ANTICONVULSANT HYPERSENSITIVITY SYNDROME LEADING TO REVERSIBLE MYOCARDITIS

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ABSTRACT

A 67-year old Caucasian female was diagnosed with anticonvulsant hypersensitivity syndrome (AHS) after she developed the triad of high fevers, maculo-papular rash and internal organ involvement ten weeks after the institution of prophylactic phenytoin for resection of a meningioma. She developed congestive heart failure, with a substantial reduction in ejection fraction (EF) by an echocardiogram and serum cardiac enzyme elevation. In the setting of AHS, this was consistent with a drug-induced myocarditis. Treatment consisted of removal of the offending drug, diuretics and high dose steroids. Six weeks later her symptoms had completely resolved, with a return to a normal EF.

Key words: Phenytoin, anticonvulsant hypersensitivity syndrome, myocarditis, heart failure, steroids

The anticonvulsant hypersensitivity syndrome (AHS) was first described in 1950, although confusion still abounds regarding the syndrome and its manifestations. The triad of fever, rash and internal organ involvement occurring 1 to 8 weeks after exposure to an anticonvulsant heralds this rare (1 in 1000 to 10,000 exposures) but serious reaction.[1]

AHS was previously termed 'dilantin hypersensitivity syndrome' but a name change evolved from the fact that the characteristic constellation of signs and symptoms were subsequently reported with carbamazepine and phenobarbital.[2,3] Rash, fever and liver involvement are the most frequent findings in this syndrome.[4,5] Lymphadenopathy and eosinophilia are often cited as well, although these are non-specific markers.[3,6] Early recognition of this reaction is important since it has a mortality rate of about 10%.[7-9]

Hypersensitivity myocarditis is an inflammatory disease of the myocardium usually related to a drug allergy. It is a rarely recognized clinical entity since the diagnosis is usually retrospective and circumstantial.[10] In the presence of signs and symptoms of hypersensitivity (skin rash, fever and eosinophilia), non-specific cardiac findings (electrocardiographic changes, unexplained tachycardia or serum cardiac enzyme elevations) are suggestive of hypersensitivity myocarditis.[11]

