SHORT REPORT

Genetic epilepsy with febrile seizures plus: definite and borderline phenotypes

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ABSTRACT

Generalised epilepsy with febrile seizures plus (GEFS+) is the most studied familial epilepsy syndrome. However, characteristics of UK families have not previously been reported. Among the first 80 families recruited to our families study, four broad subphenotypes were identified: families with classical GEFS+; families with borderline GEFS+; families with unclassified epilepsy; and families with an alternative syndromal diagnosis. Borderline GEFS+ families shared many characteristics of classical GEFS+ families—such as prominent febrile seizures plus and early onset febrile seizures—but included more adults with focal epilepsies (rather than the idiopathic generalised epilepsies predominating in GEFS+) and double the prevalence of migraine. Thus the authors believe that a novel and robust familial epilepsy phenotype has been identified. Subcategorising families with epilepsy is helpful in targeting both clinical and research resources. Most families with GEFS+ have no identified causal mutation, and so predicting genetic homogeneity by identifying endophenotypes becomes more important.

INTRODUCTION

Generalised epilepsy with febrile seizures plus (GEFS+) was first proposed as a diagnostic entity in 1997.[1] The families broadly have idiopathic generalised epilepsy but with a predominance of febrile and febrile seizures plus (FS+); indeed, FS are considered the prototype seizure in GEFS+. Additionally, young children with catastrophic epilepsy syndromes (such as severe myoclonic epilepsy of infancy (SMEI)) occur more frequently among GEFS+ families than expected by chance. Family members with specific electroclinical syndromes (such as childhood absence epilepsy or juvenile myoclonic epilepsy) would be unusual but are seen infrequently. However, the occurrence of occasional family members with focal epilepsies has led to the suggestion that the GEFS+ acronym better describes *genetic* epilepsy with FS+. GEFS+ is now widely recognised and is a core diagnosis seen in studies of families with epilepsy.

Berkovic and Sheffer's original GEFS+ description defined a GEFS+ 'spectrum', ranging from individuals with simple FS and FS+ up to SMEI. The generalised epilepsy phenotypes included absence seizures, myoclonic seizures and, more rarely, atonic and myoclonic–astatic seizures. It was also suggested that the pedigree showed an autosomal dominant pattern with incomplete penetrance.[1] The gene mutations thus far described in association with GEFS+ have coded for ion channels: private mutations in *SCN1A, SCN1B* and *GABRG2* genes occur in 10% of families with the GEFS+ phenotype.[2 3] Although the genetic causes of most epilepsies (including GEFS+) have yet to be elucidated, it is still widely believed that most epilepsies have some genetic component.[4] Siblings of an individual with confirmed seizures have an approximately fivefold risk of developing epilepsy (compared with a background risk of 0.75%), depending on the age of onset of the seizures. A monozygotic twin with an affected twin has between 37% and 80% risk of developing epilepsy, compared with between 3% and 32% for a dizygotic twin.[5] This also implies an environmental aspect to the aetiology; in the case of GEFS+, this may be the infantile illness needed to provoke typical and FS+. Mutations in the sodium channel may also lead to an increased risk of febrile convulsions which itself increases the risk of developing epilepsy.[6] This would certainly seem logical, as sodium channel defects are known to causes disorders influenced by temperature, such as paramyotonia congenita.[7]

More than 600 *SCN1A* mutations have been described,[8 9] missense mutations being the most frequent. Frameshift and nonsense mutations are associated with the more deleterious epilepsies, such as SMEI.[2 3 10] The mutations are spread throughout the gene but occur most frequently outside the pore forming region.[11 12] Initially, the GEFS+ family phenotype was tightly defined but the borders of both epilepsy within GEFS+ families and the epilepsy caused by *SCN1A* mutations are increasingly blurred. GEFS+ families from the UK have not been previously systematically described and analysed, despite the original family described being Anglo-Australian.[1] We present our experience and the clinical description of our GEFS+ families.

METHODS

Eighty families were consented and recruited for future genetic analysis (MREC approval 05/MRE09/78). Families were referred by epilepsy clinicians or self-referred following advertisements placed in epilepsy charity magazines. All available family members were interviewed by neurologists with clinical experience of epilepsy (JAJ, RHT). The characteristics of individuals were ascertained via semistructured interview and the pedigrees charted. Focused comorbidity data were collected, including conditions with a presumed channelopathy basis (migraine) and conditions associated

with increased frequency of microdeletions and insertions (learning difficulties). Consensus as to whether the families met the original (1997) criteria for GEFS+ was achieved following debate within a team comprising two clinical research fellows, a professor of molecular genetics, a paediatric neurologist and a genetic counsellor. Families were divided into four groups: classical GEFS+, borderline GEFS+, unlikely to be GEFS+ (broadly unclassified epilepsies) and those with another specific familial epilepsy syndrome. The characteristics of the individuals with epilepsy from within these families were extracted for analysis and the χ^2 test (with Yates' correction when needed) was used. People were identified as having FS (simple FS), FS+ (generalised or partial seizures that continue to occur after the age of 5 years, or in the absence of a very high temperature),[1] generalised tonic–clonic seizures (GTCS) as an adult (beyond age 18 years) or other types of seizures. Focal epilepsy syndromes were confirmed by reviewing clinic letters.

