain anticonvulsant agents. This syndrome should be considered in patients recently started on phenytoin, carbamazepine, or phenobarbitone who present with the classic triad of fever, rash, and lymphadenopathy (Barghava, 2001; Mason, 2007). The skin is affected in nearly 90% of AHS cases, and ranges from a mild exanthematous pruritic rash to severe exfoliating dermatitis. The torso and extremities are most frequently affected; palms and soles are usually spared. The cutaneous involvement is often synchronous with the onset of the fever. The typical febrile pattern is intermittent and can be found to be as high as 40°C. Lymphadenopathy is typically diffuse. If pharyngitis is present (10% of cases), cervical lymph nodes may be prominent. Liver damage is found in 50% of AHS cases and is an indicator of poor prognosis. Infrequent clinical manifestations include interstitial nephritis, myocarditis, colitis, myoarthralgias, and splenic rupture (Fervenza et al., 2000; Zaidi, 2005; Korem et al., 2006). The clinical findings of AHS can become clinically apparent 1 week after exposure and up to 3 months after discontinuation of the responsible agent.

AHS is often more severe in previously sensitized individuals. The mortality for AHS with hepatic failure has been reported to be as high as 50%. The severity and prognosis of the disease depends on the degree of internal organ involvement. Early clinical recognition of the disease and prompt discontinuation of the offending drug are essential in order to prevent adverse outcomes (Vittorio & Muglia, 1995).

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Initial therapeutic approaches traditionally involve cessation of any causative medication and aggressive supportive measures: intravenous hydration, antihistamines, and corticosteroids (Morkunas & Miller, 1997; Kennebeck, 2000; Knowles & Shear, 2007). In addition, intravenous immunoglobulin (IVIG) may effectively modulate the overreactive immune system in AHS (Scheuerman et al., 2001; Mostella et al., 2004). No prospective randomized trials have assessed the efficacy of AHS treatments; however, several reports describe the successful immunomodulatory benefits of IVIG (Scheuerman et al., 2001; Mostella et al., 2004; Li et al., 2005; Ting, 2007).

Although treatment for this syndrome remains controversial and relies heavily on anecdotal evidence, it has been suggested that progression of hepatic injury may be prevented by the addition of N-acetylcysteine (N-AC). N-AC scavenging properties may palliate and even further prevent free radical-mediated liver damage (Ben-Ari et al., 2000). The potential benefits and risks of N-AC administration in patients with AHS have been documented. Based on the nature of AHS, we postulate that a combination of IVIG and N-AC administration work synergistically to attenuate the immunopathic reactions seen in this disease.

Report of a Case

A 59-year-old African American female presented to the emergency department with a chief complaint of a pruritic rash. One month prior to her presentation, the patient had been started on 300 mg oral phenytoin daily for the treatment of a newly diagnosed seizure disorder. The rash was first noticed 2 weeks prior to her hospital visit and spread from her legs to the torso, arms, and face. In addition, the patient complained of neck fullness, dysphagia, and decreased appetite. She complained of a subjective fever but denied any other symptoms. Her past medical history was significant for essential hypertension, emphysema, and dyslipidemia. Her medications included oral lisinopril 10 mg daily, inhaled tiotropium 18 μg daily, and inhaled albuterol as needed. The patient denied the use of illegal substances. Her past family history was unremarkable. No drug or environmental allergies were reported.

On presentation to the emergency department, her temperature was 38.8°C, blood pressure 140/83 mmHg, respirations 18 per minute, and a pulse of 117 beats per minute. On physical exam, the rash predominated on her extremities and torso. The lesions were erythematous, raised, diffuse, and nonblanching. There was minimal oral mucosal enanthema. There was palpable bilateral anterior cervical lymphadenopathy. These lymph nodes were indurated, tender, and enlarged. The abdominal exam was benign, without hepatosplenomegaly. The rest of the exam was unremarkable.

Initial liver tests showed: alkaline phosphatase (ALP) 510 UI/L (reference range 50–180 UI/L), alanine aminotransferase (ALT) 331 UI/L (reference range 0–65 UI/L), aspartate aminotransferase (AST) 109 UI/L (reference range 0–60 UI/L). A skin biopsy was performed and demonstrated an inflammatory infiltrate that was predominantly perivascular and lymphocytic in nature. There were no vasculitic features or necrosis, making the diagnosis of Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN) less likely. Based on these clinical findings and the biopsy results, AHS was diagnosed. Her anticonvulsant medications were immediately discontinued. The patient received IV fluid hydration, corticosteroids, and antihistamines. On hospital day 4, her AST was 174 UI/L and ALT 71UI/L. She was discharged on a 5-day methylprednisolone taper (32 mg on day 1, 16 mg on day 2, 8 mg on day 3, 4 mg on day 4, and 2 mg on day 5). She was instructed to discontinue the phenytoin.

