Episodic loss of consciousness: how genetic testing points to diagnosis

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Loss of consciousness is a common reason for referral to hospital services, both acute and elective, for diagnosis and management. The differential diagnosis lies between syncope and seizure, and there are well-recognised clinical markers which may help in this differentiation. Nevertheless, diagnosis can be challenging, particularly if an eyewitness account from a reliable informant is lacking, and potentially confusing if ancillary investigations are used in place of history, as shown in the following case.

Presentation
This lady presented in her early 40s with episodic loss of consciousness. The events were intermittent, with no obvious warning or premonitory symptoms. Almost all occurred while either sitting or standing, although one had occurred while lying in bed. Episodes were not accompanied by incontinence of urine, and she had sustained no injury in the attacks. No eyewitness account of the episodes was available.

Prior history
There was a prior history of episodic loss of consciousness occurring in the patient’s teenage years. Old medical records were not available, but she could recall that an electroencephalogram (EEG) had been performed and she was familiar with the name of Epilim, raising the possibility that she had been treated with this medication for presumed epileptic seizures.

Thereafter, there had been no further blackouts for approximately 25 years, and aside from depression, treated with venlafaxine, she had remained in good health. Although never formally assessed, her cognition was not entirely normal, and she had never been gainfully employed. There was no family history of cardiac or seizure disorder.

Referral to cardiology
Initial referral for the episodes of unconsciousness was to cardiology services. Investigations included electrocardiogram (ECG), which showed sinus rhythm, with a normal corrected QT interval ($\text{QT}_c = 453\text{ms}$), and transthoracic echocardiogram which was within normal limits. Tilt table testing was undertaken. Cardiac sinus massage was negative. After around 30 minutes of head-up tilt, she started yawning, became faint and sweaty, and then hypotensive and moderately bradycardic. In light of these findings a diagnosis of vasovagal (vasodepressor) syncope was made.

Neurological referral
Meantime, neurological referral had also been initiated, because of the patient’s one episode of loss of consciousness whilst lying and the previous possible history of epilepsy. In addition, the diagnosis of syncope had called into question the previous diagnosis of an underlying epilepsy syndrome, namely Sotos syndrome, based as it was solely on clinical features.

Repeat EEG showed irregular spike and wave discharges on photic stimulation at 8–10Hz, without electroclinical correlate. The findings were consistent with a generalised epilepsy syndrome.

In view of the EEG findings and the previous clinical diagnosis, neurogenetic testing was undertaken to examine the nuclear receptor-binding SET domain protein 1 (NSD1) gene, mutations in which are a common cause of Sotos syndrome. This showed the heterozygous c.6014G>A missense variant (p.Arg2005Gln), which has been previously reported as pathogenic for Sotos syndrome, hence confirming this diagnosis.

Taking this result, along with the absence of features of
presyncope reported in her attacks (unlike her experience on the tilt table), and the abnormal EEG, the episodes of loss of consciousness were thought more likely to be epilepsy than syncope.

The tilt table findings were thought to be incidental to the actual episodes of loss of consciousness, although dual diagnosis could not be entirely excluded in the absence of witness account. With introduction of an anti-epileptic drug (levetiracetam), the episodes of loss of consciousness settled, according to the patient’s account, over more than 12 months of follow up.

**Discussion**

Sotos syndrome, also sometimes known as ‘cerebral gigantism’, is a childhood overgrowth syndrome first described in 1964 and characterised by distinctive facial appearance, height and head circumference above the 97th percentile, advanced bone age and mild-to-moderate developmental delay.2 This is one of the genetic dysmorphology syndromes that may be complicated by epilepsy.3 Seizures are said to occur in about one quarter of patients, with tonic-clonic, absence and temporal lobe seizures recorded, which generally respond well to a single anti-epileptic medication.3

Mutations in the gene encoding NSD1 on chromosome 5q35, including nonsense, frameshift, and deletion mutations producing haploinsufficiency, have been shown to be the major cause of Sotos syndrome (OMIM#117550).4 This, Sotos 1 syndrome, is now distinguished from Sotos 2 syndrome on genetic grounds, the latter cases showing heterozygous mutations in the nuclear factor I, X type gene (NFIX) on chromosome 19p13.3 (OMIM#614753).5 The specific NSD1 mutation found in our patient, p.Arg2005Gln, has previously been reported as pathogenic for Sotos syndrome.6,7

Familial cases of Sotos 1 syndrome are rare, for example found in only 13 of 239 NSD1 positive cases reported by Tatton-Brown et al.,7 suggesting that family history is unlikely to be helpful in this situation, contrary to clinical experience in some other forms of epilepsy in which family history and additional clinical features observed along with the seizure disorder (eg occipital seizures) have assisted genetic diagnosis.8

The International League Against Epilepsy (ILAE) 2010 classification of the epilepsies designated some epilepsy syndromes as ‘genetic epilepsies’.9 Since not all patients with Sotos syndrome develop seizures, it may not be deemed appropriate for classification in this group, bearing in mind that on the one hand the use of EEG findings in isolation risks false positive diagnosis of epilepsy, whereas on the other hand the frequency of epileptic seizures may be an underestimate of those with subclinical epileptiform activity on EEG.

The most recent ILAE classification has a category of genetic disorders that also have developmental consequences arising directly from the effect of the genetic mutation, in addition to the effect of the frequent epileptic activity on development.10 Sotos syndrome might therefore be classified in this group.

In summary, in addition to careful characterisation of ictal semiology when possible,1 recognition of characteristic dysmorphic features and subsequent targeted genetic testing may be helpful in the diagnosis of epilepsy syndromes.5,8

**Declaration of interest**

No conflicts of interest were declared.

**References**