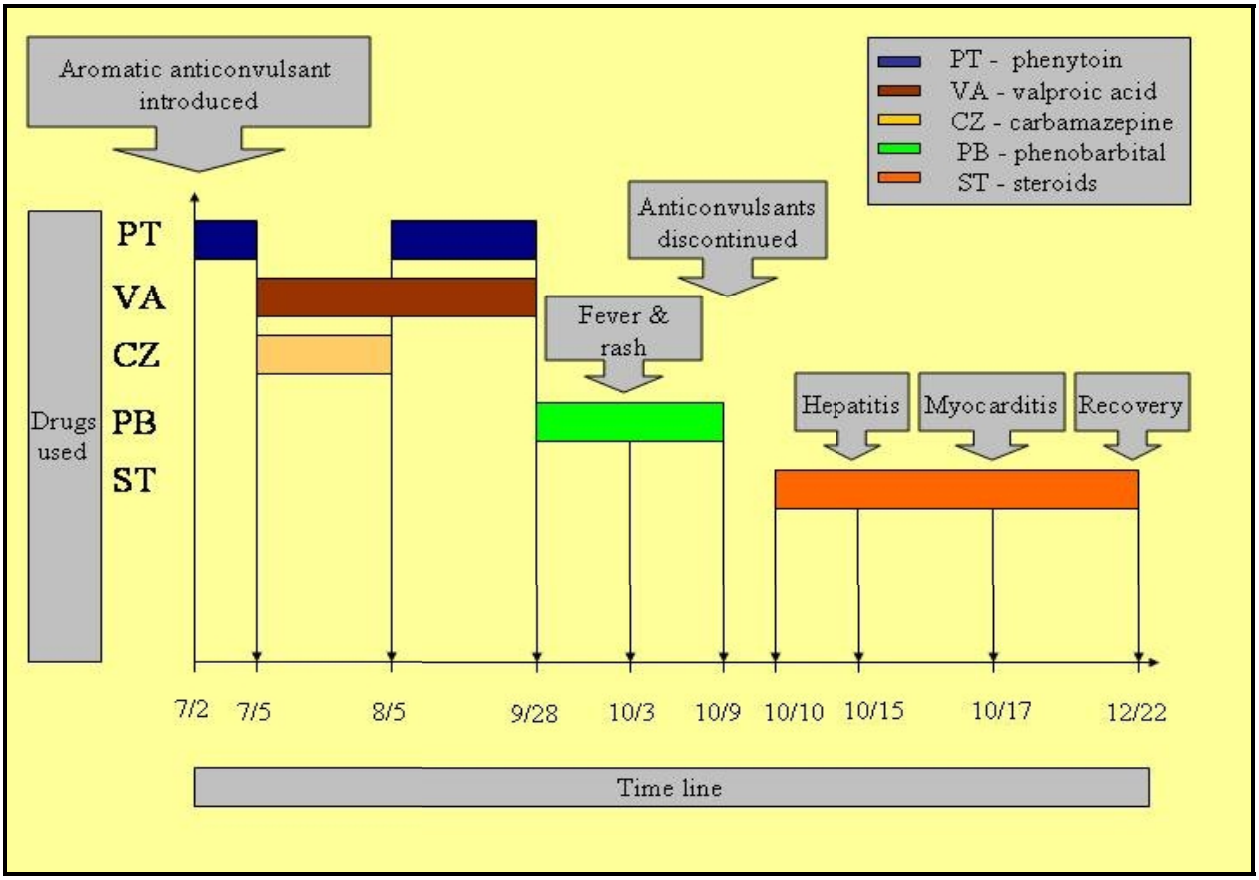
The actual incidence of hypersensitivity myocarditis cannot be accurately estimated,[10] although myocarditis has frequently been recognized as a complication of drug therapy. French and Weller first reported myocarditis in 1942 as a consequence of sulfonamide therapy.[11-13] Subsequent recognition of the etiological cause leading to hypersensitivity myocarditis has been hampered by difficulty in differentiating drug-induced from other idiopathic causes of myocarditis.

We report a case of reversible myocarditis as part of AHS. The patient received phenytoin and carbamazepine ten weeks prior to the development of a generalized rash, multiple episodes of high fevers, eosinophilia, internal organ involvement (hepatitis) and subsequent myocarditis, which completely resolved after removal of the offending drugs and a prolonged course of oral steroids.

Case Report

A 67-year old Caucasian female was diagnosed with a left-sided meningioma and was prophylacticaly placed on phenytoin 300mg po daily for a total of three days. This was resected with no complications. Prior to her operation she had normal laboratory parameters, and a normal cardiac echocardiogram with an ejection fraction (EF) of 60%. Her post-operative course was complicated by multiple seizure episodes. The phenytoin was replaced by valproic acid 500mg po bid and carbamazepine 200mg po bid (Fig 1).

FIGURE 1 Time-line of events (development of AHS, myocarditis and clinical recovery) in relation to the use of anticonvulsants and steroids.



Four weeks post-operatively she developed high fevers and a change in her mental status. Magnetic resonance imaging (MRI) of the brain showed enhancement in the region where the meningioma was removed. There was concern for a primary intracranial infection.

A two-week course of intravenous antibiotics (vancomycin, metronidazole and ceftriaxone) was started. The valproic acid was continued, carbamazepine was stopped (after a total of four weeks) and phenytoin was re-introduced (Fig 1). She received combination therapy with valproic acid and carbamazepine for four weeks.

The intermittent high fevers persisted and she developed new onset neutropenia. A gallium scan showed circumferential uptake at the fronto-parietal region of the cortex and a repeat MRI of the brain showed a small fluid collection at the site of the original resection. A repeat craniotomy showed no signs of infection. Granulocyte-colony stimulating factory (G-CSF) was started for the neutropenia. Given the strong suspicion of medications as the source of her fever, all her previous medications were discontinued.

