Severe infantile epilepsies: molecular genetics challenge clinical classification

In 1978, Charlotte Dravet described the ‘cryptogenic’ epilepsy syndrome severe myoclonic epilepsy of infancy (SMEI) (Dravet, 1978). This severe generalized epileptic encephalopathy begins at around 6 months of age with febrile hemiclonic or generalized status epilepticus. Hemiconic status typically recurs involving each side independently. After 1 year of age, other seizure types appear including absence, partial, atonic and often myoclonic seizures. Early development is normal, with slowing and regression after 1 to 2 years; pyramidal features and ataxia may also evolve. The prognosis is poor. The recent draft proposal of the ILAE classification suggests the eponymous name Dravet syndrome instead of SMEI in recognition that not all cases experience myoclonic seizures (Engel, 2001).

SMEI is associated with a family history of seizures in 50% of patients. Affected relatives of SMEI probands have epilepsy sub syndromes such as febrile seizures and mild generalized epilepsies. These phenotypes are consistent with the generalized epilepsy with febrile seizures plus (GEFS+) spectrum (Singh et al., 2001). GEFS+ is a familial epilepsy syndrome characterized by heterogeneous phenotypes with most individuals having benign childhood seizure disorders ranging from classical ‘febrile seizures’ to ‘febrile seizures plus’ where febrile seizures continue past early childhood or afebrile convulsions occur (Scheffer and Berkovic, 1997). Within the GEFS+ spectrum, more severe phenotypes can occur including myoclonic-astatic epilepsy and temporal lobe epilepsy. GEFS+ is associated with mutations in SCN1A, SCN1B, SCN2A (genes encoding the alpha 1, alpha 2, beta 1 sodium channel subunits) and GABRG2 (gamma 2 subunit of the GABAA receptor) (Mulley et al., 2003).

The relationship between SMEI and GEFS+ became more intriguing when, in 2001, Claes and colleagues shed new light on the aetiology of SMEI. De novo mutations of SCN1A were identified in all seven SMEI patients studied (Claes et al., 2001). They reasoned that GEFS+ and SMEI share a predilection for fever-induced seizures and examined SCN1A as a candidate gene, following its proven association with GEFS+. Mutations in SCN1A were confirmed by Japanese groups with mutation rates of 77–82% in SMEI series (Ohmori et al., 2002; Sugawara et al., 2002). However, French, Italian, Australian and Canadian groups are obtaining significantly lower rates with only ~35% SMEI cases positive for SCN1A defects (F. Zara, personal communication; I. Scheffer, unpublished data). Where examined, most cases arise from de novo mutations. To some extent this disparity between mutation rates in different centres may be due to bias of ascertainment, such as diagnostic inclusion only of patients with SMEI with severe intellectual disability in some studies (mild intellectual disability can occur; C. Dravet, personal communication) (Claes et al., 2001), or phenotypic variability such as whether myoclonic seizures are an essential component for the diagnosis of SMEI.

In this issue of Brain, Fujiwara and coauthors contribute to the emerging picture by confirming high positive mutation rates with 30 out of 35 cases with SCN1A mutations (Fujiwara et al., 2003). More importantly however, they broaden the phenotypic spectrum of SCN1A defects to include an entity recognized primarily in the Japanese literature, intractable childhood epilepsy with generalized tonic–clonic seizures (ICEGTC). Children with ICEGTC develop febrile seizures by 1 year of age, often recurring in clusters or status epilepticus, with convulsions remaining the predominant seizure type. Cognitive decline is usual and neurological deficits may develop. This molecular finding reinforces the clinical continuum including SMEI and ICEGTC which also encompasses entities such as ‘SMEI borderlands’ and severe idiopathic generalized epilepsy of infancy with generalised tonic–clonic seizures (Doose et al., 1998). Phenotype–genotype correlation will be important to understand these phenotypic differences. Indeed, further studies of large series of SCN1A mutations in severe epileptic encephalopathies of the first year of life will contribute to our understanding of the phenotypes associated with SCN1A defects. Only by understanding the breadth of phenotypes associated with SCN1A defects will we be able to make early diagnoses and harness appropriate therapies that may potentially improve outcome.

Significantly, Fujiwara and colleagues report inherited SCN1A defects in two patients with ICEGTC whose mothers had phenotypes consistent with GEFS+. They conclude that ICEGTC forms a severe phenotype within the GEFS+ spectrum. This finding of inherited SCN1A mutations is consistent with the family history of GEFS+ in a notable proportion of these patients. SCN1A is the second, and
probably more important, gene to contribute to these phenotypes in GEFS+ families, following the report of an inherited GABRG2 mutation in a patient with SMEI (Harkin et al., 2002). In the case of familial mutations, the SCN1A or GABRG2 defects are associated with mild phenotypes in most family members. Thus the severe SMEI phenotype is likely to result from the cumulative effects or interaction of few or several genes, of which the reported GEFS+ gene is merely one player.

Mutational analysis of SCN1A defects initially seemed straightforward, implicating missense mutations with the milder familial GEFS+ phenotypes and more severe truncation mutations in SMEI. As more mutations are discovered, the molecular picture is becoming less clearcut with de novo missense, frameshift and nonsense mutations associated with SMEI.

Unfortunately, the molecular puzzle remains unsolved. Why do 50% of children with SMEI have a family history of seizures yet de novo SCN1A mutations occur in 80% of cases? In patients with de novo SCN1A mutations and a family history of GEFS+, one hypothesis is that additional GEFS+ genes contribute to the SMEI phenotype. In other words, perhaps the familial gene is necessary, but not sufficient for the patient to develop SMEI, and the interaction with the de novo SCN1A mutation produces this severe syndrome.

For now, the clinician is left with the question, is a severe SCN1A defect diagnostic for SMEI? The answer is that if present, it strongly supports the diagnosis but is probably not the whole answer. The diagnosis of SMEI must remain a clinical one—it is still likely that complex inheritance plays a role even in de novo mutations. Looking to the future, elucidation of the molecular basis of SMEI is the first step in understanding the underlying pathophysiology; functional studies of these molecular defects will be crucial if we are to improve outcome of this devastating disorder.

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References


