Concordance of primary generalised epilepsy and carbamazepine hypersensitivity in monozygotic twins

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Summary
In this paper we describe the previously unreported phenomenon of a carbamazepine-induced mucocutaneous syndrome in identical twins. These twins had developed primary generalised epilepsy within 2 months of each other.

Keywords: carbamazepine; hypersensitivity; twins; epilepsy

Treatment with anticonvulsant medication can be complicated by severe delayed hypersensitivity reactions. It has been proposed that the metabolism of aromatic anticonvulsants (phenytoin and carbamazepine) to toxic arene oxide metabolites may be involved.[1] Familial clustering suggests the existence of a genetic predisposition to hypersensitivity reactions to phenytoin.[2] There have been no previous reports of twins developing hypersensitivity reactions to any of the anticonvulsant drugs. Family and twin studies in epilepsy have been more extensive. Within affected sibships, the frequency of concordance for epilepsy in non-twin siblings is 12%, similar to the frequency in co-twins of dizygotic probands (9%), but this is much less than the frequency in co-twins of monozygotic probands (38%).[3] This presumably reflects a major genetic component to certain epilepsies.

We describe a pair of identical twins that both developed primary generalised epilepsy and a carbamazepine-induced drug eruption within 2 months of each other.

Case report

A 16-year-old man presented with two generalised tonic–clonic seizures without aura over a period of 2 months, for which he had been commenced on carbamazepine. He was one of a twin pair born by elective Caesarean section at 34 weeks gestation, both having identical birth weights of 2.3 kg. Neither twin had a history of neonatal problems or febrile convulsions, and there was no family history of epilepsy. Physical examination of the patient was normal. Computed tomography of the brain was normal and electroencephalogram (EEG) showed mild changes with one episode of generalised sharpened forms. A diagnosis of primary generalised epilepsy was made. Ten weeks after treatment had been started he developed soreness of the mouth and lips, and on examination was found to have angular kelitis, ulceration of the lips and buccal mucosa, conjunctival injection, and a diffuse erythematous macular rash over the limbs and trunk and face (see figures).

Blood tests, including a full blood count and liver function tests, were normal, and mild mucocutaneous drug eruption was diagnosed. Carbamazepine was withdrawn and replaced by sodium valproate, with hydrocortisone ointment and antibacterial mouthwash also prescribed. Over the next few weeks the mucocutaneous inflammation settled and the patient remained seizure free.

The twin brother of this patient was also seen at the age of 16, once again with two generalised tonic-clonic seizure without aura 2 months apart, which came on 2 months after his brother's seizures. EEG was abnormal with some generalised epileptiform discharges consistent with primary generalised epilepsy. He

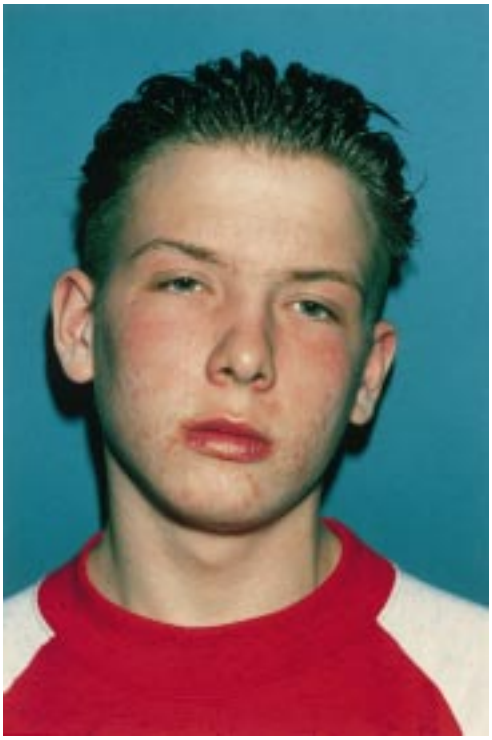

Figure 1 First twin, with generalised erythematous rash (reproduced with his permission)

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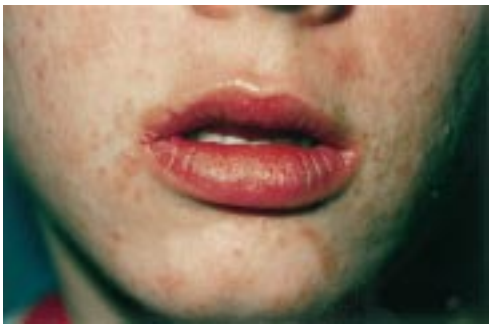

Figure 2 First twin, showing peri-oral mucocutaneous involvement (reproduced with his permission)

had also been commenced on carbamazepine, but after 4 weeks his mother stopped it having noticed similar mucocutaneous changes involving his skin and peri-oral region. The skin reaction settled and good epileptic control has since been maintained on sodium valproate.

The mother thought that the twins were identical, and genomic fingerprint testing revealed a probability of 1023 out of 1024 that they were monozygotic.

Discussion

Dose-independent effects of carbamazepine are often severe and include blood dyscrasias, hepatotoxicity, renal disorders and skin reactions. The dermatological sequelae have been reported to occur in 3–4% of patients and are usually mild rashes only.[4] It has been reported that abnormal detoxification of reactive, electrophilic, metabolites may be the common pathway for hypersensitivity reactions in the aromatic convulsants carbamazepine, phenytoin and phenobarbitone.[1]

Drug-induced mucocutaneous syndrome in twins has not previously been reported for any medication. The similarity in concordance in our patients for onset of epilepsy and reaction to carbamazepine is noteworthy. Both primary generalised epilepsy and drug-induced hypersensitivity reactions are likely to be multifactorial, with a significant genetic (presumably polygenic) as well as environmental component. The presence of similar mucocutaneous reaction to carbamazepine in these identical twins, supports the evidence for a genetic component to anticonvulsant hypersensitivity, which may act via abnormal detoxification of reactive metabolites.[2]

In monozygotic twin pairs in which one of the probands suffers a delayed hypersensitivity reaction to a particular medication, careful consideration should be given to commencing the same drug in the second twin, especially if the drugs belong to the same 'family' of medications, such as the aromatic anticonvulsants.

Learning point

Delayed hypersensitivity is a severe potential side-effect of many medications. If one monozygotic twin develops this reaction to a particular medication, serious consideration should be given before it is commenced in the other twin.

1 Shear NH, Spielberg SP, Cannon M, Miller M. Anticonvulsant hypersensitivity syndrome: in vitro risk assessment. *J Clin Invest* 1988;**82**:1826–32.
2 Gennis MA, Vemuri R, Burns EA, Hill JV, Miller MA, Spielberg SP. Familial occurrence of hypersensitivity to phenytoin. *Am J Med* 1991;**91**:631–4.
3 Berkovic SF, Howell RA, Hay DA, Hopper JL. Twin birth is not a risk factor for seizures. *Neurology* 1993;**43**:2515–9.
4 Ashmark H, Wilholm B. Epidemiology of adverse reactions to carbamazepine as seen in a spontaneous reporting system. *Acta Neurol Scand* 1990;**81**:131–40.