These included valproic acid (discontinued after ten weeks) and phenytoin (discontinued after

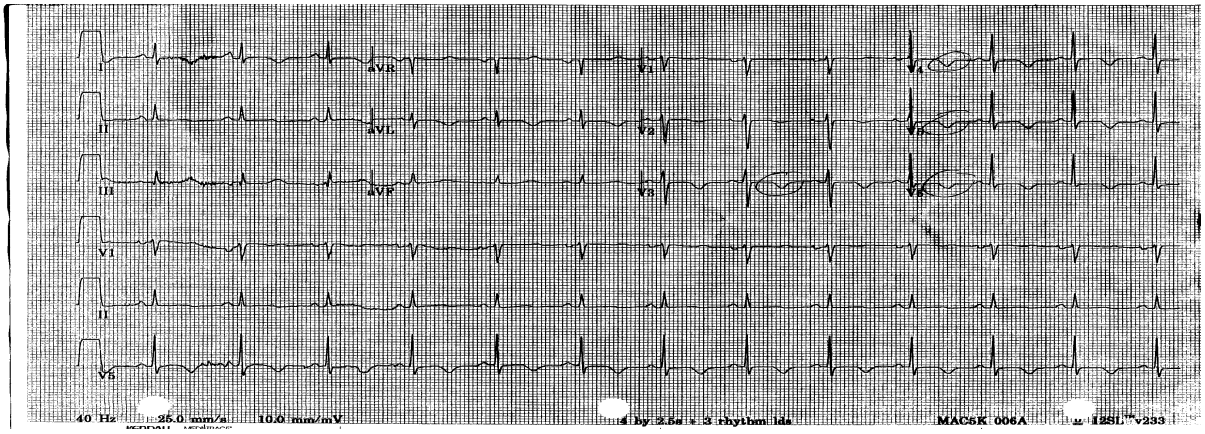
seven weeks). Prior to the discontinuation of both drugs, combination therapy with phenytoin and carbamazepine had been given for a total of seven weeks. Phenobarbital was started at 100mg po bid as monotherapy for seizure prophylaxis.

She subsequently developed a generalized maculo-papular rash over her trunk, back, extremities and anasarca. Extensive laboratory evaluation revealed eosinophilia and elevated liver function tests. Her complement titers and an erythrocyte sedimentation rate (ESR) were normal. She had a negative ribo-nucleotide protein antibody (RNP) with minimal elevation of her rheumatoid factor (RF). Serum levels of phenytoin (since it was recently discontinued) and phenobarbital were not toxic. Computed tomography (CT) scans of her thorax, pelvis and abdomen revealed diffuse lymphadenopathy with generalized anasarca**.** The phenobarbital was stopped after a total of twelve days. The rash gradually improved with 60mg po daily of prednisone and topical steroids and she was discharged for home.

The patient's constellation of symptoms including intermittent high fevers, diffuse maculo-papular rash, generalized lymphadenopathy, elevated liver function tests, and eosinophilia following the introduction of anticonvulsants, were attributed to AHS.

A week after her discharge she slowly developed progressive dyspnea on exertion and orthopnea with the need for supplemental oxygen. She was readmitted for management of new-onset congestive heart failure. On readmission her laboratory parameters showed evidence of abnormal liver function tests: raised alanine transferase at 146 U/L (normal range 10-50 U/L) and elevated alkaline phosphatase at 121 U/L (normal range 40-110 U/L). There was minimal elevation of total bilirubin at 1.3 U/L (normal range 0.1-1.0 U/L). Lactate dehydrogenase was also raised at 584 U/L (normal range 100-250 U/L).

FIGURE 2 Electrocardiogram showing T wave inversions in the lateral leads.



An electrocardiogram (EKG) showed T wave inversions in the anterior and lateral chest leads (Fig. 2). A chest roentograph showed bilateral pleural effusions, moderate cardiomegaly with pulmonary edema.

A trans-thoracic echocardiogram (TTE) revealed a reduced EF of 20% with a small pericardial effusion, global hypo-kinesis and no valvular abnormalities. The reduced systolic dysfunction was a significant change from her previous echocardiogram, which showed an EF of 60%, with normal ventricular function and no pericardial effusion. Antibody titers for Coxsackie A virus and Parvovirus B19 were negative.

