Glandular fever-like syndrome, pulmonary eosinophilia and asthma associated with carbamazepine

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Summary
An 8-year-old boy is described who developed hypersensitivity to carbamazepine manifested by fever, rash, lymphadenopathy, hepatosplenomegaly and asthma with eosinophilia. The abnormal reaction resolved rapidly following cessation of the drug.

Introduction
Carbamazepine is an important drug in the treatment of epilepsy in childhood. A number of side effects have been reported including extrapyramidal symptoms, lethargy, psychoses, skin eruptions and less commonly blood dyscrasias and liver damage (Gayford and Redpath, 1969).

Drug-induced lung disease has been described in association with a number of drugs most notably nitrofurantoin and sulphonamides (Rosenow, 1972). A syndrome of fever, rash, lymphadenopathy and hepatosplenomegaly mimicking glandular fever or lymphoma has also been described particularly in association with the hydantoins (Heitzman, 1967). Both of these complications have been recognized only rarely with carbamazepine therapy. A child is described who suffered an acute illness exhibiting features of both pulmonary eosinophilia with asthma and a glandular fever-like syndrome.

Case report
An 8-year-old boy with a mild non-progressive right-sided hemiplegia of unknown origin presented in January 1981, having had a prolonged generalized convulsion. An electroencephalogram performed following this episode showed marked left-sided abnormalities, and carbamazepine 100 mg twice daily was started. He was referred back 5 weeks later with a 3-week history of gradually worsening pruritic rash, increasing lethargy, anorexia and a 3-day history of dry cough and wheeze. There was no relevant past medical history or family history of allergy or asthma.

On examination, he was febrile with a severe generalized maculopapular erythematous rash. He had generalized lymphadenopathy and both liver and spleen were palpable 4 cm below their respective costal margins. Some palatal petechiae were present. He was tachypnoeic with marked expiratory wheezing. His peak flow rate was 140 l/min (50% of expected value). Chest X-ray showed increased bronchovascular markings and patchy shadowing at the left hilum. Initial haemoglobin was 11.5 g/dl; white blood cell count 8.0 × 10⁹/l; differential, neutrophils 23%, lymphocytes 42% (some atypical) and eosinophils 29%. The erythrocyte sedimentation rate was 15 mm in the first hour. Paul Bunnell test was negative. Liver and renal function were normal and microbiological investigation failed to find any evidence of bacterial, fungal, viral or parasitic infection.

He was treated with chlorpheniramine and nebulized salbutamol. Some temporary relief of his symptoms was obtained but after a brief cessation of these drugs he again worsened and carbamazepine was stopped. Within 48–72 hr his rash and wheezing markedly improved. The lymphadenopathy and hepatosplenomegaly gradually disappeared and his peripheral eosinophil count and erythrocyte sedimentation rate returned to normal. He continued to require treatment with oral salbutamol for 2 weeks following his admission but his respiratory function then returned to normal and salbutamol was discontinued.

It was not felt justifiable to expose him to a further course of carbamazepine in order to prove the diagnosis of drug hypersensitivity and he has subsequently been treated with sodium valproate.

Discussion
Phenytoin is recognized as causing a combination of pulmonary abnormalities and lymphadenopathy (Rosenow, 1972; Heitzman, 1967) but this combination of side effects has been described only once previously in association with carbamazepine and that was in a patient whose clinical course was complicated by tuberculosis (Cullinan and Bower, 1975). There have been only two other reports of patients treated with carbamazepine developing...
pulmonary eosinophilia and asthma (Stephen, Parks and Tempest, 1978; Tak Lee, Cochrane and Amot, 1981). Lymphadenopathy, rash and fever has been reported slightly more frequently as a side effect of carbamazepine (Virolainen, 1971; Houwerzijl et al., 1977), but hepatosplenomegaly has not been a marked feature.

It is considered that the clinical signs exhibited in this patient were entirely due to carbamazepine as the clinical features and eosinophilia resolved rapidly following withdrawal of the drug. He did not have the classical pulmonary infiltrates described previously in patients with chest complications, but his respiratory symptoms and signs were comparable.

The exact aetiology of these complications is unknown but is likely to be due to a hypersensitivity reaction. Lymphocyte transformation in peripheral blood is recognized in hypersensitivity reactions due to para-amino salicylic acid and phenytoin and has also been reported in the presence of carbamazepine (Virolainen, 1971). It is thought probable that the clinical syndromes occurring with drug hypersensitivity are as a result of immune complex formation between drug and antibody in addition to blast transformation (Holborrow and Reeves, 1977).

The diagnosis of drug hypersensitivity to carbamazepine can be established either by in vivo re-exposure to the drug or by in vitro stimulation tests but both have variable reliability in the months immediately following the hypersensitivity reaction (Houwerzijl et al., 1977). The tests should be employed if there is clinical doubt of the diagnosis or where there is felt to be no reliable alternative to carbamazepine for a particular patient. The incidence of reactions of these types to carbamazepine is low but the drug is increasingly prescribed and an awareness of the spectrum of its possible side effects does, therefore, assume additional importance.

References
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*Postgrad Med J* 1982 58: 100-101
doi: 10.1136/pgmj.58.676.100

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