Anticonvulsant hypersensitivity syndrome

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Introduction

Anticonvulsant hypersensitivity syndrome (AHS) is a drug induced, multiorgan syndrome which is potentially fatal. This syndrome has been reported with anticonvulsants such as carbamazepine, phenytoin, phenobarbitone, primidone and clonazeparn. Other medicines such as sulphones, sulphonamides, allopurinol and piroxicam (NSAIDs) have also caused multiorgan hypersensitivity syndrome. Incidence of AHS ranges between 1 in 1000 and 1 in 10,000 exposures. Patients with Human Immunodeficiency Virus infection and cancer carriers are at a higher risk for this adverse drug reaction.

Case history

A 22 year old man was admitted to dermatology unit Teaching Hospital Karapitiya with fever and generalized macular papular rash of 2 weeks duration. He was apparently well before. He had developed a headache followed by a fit 3 months ago for which phenytoin sodium 100mg daily was started after preliminary investigations including an electroencephalogram (EEG). After 6 weeks of therapy, a morbilliform rash appeared on face and trunk, with high spiking fever. After 2 weeks elapsed from onset of the presentation of rash and fever, its persistence prompted the patient to present at this hospital.

Physical examination revealed non pruritic maculo papular rash on face and trunk which progressively extended to extremities. Other symptoms were mouth ulcers involving buccal mucosa and lips, generalized lymphadenopathy, temperature, weakness and malaise. There was no hepatosplenomegaly, and the patient was not icteric.

Laboratory findings: neutrophil leukocytosis; total 12,800 with 77% neutrophils, lymphocytes 21%, eosinophils 2%, haemoglobin 14.2g/dl and erythrocyte sedimentation rate 18 mm/h^{-1}, blood urea 22 mg/dl. Liver transaminases were requested. Before the availability of reports clinical differential diagnosis were,

1. Anticonvulsant hypersensitivity syndrome
2. Toxic erythema due to phenytoin

Phenytoin was omitted and was substituted with sodium valproate 200 mg twice daily. The patient showed considerable improvement of constitutional symptoms specially fever by 5th day, but skin rash persisted. Therefore sodium valproate was omitted considering valproate induced erythema may contribute to persistent rash. On 7th day fever spikes reappeared (102°F) with clinical deterioration of the patient. At that time he had fever, rash, vomiting, diarrhea and deep icterus without hepatomegaly. Investigations at that time revealed SGOT 438 IU/l (0-35), SGPT 1.400 IU/l (0-35), alkaline phosphatase 781 IU/l (30-120), total billrubin 152 mg/dl (0-2) with direct fraction-98mg/dl, prothrombin time 2.7 (control 1.2). Ultra sound scan of the abdomen excluded hepatomegaly.

The patient was started on oral prednisolone 1 mg/kg body weight (45 mg/day). In spite of vigorous management patient developed features of acute liver failure with increasing liver enzyme levels repeat SGOT 900 IU/1, SGPT 2010 IU/I and alkaline phosphatase 1600 IU /1. The morbilliform rash progressed to full desquamation. After being in hospital for 18 days patient died of fulminant hepatic failure.

Discussion

Onset of AHS is between 1 week and 3 months after the initial drug exposure. The hallmarks of features are fever, cutaneous rash and lymphadenopathy accompanied by multisystem abnormalities (Table 1)[1]. High and spiky fevers are characteristic, although intermittently elevated temperature may persist for weeks after the offending drug is discontinued. Rash in most cases start as symmetrical and pruritic erythematous macular eruption. It is at first observed on the face and trunk, followed by the extremities. Also it may appear as eczema, bullae, purpura, atypical target lesions, Stevens – Johnson syndrome and Toxic Epidermal Necrolysis.

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Table 1. Common features and incidence rate of anticonvulsant hypersensitivity syndrome

Fever – 90-100%

Rash – 90%

Lymphadenopathy – 70%

Hepatomegaly/hepatitis – 50-60%

Leukocytosis with eosinophilia – 50%

Facial or periorbital oedema – 25%

Conjunctivitis/pharyngitis – 10%

Generalized pustulation has also been reported. Desquamation occurs with resolution. Other distinctive cutaneous effects include periorbital and facial oedema and conjunctivitis. Patients present a spectrum of clinical presentation ranging from mild to severe (Table 2). Hepatic involvement is the commonest, followed by the kidney (e.g. interstitial nephritis, vasculitis). The mortality rate is 18-40% if hepatitis is present[2]. Thyroid involvement may appear as hypothyroidism 3 months after onset of reaction, which is transient and disappear in most patients within 12-18 months.

Many theories have been advanced to account for the pathogenesis. AHS caused by the aromatic anticonvulsants phenytoin, carbamazepine, phenobarbitone follow a metabolic pathway common to all hydroxylated aromatic compounds. The intermediate metabolites of this reaction – arene oxides are toxic. They have the capacity to bind covalently to cell macromolecules and produce cell damage or elicit a secondary immunologic response. It is thought that insufficient detoxification of these metabolites may account for the clinical picture. A hereditary deficiency in epoxide hydrolase function – an enzyme active in conjugation phase of these drugs may predispose certain individuals to AHS[3].

The differential diagnosis includes other cutaneous drug reactions, acute infections (Epstein-Barr virus, viral hepatitis), lymphoma or pseudolymphoma, collagen vascular diseases and serum sickness like illness.

Early withdrawal of the drug is essential to avoid progressive development of symptoms and represents the most important step to restore health. Even though the efficacy of corticosteroids is debatable, some authors recommend the use of prednisolone at the dosage of 1-2 mg/Kg/day if symptoms are severe[4,5]. It appears that they may benefit the cutaneous but not the systemic manifestations of the syndrome[1].

Re-exposure to anticonvulsant drugs is followed by a quick, severe reappearance of all symptoms, which strongly argue against their prescription. The incidence of cross reactivity among the aromatic anticonvulsants is greater than 75%. In cases where discontinuation of anticonvulsant is ill advised, therapy with benzodiazepines, valproic acid (not to be used in the acute phase of the syndrome for risk of hepatitis) or newer drugs such as gabapentine, topiramate or vigabatrin to be considered to prevent and control seizures.

The first degree relatives of an affected patient have four fold risk of drug sensitivity than the population at large. Therefore, family counseling is very important in the management of these patients.

Table 2. Spectrum of clinical presentation of anticonvulsant hypersensitivity syndrome

Organ involved	*Mild*	*Moderate*	*Severe*
Skin	Exanthema	Urticaria	SJS/ TEN
Bone marrow	Leukopenia	Agranulocytosis	Aplastic anaemia
Liver	Mild elevation LFT	Hepatitis	Fulminant hepatic necrosis
Muscle	Elevated CK level	Myositis	Rhabdomyolysis
Kidney	Haematuria	Nephritis	Acute renal failure
Heart	Pericarditis	Carditis	Congestive heart failure
Lung	cough	pneumonitis	ARDS

LFT – liver function test, CK – creatine kinase, ARDS – adult respiratory distress syndrome

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