Additional testing was done to evaluate for an ischemic cause of her systolic dysfunction. A

stress thallium scan showed a large area of ischemia in the anterior wall with extension to the antero-septal junction, the apex and the distal lateral wall. The area at risk was consistent with involvement of the left anterior descending and the left circumflex artery. A cardiac catheterization was done which showed no evidence of coronary artery disease, with mild elevation of left ventricular end diastolic pressure (LVEDP) and mild pulmonary hypertension.

Her dyspnea resolved after diuresis with intravenous furosemide. She was started on a daily dose of 20mg daily of furosemide, 200mg po bid metoprolol and 5mg daily of lisinopril for her heart failure. Prednisone at 60mg po daily was re-started to taper over eight weeks. A TTE at follow-up six weeks later showed an EF of 45%, which was markedly improved. At this time her symptoms of congestive heart failure had completely resolved. Following the recent diagnosis of AHS, her congestive heart failure with the severe reduction in EF (with no evidence of any occlusive coronary disease on cardiac catheterization) could similarly be explained due to an anticonvulsant-induced myocarditis as a component of AHS.

DISCUSSION

AHS is an idiosyncratic reaction to aromatic anticonvulsants that can result in severe multi-organ dysfunction and death. The constellation of symptoms associated with AHS includes a classic triad of fever, rash and internal organ involvement (most commonly liver) that occurs within three months of therapy while the patient is receiving one of the associated anti-epileptic agents.[14]

Phenytoin was associated with severe reactions as early as 1938 and the systemic symptoms of AHS were first described in 1950.[1,7] The risk of developing an AHS, within 60 days in new users of phenytoin or carbamazepine is estimated to be 2.3 to 4.5 per 10,000 and 1 to 4.1 per 10,000 respectively.[1,12] Phenytoin, carbamazepine, primidone and phenobarbitone, all classified as aromatic anticonvulsants, can produce an identical, multisystem hypersensitivity reaction between 4 weeks and 3 months of starting the drug.[6] More cases are reported of reactions to phenytoin and carbamazepine, since these two drugs are used more than phenobarbital.

For phenytoin alone the mean interval to onset of AHS is 17-21 days and for carbamazepine the onset is generally between 21 and 28 days.[8] AHS is not related to dosage or serum concentrations of anticonvulsants. Most patients present with fever, malaise and lymphadenopathy,[1] our patient had high fevers, chills, lymphadenopathy, eosinophilia and hepatitis over a course of 10 to 12 weeks after the initial use of phenytoin with subsequent development of a maculopapular rash consistent with AHS.[4,5] Hematological abnormalities are common in AHS.[4,5,15] Neutropenia and eosinophilia were prominent in our patient.

The dermatological findings begin as a patchy macular erythema that evolves into a dusky, pink-red, confluent, papular rash, which is usually pruritic. The trunk, face and upper extremities are affected first.[2] These cutaneous effects can range from an exanthematous eruption to the more serious Stevens-Johnson syndrome, facial edema or even toxic-epidermal necrolysis.[1,6] In our patient a maculo-papular rash developed over the trunk initially and then spread to the upper and lower extremities.

Internal organ involvement may not develop for one to two weeks and sometimes may be delayed up to a month. The liver is the most commonly involved internal organ, although other organs including the kidneys (interstitial nephritis, vasculitis), central nervous system (encephalitis, aseptic meningitis), lungs (interstitial pneumonitis, respiratory distress syndrome) or the heart (myocarditis) can be involved.[1,16] Hypereosinophilia has been reported to account for involvement of other organs including myocarditis and pericarditis.[6,9]

Initially AHS was reported to be due to phenytoin alone. However there is frequent cross-reactivity between phenytoin, carbamazepine and phenobarbital, all aromatic anticonvulsants, which has been observed to be as high as 70-80 %.[9] In one series it was shown that 75% of patients with AHS to one of the oxide producing anticonvulsants showed in-vitro cross reactivity to the other two.[8] Spielberg et al[17] studied 53 patients of whom 25 received more than one anticonvulsant drug in-vivo. Twenty-one of these patients developed AHS to two or more of these anticonvulsants.[17] Our patient was given

phenytoin, carbamazepine, and phenobarbital (either singularly or as combination therapy).

