

Generalized epilepsy with febrile seizures-plus context

Author: Doctor Isabelle Gourfinkel-An¹

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¹Unité d'Epileptologie, Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France. isabelle.an@psl.ap-hop-paris.fr

[Abstract](#)

[Keywords](#)

[Disease name and synonyms](#)

[Excluded diseases](#)

[Definition](#)

[Differential diagnosis](#)

[Prevalence](#)

[Clinical description](#)

[Disease course and treatment](#)

[Etiology](#)

[Diagnostic methods](#)

[Unresolved questions](#)

[Perspectives](#)

[References](#)

Abstract

Generalized epilepsy with febrile seizures-plus context (GEFS+) refers to a rare heterogeneous familial condition, which has been recently described. Its prevalence is not yet established. Patients affected with GEFS+ display febrile seizures persisting sometimes beyond the age of 6 years, and/or a variety of afebrile seizure types. Disease course and response to antiepileptic treatment show an important intrafamilial variation: in some patients, afebrile seizures may either occur rarely, or disappear after some years of disease evolution, whereas epilepsy is severe and pharmaco-resistant in other members of the same family. GEFS+ is transmitted as an autosomal dominant trait with incomplete penetrance (70-80%) and is associated with genetic heterogeneity. GEFS+ belongs to the group of channelopathies, as it is associated with mutations in genes encoding different subunits of the neuronal voltage-gated sodium channel and the gamma-2 subunit of the GABAA receptor.

Keywords

Epilepsy, febrile seizures, voltage-gated sodium channel, GABAA receptor, channelopathies.

Disease name and synonyms

Generalized epilepsy with febrile seizures-plus context (GEFS+)

Excluded diseases

Familial febrile seizures that are not associated with afebrile seizures (excepted temporal lobe epilepsy mediated by hippocampal sclerosis that may complicate of febrile seizures) and with a genetic basis different from that of GEFS+ context.

Definition

GEFS+ refers to a rare heterogeneous familial condition, which has been recently described (Scheffer and Berkovic, 1997). In this familial context, patients affected display febrile seizures sometimes persisting beyond the age of 6 years (called febrile seizures "plus"), and/or a variety of afebrile seizure types.

Differential diagnosis

Other familial epileptic syndrome in which afebrile seizures may be fortuitously associated with febrile seizures (as febrile seizures are frequent events, affecting 3-5% in general population).

Prevalence

As GEFS+ context has been recently identified, its prevalence is currently unknown.

Clinical description

GEFS+ is characterized by an heterogeneous familial phenotype: some affected members have particular febrile seizures persisting beyond the age of 6 years and that are often particularly repetitive, whereas other members have "classic" febrile seizures disappearing before this age. Varied forms of afebrile seizures are also observed in these families: generalized seizures (tonic-clonic, myoclonic, atonic, absence seizures) have been described in the first reported families. Nevertheless, different types of seizures have been later observed in other families (hemiconvulsive or tonic seizures, temporal or frontal seizures). These afebrile seizures may begin in childhood in association with febrile seizures, after a seizure-free period, or later in life, sometimes in patients without history of febrile seizures. Several types of seizures can coexist in a given patient showing electroclinical features that are more or less typical of generalized idiopathic epilepsies, myoclonic-astatic epilepsy (Doose syndrome) (Singh *et al.*, 1999) or severe myoclonic epilepsy (Singh *et al.*, 2001; Veggiotti *et al.*, 2001; Harkin *et al.* 2002). However electroclinical patterns that do not correspond to the international classification of epilepsies can also be observed (C.C.T.I.L.A.E, 1989).

Disease course and treatment

Disease course and response to antiepileptic treatment show an important intrafamilial variation: in some patients, afebrile seizures may either occur rarely, or disappear after some years of disease evolution, whereas epilepsy may be severe in others. Within the same GEFS+ family, seizures can be controlled in some members using an antiepileptic monotherapy, whereas epilepsy reveals to be pharmaco-resistant in other members. Additionally, some patients are intellectually disabled. When available, neuroimaging of epileptic patients is normal.

Etiology

It has long been suspected that genetic factors play a prevalent role in the etiology of idiopathic

epilepsies, most of which are characterized by a complex inheritance. However, some rare idiopathic epilepsies with monogenic inheritance have now been identified. GEFS+ context belongs to this last group of epileptic diseases.

GEFS+ is transmitted as an autosomal dominant trait with incomplete penetrance (70-80%), and is genetically heterogeneous. The first disease locus has been mapped to the region 19q13.1, and a mutation (Cys121Trp) in the *SCN1B* gene coding for the beta-1 subunit of the neuronal voltage-gated sodium channel has been identified in one family (Wallace *et al.*, 1998). Since then, very few mutations in *SCN1B* have been identified in families with GEFS+ (Wallace *et al.*, 2001a, 2002; Audenaert *et al.*, 2003). The majority of families with GEFS+ are not linked to this locus.