RESULTS

Characteristics of the families

Of the first 80 families, 29 were recruited via neurologists, 19 by paediatricians and 17 were self-referrals, seven from epilepsy nurse specialists, four through clinical databases, three from the learning disability service and one from clinical genetics. Fourteen families were classified as classical GEFS+ and 10 as borderline (figure 1). In eight families, GEFS+ was considered unlikely and the epilepsy phenotype was unclassifiable; 48 had another specific syndromal diagnosis. Borderline GEFS+ families had a greater mix of epilepsy diagnoses (including electroclinical syndromes, such as juvenile myoclonic epilepsy, and focal epilepsies, such as temporal lobe epilepsy) than those with definite GEFS+. Idiopathic generalised epilepsy comprised 80% of diagnoses that persisted into adulthood in definite GEFS+ but only 60% for borderline families ($p<0.01$), where there were twice as many adults with focal epilepsies.

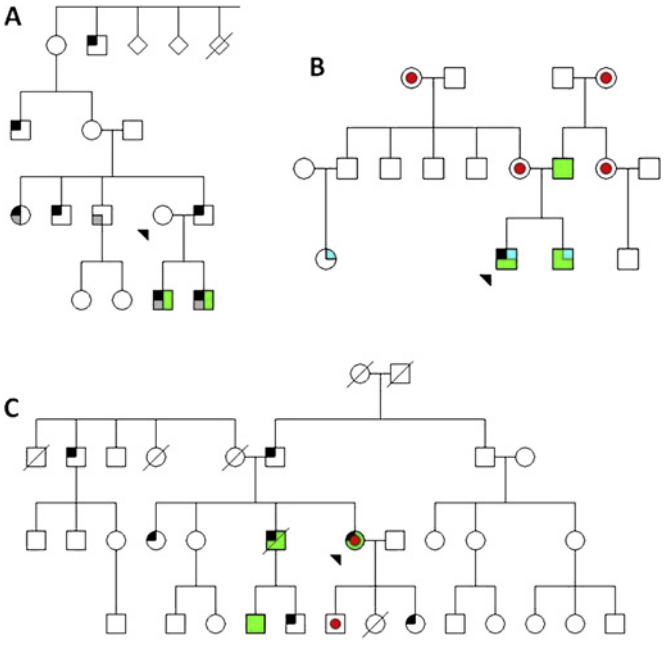

Figure 1 Generalised epilepsy with febrile seizures plus (GEFS+) and borderline GEFS+ pedigrees. Pedigree A, GEFS+; pedigrees B and C, borderline GEFS+. Febrile seizures (top left quadrant black), afebrile seizures (bottom left quadrant grey), generalised tonic–clonic seizures as an adult (shaded symbol), migraine (central circle), learning difficulties (top right quadrant grey).

Individual characteristics

Classical GEFS+ families—120 individuals had seizures: 77 had FS (64.2%) and of these, seven also had afebrile seizures (AFS) (5.8%) and 18 later had adult GTCS (1.5%); 23 had AFS (19.2%) with five later going on to have adult GTCS (4.2%); 22.5% (27 people) had adult GTCS with no preceding febrile seizures.

Borderline GEFS+ families—83 people reported seizures: 43 had FS (51.8%), three with both FS and AFS (3.6%) and nine later having adult GTCS (10.8%); 11 people had AFS (13.3%), three of whom later developed GTCS (3.6%); 27 people (32.5%) had adult onset GTCS only.

Unclassified familial epilepsy—80 had seizures or epilepsy: 20 had FS (25%), three of whom (3.8%) had both FS and AFS and five later had adult GTCS (6.3%); 13 had AFS (16.25%), four of whom (5%) later had adult GTCS; 45 (56.3%) had adult GTCS only.