The likelihood of AHS being caused by phenytoin, carbamazepine or phenobarbital was assessed as 'probable' according to the Naranjo algorithm for adverse drug reactions. The Naranjo's algorithm categorizes adverse reactions as definite (score > 9), probable (score between 5-8), possible (1-4) and doubtful (< 1).[18]

Although the pathogenesis of AHS is largely unknown, the belief is that it is caused by the formation of a toxic metabolite. The P-450 enzyme system metabolizes the aromatic amines to a common arene oxide metabolite, which is normally detoxified by epoxide hydrolase. A genetically determined inability to detoxify these metabolites, due to a defect in the enzyme epoxide hydrolase has been observed in patients with AHS.[8,9] There is some evidence to suggest that the diminished activity, or a relative deficiency of epoxide hydrolase is related to an autosomal co-dominant inheritance at the cellular level.[19] Defective detoxification of the intermediate reactive metabolites (arene oxides) of the aromatic anticonvulsants, may lead directly to cell death, mutations and tumors or contribute to the formation of an antigen that triggers an immune response leading to multi-organ involvement.[9,14] Others have proposed that AHS is a form of graft versus host disease or a reaction secondary to circulating antibodies.[2]

In our patient the clinical picture of high fevers, rash, lymphadenopathy and hepatitis, ten weeks after administration of anticonvulsants is consistent with the diagnosis of AHS. The sudden development of congestive heart failure was initially difficult to explain. Her echocardiogram showed a significant reduction in EF and a positive stress thallium showing a large area of ischemia. Accompanied with elevation in the LDH, these findings were suspicious for myocardial ischemia. However there was no evidence of any occlusive coronary disease on a left heart catheterization.

Myocarditis is largely a diagnosis of exclusion. Although the etiology of myocarditis often goes unnoticed, the final diagnosis is largely dependent on clinical suspicion rather than a definitive diagnostic test.

In retrospect, this case illustrates the potential occurrence of cardiac findings (unexplained tachycardia, electrocardiographic findings suggestive of ischemic heart disease and borderline elevation of lactic dehydrogenase) consistent with a myocarditis.[11,20,21]

Such cardiac findings of recent onset, especially in the presence of signs and symptoms of AHS, should be considered strongly suggestive of drug-induced myocarditis as part of the AHS. The clinical features of myocarditis, regardless of the etiology, are varied. The spectrum includes electrocardiographic abnormalities, signs and symptoms of left and right heart failure or severe left ventricular dilation on echocardiogram. Some patients have reportedly been completely asymptomatic. Previous reports have shown that viral myocarditis may mimic the findings in acute myocardial infarction, pericarditis or severe myocardial ischemia,[20,22] though this has not been established with drug-induced causes of myocarditis.

Despite its limited sensitivity and specificity, the gold standard for the diagnosis of myocarditis is an endomyocardial biopsy, which was a limitation of this case report. Nevertheless several non-invasive strategies have been used to identify myocarditis. These include anti-myosin scintigraphy, contrast enhanced magnetic resonance imaging and echo-cardio-graphic image processing.[22] Our patient had multiple echocardiograms done before, during and after the resolution of the AHS.