Five days after the initial discharge, the patient returned to the emergency department. At this time the patient complained of worsening rash, generalized increased pruritus, and diffuse abdominal discomfort. Admission temperature was 38.6°C, heart and respiratory rate 114 and 26 per minute, respectively. Her lips were swollen, although there was no edema or airway compromise present. The skin lesions were erythematous, maculopapular, and tender to palpation (Figs. 1 and 2). These affected areas were nonconfluent, global, and diffuse. Her oral mucosa was spared. White blood cell count was 16,200 cells/L (reference range 3,500–10,600 cells/L), ALP 402 UI/L, ALT 226 UI/L, and AST 257 UI/L. A drug screen was negative, and the phenytoin level was undetectable. Initial treatment included IV fluids, IV corticosteroids, and antihistamines.

The patient's respiratory status and liver enzymes worsened. On hospital day 5, she was admitted to the ICU for respiratory compromise and impending hepatic failure. She continued to require supplemental oxygen and aggressive fluid resuscitation. On hospital day 6, the AST and

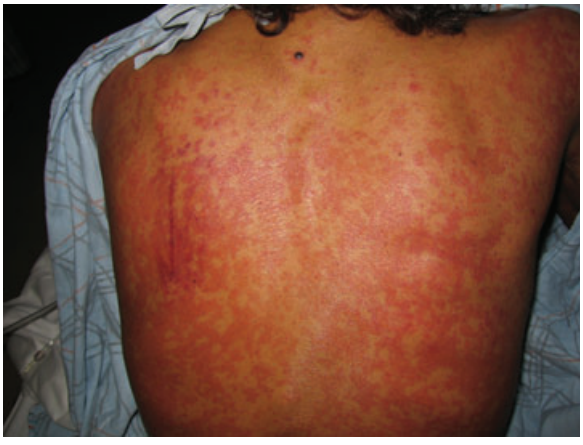

Figure 1.
Erythematous maculopapular rash in back.
Epilepsia © ILAE

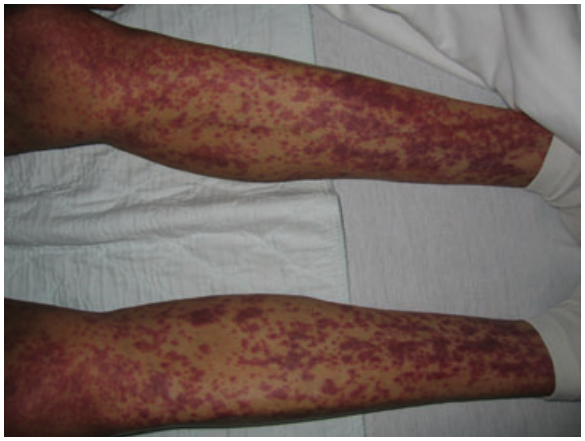

Figure 2.
Rash in lower extremities.

ALT levels were above the upper limit of measurement (>3000 UI/L). The liver function and overall clinical picture continued to decline. Given the severity of the situation, the decision to start N-AC and IVIG was made. The IVIG was administered at 1 g/kg daily for 2 days. The loading dose for IV N-AC was 150 mg/kg IV in 200 mL 5% dextrose over 60 min. After the initial dose, the infusion was maintained at 50 mg/kg IV in 500 mL 5% dextrose over 4 h, followed by 100 mg/kg IV in 1000 mL 5% dextrose over 16 h.

Following the administration of these agents, her overall clinical condition markedly improved over the next 2 days. On hospital day 11, her rash and lymphadenopathy had resolved. The patient was discharged home on oral methylprednisolone 50 mg daily for 2 weeks. On a subsequent outpatient follow-up visit, given the paucity of signs and symptoms, her methylprednisolone was tapered within 5 days (32 mg on day 1, 16 mg on day 2, 8 mg on day 3, 4 mg on day 4, and 2 mg on day 5). One month later, her liver function tests returned to normal levels. Anticonvulsants were not resumed. To date she remains seizure-free and asymptomatic. She wears an AHS medical alert bracelet.

Discussion

AHS is a drug-induced, potentially fatal, multiorgan condition that may develop after the ingestion of certain anticonvulsants. Common offenders include phenytoin, carbamazepine, and phenobarbital. Additionally, AHS cases associated with lamotrigine and oxcarbazepine have been described (Fervenza et al., 2000; Pastor-Milán et al., 2003). Cross-sensitivity between causative agents has been reported to be as high as 80% (Brown et al., 1997).

This condition has an estimated incidence between 1/1,000 to 1/10,000 exposures, although it is thought to be unrecognized and underreported. It has an autosomal dominant inheritance pattern; siblings of affected patients may have an increased susceptibility to develop this condition. In addition, the African American population is more frequently affected (Bohan et al., 2007). There is no relationship between drug serum levels and aggressiveness of the disease (De Vriese et al., 1995; Mason, 2007). Severe cases develop multiple organ failure and ultimately death.