A second disease locus mapping to region 2q21-q33 has been reported (Baulac *et al.*, 1999; Moulard *et al.*, 1999; Peiffer *et al.*, 1999; Lopes-Cendes *et al.*, 2000). In two French families, two different mutations (Arg1648His and Thr875Met) have been first identified in the *SCN1A* gene, which encodes the alpha-1 subunit of the same voltage-gated sodium channel (Escayg *et al.*, 2000). Later, many additional point mutations in the *SCN1A* gene have been described in other families with GEFS+ (Escayg *et al.*, 2001; Wallace *et al.*, 2001a; Ito *et al.*, 2002; Cossette *et al.*, 2003; Annesi *et al.*, 2003) or in families or isolated cases presenting with a more homogeneous phenotype associating febrile seizures and partial epilepsy (Sugawara *et al.*, 2001a; Abou-Khalil *et al.*, 2001).

Interestingly, mutations in *SCN1A* were also identified in sporadic [severe myoclonic epilepsy in infancy](#) (SMEI): they correspond to *de novo* mutations or mutations transmitted by asymptomatic (or mildly affected) parents (Claes *et al.*, 2001; Nabbout *et al.*, 2003).

Moreover, GEFS+ has been recently linked to mutations in the *SCN2A* gene, which is also located in 2q21-q33 and encodes the alpha-2 subunit of the voltage-gated sodium channel (Sugawara *et al.*, 2001b).

Electrophysiological studies have demonstrated that mutations in the beta-1, alpha-1 and alpha-2 subunits interfere with the functional properties of the sodium channel (Wallace *et al.*, 1998; Alekov *et al.* 2000; 2001; Sugawara *et al.*, 2001b; Meadows *et al.*, 2002).

GABAA receptor is also involved in the pathophysiology of GEFS+, as mutations in *GABRG2* gene (located in 5q34) encoding the gamma-2 subunit of the GABAA receptor, with variable effects on the channel properties, have been identified in families with GEFS+ (Baulac *et al.*, 2001; Harkin *et al.*, 2002) and in a family with

febrile seizures and absence seizures (Wallace *et al.*, 2001b; Kananura *et al.*, 2002; Marini *et al.*, 2003).

However, other loci are probably involved, as numerous families with GEFS+ phenotype are not linked with the loci described above.

As a disease caused by mutations in genes encoding voltage-gated ion channels subunits, GEFS+ belongs to the group of "channelopathies", along with two other familial idiopathic epileptic syndromes: the autosomal dominant [nocturnal frontal lobe epilepsy](#) (in which different subunits of the neuronal nicotinic acetylcholine receptor are involved) and the [benign familial neonatal convulsions](#) (mediated by mutations of voltage-gated potassium channel genes).

Diagnostic methods

Diagnosis of GEFS+ is first based on clinical criteria. Genetic analysis of families with GEFS+ phenotype is under investigation.

Unresolved questions

The genetic heterogeneity of GEFS+ has been clearly established. Different genes, which are either functionally linked (*i.e.* genes encoding different subunits of the voltage-gated sodium channel) or not functionally linked (*i.e.* genes encoding subunits of the voltage-gated sodium channel and genes encoding subunits of the GABAA receptor), and different mutations may underlie the same familial epileptic syndrome. In addition, significant intrafamilial phenotypic heterogeneity is associated with the GEFS+ context. It has been suggested that expression of the mutated genes differs among family members, causing clinical heterogeneity. Alternatively, the gene may intervene in epileptogenesis at a very general level, affecting epileptic susceptibility or modulating the epileptic threshold, and additional genetic or environmental factors may influence the electroclinical profile of the disease in each affected subject.

Perspectives

In the short term, progress in establishing the genetics of GEFS+ will have more important implications for the elucidation of the syndrome's pathophysiology than for clinical practice. Moreover, predictive diagnosis in presymptomatic individuals raises ethical problems due to the syndrome's incomplete penetrance and variable expressivity.

It is however noteworthy, from a pathophysiological point of view, that the voltage-gated sodium channel and GABAergic neurotransmission are already targets of

numerous antiepileptic drugs. Recent genetic discoveries in GEFS+ should help towards the understanding of both the pharmacological response (or resistance) of some epileptic patients to antiepileptic drugs, and the adverse effects that are sometimes associated with these treatments. These discoveries should also facilitate the generation of new antiepileptic drugs.

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