Generalized epilepsy with febrile seizures plus and classical idiopathic generalized epilepsy

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Abstract

The idiopathic generalized epilepsies (IGE) comprise two major groups: the classical IGE and generalized epilepsy with febrile seizures plus (GEFS+). The classical IGE syndromes include childhood absence epilepsy; juvenile absence epilepsy; juvenile myoclonic epilepsy; and epilepsy with generalized tonic-clonic seizures alone. GEFS+ is a familial epilepsy syndrome, characterized by a spectrum of phenotypes. The phenotypes of GEFS+ include febrile seizures (FS), febrile seizures plus (FS+), FS/FS+ and absences, myoclonic, atonic or partial seizures, myoclonic-astatic epilepsy and severe myoclonic epilepsy of infancy. Our study of 121 individuals in 20 families, where 84 had previously recognized GEFS+ phenotypes, expands the phenotypic spectrum of GEFS+ syndrome to include afebrile generalized tonic-clonic seizures with generalized spike wave or normal EEG in the absence of FS. To date, there are three ion channel genes (SCN1A, SCN1B and GABRG2) confirmed as having a role in GEFS+, but none has been implicated in the majority of patients with GEFS+ phenotypes, such as those found in small families. Indeed it is likely that in most families, GEFS+ is a polygenic disorder resulting from the cumulative effect of a number of genes of lesser effect rather than the genes so far characterized in the few large families ascertained. Small GEFS+ families and bilineal inheritance in some add support for complex inheritance in a significant proportion of families. The phenotypes of classical IGE occur in some GEFS+ families. The percentage of classical IGE phenotypes is 9% (11/121) of affected individuals in our study. This suggests that classical IGE phenotypes and GEFS+ phenotypes overlap in some GEFS+ families. Our study provides new insights into the inter-relationship of GEFS+ and classical IGE, where shared genetic determinants probably account for the overlap of these syndromes in some families.

INTRODUCTION

Generalised epilepsy with febrile seizures plus (GEFS+) is a genetic epilepsy syndrome diagnosed on the basis of a number of family members with phenotypes within the GEFS+ spectrum. The phenotypes of GEFS+ include febrile seizures (FS), febrile seizures plus (FS+), FS/FS+ and absences, myoclonic, atonic or partial seizures, myoclonic-astatic epilepsy and severe myoclonic epilepsy of infancy (or Dravet syndrome). Although GEFS+ is an idiopathic generalised epilepsy (IGE), it is only rarely seen in association with the classical IGE syndromes of childhood absence epilepsy, juvenile myoclonic epilepsy and juvenile absence epilepsy.

There are three ion channel genes (SCN1A, SCN1B and GABRG2) confirmed as having a role in GEFS+. Mutations of these genes have been found in a small number of large multiplex GEFS+ families where the inheritance of seizures is consistent with autosomal dominant inheritance. Small GEFS+ families are more frequent than the large families reported, yet insights into the susceptibility genes for complex inheritance of GEFS+ in smaller kindreds are just beginning to emerge.

Here, we report 20 new GEFS+ families varying in size from 2 affected members to 12 affected individuals. We analyze the phenotypes within these families and compare them with previously reported GEFS+ families. In addition, we examine the overlap of GEFS+ and IGE phenotypes found within a subset of families.

EPILEPSY PHENOTYPES IN GEFS+ FAMILIES

Our study of 121 individuals distributed in 20 families had seizures, 84 with previously recognized GEFS+ phenotypes: FS in 37, FS+ in 16, FS+ with other seizure types (absence, atonic) in 7, myoclonic-astatic epilepsy in 7, and partial epilepsy with or without FS in 17 individuals. In 8 families, an additional 11 individuals had IGE: childhood absence epilepsy in 5, juvenile
myoclonic epilepsy in 5, juvenile absence epilepsy in 1. Twenty six individuals had other phenotypes: afebrile generalized tonic-clonic seizures in 5, Lennox-Gastaut syndrome in 1, unclassified seizures in 17, unconfirmed seizures in 3 individuals.

In studying many families with GEFS+, we have occasionally encountered family members who have isolated or rare afebrile generalized tonic-clonic seizures. In our new families, we found 5 individuals who had afebrile generalized tonic-clonic seizures without preceding FS. The EEG results were normal in 3 patients; no EEG results were available for the other two. Baulac et al reported an individual with afebrile generalized tonic-clonic seizures associated with an SCN1A mutation in a GEFS+ family.6 Bonanni et al reported 7 GEFS+ families with 39 affected individuals without mutations of known GEFS+ genes.7 Six individuals in four families had afebrile generalized tonic-clonic seizures. Two of these 6 individuals showed 3 Hz generalised spike and wave on EEG and were classified as IGE with generalized tonic-clonic seizures. These data suggest that isolated afebrile generalized tonic-clonic seizures also form part of the GEFS+ spectrum.

THE PHENOTYPES OF GEFS+ AND CLASSICAL IGE OVERLAP FAMILIES

In 20 GEFS+ families, the phenotypes of GEFS+ and classical IGE overlapped in 8 families. The classical IGE phenotypes in GEFS+ families included five childhood absence epilepsy patients (one twin pair) in 4 families, five juvenile myoclonic epilepsy patients in 4 families, and 1 juvenile absence epilepsy patient in one family. In these 11 classical IGE patients 2 had a history of FS.

This is not the first time that classical IGE have been found in GEFS+ families. Molecular studies have shown that GABAA receptor subunit gene mutations may occur in GEFS+ and classical IGE families. Specifically GABRG2 gene mutations have been reported in a large family with GEFS+ and childhood absence epilepsy phenotypes.2 Sodium channel subunit mutations more commonly are found in GEFS+ families but classical IGE may also be seen. For example, early-onset absence epilepsy without FS occurred in one member of a GEFS+ family with a SCN1B mutation.5 Rare individuals in GEFS+ families have been reported with juvenile myoclonic epilepsy. In some cases they carry the familial sodium channel SCN1A mutation; whereas, in others they do not.8

EVIDENCE FOR COMPLEX INHERITANCE IN SOME GEFS+ FAMILIES

In 20 GEFS+ families, 10 families were consistent with autosomal dominant inheritance. Bilateral inheritance was present in 8 families, involving 14 affected members. Another 2 GEFS+ families were small, each only had 2 affected members. Bilateral inheritance and small GEFS+ families add support for complex inheritance in a significant proportion of families.

This study expands the phenotypic spectrum of GEFS+ syndrome to include afebrile generalized tonic-clonic seizures with generalized spike wave or normal EEG in the absence of FS. Our findings emphasize the inter-relationship of GEFS+ and IGE; shared genetic determinants probably account for the overlap of these syndromes in some families.

REFERENCES