Supportive care is the first line of therapy in patients with AHS, including the use of topical steroids for skin care to alleviate symptoms. Discontinuing the offending medication is essential.[10,11,23] There has been much debate over the use of corticosteroids in AHS. Although several reported cases have shown a prompt and spontaneous clinical resolution with therapy[1,2] the role of corticosteroids for internal organ involvement is controversial. Oral and intravenous steroids can be used in patients with AHS with systemic symptoms, however there have been no randomized controlled trials to prove that they either shorten the duration of the reaction, or affect morbidity and mortality.[24,25] If used, careful weaning of the corticosteroids is essential since early discontinuation will lead to a relapse of HS.[1,2] In several reported cases, the anticonvulsant associated hypersensitivity phenomenon persisted after the offending agent

was removed, despite the use of long-term corticosteroids.[10]

Although prednisone has been used to treat patients with idiopathic dilated cardiomyopathy, its efficacy has not been rigorously studied. In a prospective randomized controlled trial of using prednisone 60mg po daily for dilated cardiomyopathy, improvement was defined as an increase in EF of greater or equal to 5 percentage points.[26] The reported increases in EF with steroid use in cases of cardiomyopathy have been small, unlike the substantial improvement seen in our patient. Regardless of the etiology, in patients with myocarditis and symptoms of heart failure, initial therapy should include diuretics, an angiotensin converting-enzyme inhibitor and a beta-blocker.

The use of immunosuppressant therapy in myocarditis has been controversial. Clinicians have postulated the benefits of using immunosuppressant therapy in patients with myocarditis [16], however the results of randomized, placebo-controlled trials[27,28] have failed to demonstrate the beneficial effects of immunosuppression. Two large randomized controlled trials, the 'European Study of Epidemiology and Treatment of Cardiac Inflammatory Disease'[29] and the 'Myocarditis Treatment Trial'[30] failed to show any significant benefits in acute myocarditis with immunosuppression. Supportive treatments (anti-failure and anti-arrhythmic therapy) continue to be the cornerstone in the management of acute myocarditis.

There has also been much debate over the use of immunosuppressant therapy in the treatment of severe drug-induced cuteanous reactions. Metry et al[31] demonstrated that therapy with intravenous immunoglobulins (IVIG) had been successful in seven pediatric cases for severe drug-induced cuteanous reactions like Steven-Johnson syndrome (SJS) and toxic-epidermal necrolysis (TEN). Even though the use of IVIG has shown some benefit in cases like SJS and TEN, it is by no means considered to be standard therapy[31] for drug-induced adverse reactions. Prospective multi-center trials are still needed to determine the efficacy and safety of IVIG with other potentially effective treatment modalities in such cases.

Family counseling is a critical part of patient management in AHS because first-degree relatives of an affected individual are at an increased risk of a similar reaction.[1,2,9] All aromatic anticonvulsants should be avoided in first-degree relatives. Seizure control may be achieved with short acting benzodiazepines or an alternate anticonvulsant from a non-aromatic group like valproic acid or gabapentin. Tiagabine or topiramate may be alternatives, however the slow speed of introduction recommended for their administration may limit their usefulness in an acute setting.[14,32] The alternate anticonvulsant should only be instituted after AHS has completely subsided since most anticonvulsants have the potential of hepatotoxicity, which may further endanger the already damaged liver.[9]

Since the diagnosis of AHS was made retrospectively in our patient, valproic acid had been started prior to the complete resolution of her symptoms. This was subsequently discontinued and she received monotherapy with phenobarbital for a total of twelve days before the initiation of steroid therapy (Fig 1).

CONCLUSION

AHS is characterized by the triad of fever, rash and internal organ involvement occurring after exposure to an aromatic anticonvulsant. Anticonvulsants like phenytoin, phenobarbital and carbamazepine are frequently involved. There is high cross reactivity among phenytoin, carbamazepine and phenobarbital. The pathogenesis of AHS is largely unknown but recent research has supported the role of reactive metabolites. The patients who develop symptoms of AHS need to be recognized early and the drug immediately discontinued. The patient's first-degree relatives need to be warned of the risk associated with the use of these drugs. Although extremely rare, myocarditis can present as part of an AHS, as manifested in our patient with non-specific cardiac findings, elevated serum cardiac enzymes and the subsequent development of an acute cardiomyopathy with a reduced EF. Therapy for AHS and the myocarditis associated with it is controversial. Steroids, anti-inflammatory medications and immunosuppressive agents have been tried but have not been rigorously studied in such scenarios and further studies need to be done.

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