Although the exact pathogenesis of AHS remains unclear, it has been described that aromatic ring-containing compounds may be metabolized by the hepatic cytochrome P-450 enzyme system to arene oxide metabolites. Defects in enzymes required for the detoxification and elimination of these metabolites have been identified in patients with AHS (Dwivedi et al., 2004). The resulting accumulation of arene oxide may trigger various immunopathic phenomena that include: antigen-hapten complex formation, major histocompatibility complex activation, and T cell stimulation with subsequent cytokine release (Shear & Spielberg, 1988; Knowles et al., 1999; Krauss, 2006). These metabolites may also establish covalent bonds with cells and neighboring macromolecules, becoming directly cytotoxic to various tissues and organs. Oxcarbazepine and lamotrigine exact mechanisms of disease remain obscure.

The rationale for suggesting N-AC and IVIG for the treatment of this syndrome relies on the theoretical synergistic effects of the two agents combined. While the exact mechanism of action is not fully known, IVIG has been described as having the ability to form immune complexes that block immunoglobulin G (IgG) Fc receptors, to decrease immune-complex-mediated inflammation, to neutralize autoantibodies, and to attenuate complement-mediated damage. Eosinophilia and atypical lymphocytosis may be present in AHS; the addition of IVIG may control B and T cell proliferation and subsequently block the production of interleukin 5 (IL-5) and eosinophil maturation (Kazatchkine & Kaveri, 2001; Wu et al., 2006). Moreover, IVIG appears to block CD95 (Fas), a keratinocyte cell surface receptor described to play a role in apoptosis triggering; shown both in vitro and in patients with TEN (Viard et al., 1998; Mittmann et al., 2006).

The production of free radicals leading to hepatocellular oxidative damage has been investigated, and a number of studies have demonstrated the antioxidant role of N-AC. The use of N-AC has been shown to be particularly beneficial in acetaminophen-induced liver failure by repleting hepatic glutathione (James et al., 2003). Glutathione is a molecule involved in multiple detoxification pathways, including anticonvulsants. Depletion of such molecule may ultimately result in accumulation of pathogenic metabolites and potential deleterious effects. We postulate that this particular therapeutic effect of N-AC may be extrapolated to AHS, where the conjugation and elimination pathway of reactive arene epoxide metabolites may be impaired. Additionally, N-AC may modulate

hypersensitivity reactions by limiting the production of inflammatory cytokines and the expression of keratinocyte intercellular adhesion molecule-1 (ICAM-1). These effects may limit the extent of dermatologic and internal organ compromise seen in AHS.

Moreover, N-AC appears to buffer harmful effects of metabolites produced by neutrophil myeloperoxidase, an implicated enzyme in detoxification pathways of aromatic ring-containing anticonvulsants (De Swert et al., 1984; Gressier et al., 1994). Furthermore, N-AC has been described to have antiapoptotic properties by activation of the Ras-extracellular signal regulated kinase and to inhibit the inducible form of nitric oxide synthetase from producing inflammatory cytokines (Bergamini et al., 2001; Rota et al., 2002). Less known effects of N-AC supplementation include possible improvement of hepatic blood flow, increase in cardiac output, and optimization of oxygen delivery, extraction, and consumption (Harrison et al., 1991; Sheiner et al., 1992; Agusti et al., 1997; Devlin et al., 1997).

Both IVIG and IV N-AC can have side effects. One of the most serious adverse effects observed with IVIG is anaphylaxis. IV N-AC is generally well tolerated, and adverse effects are infrequently observed in clinical practice, although cases of tonic–clonic seizures and angioedema have been reported (Ziment, 1988; Redondo et al., 1997; Simonart et al., 1998; Walsh & Lee, 1999; Tas et al., 2001).

Immunomodulation poses a theoretical option that may be beneficial in AHS. It is our hypothesis that ''conventional'' therapeutic measures failed until the above described regimen was added. We cannot compare the described regimen versus monotherapy or the combination of high-dose steroids. It is unknown whether a different initial steroid taper could have prevented the development of recurrent AHS. It is also uncertain whether this patient would have recovered without immunomodulation. We suggest that alternative therapeutic regimens should be given special consideration, especially in those critical clinical situations in which supportive measures appear to be unsuccessful.

In conclusion, we present a case of life-threatening AHS that was successfully treated with a combination of IVIG and N-AC. While we cannot be certain that one of these therapies alone may have been effective, we hope to increase awareness and provide therapeutic options for this syndrome given its rarity, life threatening features, and pathophysiologic mechanisms. We encourage future research in this field in order to elucidate underlying mechanisms of injury and to further develop effective treatments for this entity.

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Conflict of interest: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors have any conflicts of interest to disclose.

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