FS were reported twice as often in classical GEFS+ or borderline GEFS+ families ($p<0.005$) than in those with unclassified epilepsies. FS+ were rare but occurred disproportionately in classical and borderline GEFS+ families, accounting for 24% and 19% of febrile seizures, respectively. There was also a trend towards typical FS occurring earlier in GEFS+ families. No family included any member with SMEI or a similar epileptic encephalopathy. Thirty-five people had learning difficulties (33 having a clinical diagnosis of epilepsy); there was no increased likelihood of learning difficulty across any of the four diagnostic groups. The prevalence of migraine was 12%, similar to the population estimate. However, migraine prevalence was significantly higher in the borderline GEFS+ group, with 25% of those with epilepsy also having migraine. The migraine prevalence in the classical GEFS+ group was 8.2% (classical vs borderline groups, $p<0.01$) and was 7.1% in the unlikely GEFS+ group (borderline vs unclassified, $p<0.03$). The migraine described was mostly without aura, but migraine with aura and, rarely, hemiplegic migraine were also seen.

DISCUSSION

We have reported a novel epilepsy familial subphenotype—borderline GEFS+. It is likely to be a polygenic epilepsy syndrome sharing many, but not all, points of variation with classical GEFS+. The Wales Epilepsy Research Network classification (table 1) has features which may help focus gene screening projects. We recognise some limitations to this type of work. Not every individual had an EEG and, although where possible we corroborated the stories given with medical records, it is likely that there was a degree of non-disclosure in all of the families studied. However, we believe that identifying the concept of borderline GEFS+ and its relationship with migraine (also believed to be a channelopathy) may help to explain their shared pathogenesis.[13] Recently, a dominant negative mutation in the TRESK potassium channel has been identified in a family with migraine with aura.[14] The frameshift mutation in the *KCNK18* gene renders the channel nonfunctional and may offer a therapeutic target. Antiepileptic drugs such as topiramate and sodium valproate are commonly used as secondline agents for migraine prophylaxis; indeed, the novel antiepilepsy agent retigabine is thought to act at the KCNQ/Kv7 potassium channel.[15] The concept of a genetically homogenous GEFS+ syndrome is difficult to support by intrafamilial heterogeneity, even within the subcategories

Table 1 Wales Epilepsy Research Network criteria for definite and borderline generalised epilepsy with febrile seizures plus

	Classical	Borderline	Unclassified	Other diagnoses
FS	Y	Y	Y	Y/N
FS+	Y	Y	Y /N	N
Adult epilepsy—IGE	++	+	+/−	+/−
Characteristic seizure type	FS+	FS+	GTCS without prior FS	
Migraine	+	++	+	+
Electroclinical syndromes	+/−	+	+	++
Most common seizure type	FS	FS	GTCS	Other

The characteristic seizure type is the most distinctive event that may help differentiate the subtype, whereupon the most common seizure is the most frequently occurring. FS, febrile seizures; FS+, febrile seizures plus; GEFS+, generalised epilepsy with febrile seizures plus; GTCS generalised tonic—clonic seizures; IGE, idiopathic generalised epilepsy.

proposed; borderline GEFS+ families had twice the number of adults with a symptomatic focal epilepsy (40% vs 20%) than those seen in classical GEFS+.

Febrile seizures

The most common seizure phenotype in UK GEFS+ families was the FS, occurring in over half of the individuals among classical or borderline GEFS+ families. Most did not progress to either further generalised seizures or to an adult epilepsy pattern. FS are notoriously under-reported by older relatives,[16] potentially artificially reducing their prevalence. Fifty per cent of the people who had seizures from classical or borderline GEFS+ families experienced generalised seizures (compared with 33—67% in the original Australian families).[1] FS+ were rare, and were specific (97.5%) but not sensitive for identifying GEFS+ or GEFS+ borderline families, accounting for 24% and 19% of FS, respectively. In the families with borderline GEFS+, median age of onset of FS was 12 months. This is similar to the reported median age of onset ranging between 11 and 12 months in individuals with *SCN1A* mutations[17] but earlier than the general population average of 18 months.

CONCLUSION

We have identified a novel familial subphenotype within this UK based cohort—borderline GEFS+—and have suggested criteria for identifying these families. Borderline GEFS+ families have prominent FS+ but twice the migraine prevalence of other familial epilepsy and a greater preponderance of adults with symptomatic epilepsies. Identifying families with either a classic or borderline phenotype will be important for efficient direction of resources to inform gene discovery.

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Competing interests None.

Ethics approval The study was approved by the South West Wales research ethics committee (MREC approval 05/MRE09/78).

Contributors RHT conceived and wrote the paper and is responsible for the design and data analysis. JAJ and CLH recruited and interviewed the families, and assisted in phenotyping. SB performed the data extraction, data analysis and helped write the paper. CW and PEMS referred families for the project and helped in phenotyping. MIR is the lead for the family study project and ongoing genetic studies; he assisted in writing and editing the paper. All authors meet the ICMJE criteria for an author.

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Data sharing statement We would only be happy to share anonymised individual or familial phenotype information within the context of a formal collaboration because of the nature of our ethics agreement.

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