GENETIC EPILEPSY WITH FEBRILE SEIZURES PLUS – AN OVERVIEW

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ABSTRACT
Genetic epilepsy with febrile seizures plus (GEFS+) is characterized by a group of genetic epilepsies associated predominantly with an autosomal dominant pattern, but also with de novo and autosomal-recessive inheritance, these last two found in a small number of cases. It was believed that GEFS+ is associated only with generalized seizures, but now the term “genetic epilepsy” is preferred because it has been demonstrated that GEFS+ is associated with both generalized and focal seizures. The “GEFS+ family” was defined as a family with more than two individuals with GEFS+ phenotypes, including at least one with febrile seizure or febrile seizure plus. The GEFS+ spectrum includes febrile seizures (FS), febrile seizures plus (FS+), myoclonic seizures, myoclonic-atonic seizures, absences seizures, focal or generalized seizures. The genetic mutations responsible for inhibitor-excitatory imbalance in neurons network were found in sodium voltage-gated channel alpha subunit 1 (SCN1A), sodium voltage-gated channel beta subunit 1 (SCN1B), sodium voltage-gated channel alpha subunit 2 (SCN2A), sodium voltage-gated channel alpha subunit 9 (SCN9A), gamma-aminobutyric acid type A receptor subunit gamma 2 (GABRG2), which are the main gene in GEFS+ genotype.

Keywords: GEFS+, febrile seizure, SCN1A, genetic epilepsy

INTRODUCTION
Genetic epilepsy with febrile seizures plus (GEFS+) represents a group of genetic epilepsy syndromes, associated with an autosomal dominant pattern. It was previously named and defined by Scheffer and Berkovic (1997) as generalized epilepsy with febrile seizures, “a genetic disorder with heterogeneous clinical phenotypes” because it was believed that GEFS+ was only associated with generalized seizures [1].

GEFS+ was first described on a large Anglo-Australian extended family with febrile seizures having unusual duration or severity, and afebrile seizures with various types of manifestations [1].

Now the term “genetic epilepsy” is preferred due to the presence of focal as well as generalized seizures in the phenotype of these patients [2]. The definition of family with GEFS+ or “the GEFS+ family” is: “a family with more than two individuals with GEFS+ phenotypes, including at least one with FS or FS+” [3].

GEFS+ SPECTRUM
The clinical presentation of patients with GEFS+ is highly variable, and the clinical spectrum extends from familial febrile seizures to more severe cases as myoclonic-atonic epilepsy or Dravet syndrome.

The pattern found in GEFS+ was observed to include febrile seizures (FS) or febrile seizures plus (FS+) alone or associated with myoclonic, myoclonic-atonic, absence, focal or generalized seizures. Thus, the phenotypes seen within GEFS+ spectrum vary from the mildest end, which include benign febrile seizures or febrile seizures plus, to
the most severe end where we encounter a range of epileptic encephalopathies [4-7].

Zhang Y. et al. (2017) studied 31 families with GEFS+ and they succeeded to extend the pheno-
typic spectrum of GEFS+. Therefore, they added 3 other phenotypic groups to the spectrum: focal ep-
ilepsies without FS or FS+, genetic generalized epilepsy and afebrile generalized tonic-clonic sei-
zures (GTCS) [2].

In another study performed on Japanese fami-
lies with GEFS+, febrile seizures plus were used as the core of all clinical phenotypes and other var-
ious epilepsy types which can occur later were in-
cluded afterwards. The GEFS+ spectrum that they used was classified as follows: generalized epilep-
sy including absence seizures, myoclonic seizures, atonic seizures and myoclonic-atonic epilepsy,
partial epilepsy with temporal lobe epilepsy and frontal lobe epilepsy, unclassified epilepsy with se-
vere myoclonic epilepsy in infancy (SMEI) and intractable childhood epilepsies with generalized tonic-clonic seizures (ICEGTC) [8].

**FEbrILE sEIZUrEs AND FEbrILE sEIZUrEs PLUs**

Febrile seizures (FS) are the most common phe-
notype in the GEFS+ spectrum [2] and are charac-
terized clinically by tonic-clonic seizures associat-
ed with fever (over 38°C) caused by a viral or bac-
terial infection, but without central nervous sys-
tem infection. The normal age range for this type of seizure is 6 months to 6 years, with a high preva-
ce of seizures between 18 months and 3 years of age. FS represents the mildest phenotype of GEFS+ [9].

Febrile seizures plus (FS+) is the second most common phenotype and is similar to a classic fe-
brile seizure, but these happen beyond the normal age range, which is after 6 years, with or with-
out association of afebrile generalized tonic-clonic sei-
zures, as well as febrile convulsive seizures [1].

To consider the diagnosis of FS+, patients need to fulfill one or both of the following criteria: firstly, febrile seizures that extend beyond the typical age of 6 and secondly, the occurrence of both febrile and afebrile generalized tonic-clonic seizures, which are either limited to the usual age of FS or occurring beyond that age period [10]. Usually, GTCS continue after 6 years of age and stop by adolescence, but there have been reported rare cases of afebrile GTCS in adult individuals [6,11].

**OTHER GEFS+ PHENOTYPES**

Childhood absence epilepsy (CAE) has been ob-
erved in GEFS+ families, associated with FS or FS+, with different frequencies [2]. All of these cases carried GABRG2 mutations [12,13].

Myoclonic-atonic epilepsy (MAE) belongs to the severe end of the GEFS+ spectrum and is char-
acterized by drop attacks due to myoclonic-atonic seizures. About one third of patients with MAE have febrile seizures at the onset of their seizure dis-
order and they can also have afebrile seizures [14].

Dravet syndrome or severe myoclonic epilepsy of infancy (SMEI) is a rare and malignant epilepsy
syndrome, often considered part of the GEFS+ spectrum. This syndrome develops in the first year of life and has specific seizure types, a distinctive developmental course and characteristic EEG fea-
tures [15]. The majority of the genetic mutations discovered in Dravet syndrome have been found in
the SCN1A gene and most of these mutations were de novo SNC1A gene mutations [16]. Even so,
some authors consider the Dravet syndrome as a separate spectrum, and there have been various new mutations described that have been attributed to the syndrome such as PCDH19, CHD2 and GA-
BRA1 [17].

Focal epilepsies occur in GEFS+ families less frequently than generalized epilepsies. The most common are temporal and frontal lobe epilepsy. In
the last study made by Zhang and Scheffer, it was observed that patients with temporal lobe epilepsy without a personal history of febrile seizure had a normal hippocampal structure, while individuals with temporal lobe epilepsy with a history of fe-
brile seizures had hippocampal sclerosis [2,18-20].

Atonic seizures, which usually have a good out-
come, are hard to distinguish initially from the more severe myoclonic-atonic epilepsy. They can be as-
associated with febrile seizures and the prevalence of atonic seizures is approximately 0.5%, according to the study performed by Zhang and Scheffer [2].

**GENETIC INHERITANCE**

Genetic epilepsy with febrile seizures benefits from a relatively wide and well-marked genetic heter-
ogeneity.
The major affected genes found in GEFS+ families are SCN1A, SCN1B, SCN2A, SCN9A, GABRG2 and STX1B (syntaxin 1B) [21-23].

Nine genes encode voltage-gated sodium channel α-subunits with distinct isoforms called Nav1.1 through Nav1.9. At a central nervous system level four of these isoforms are highly expressed: Nav1.1, Nav1.2, Nav1.3, and Nav1.6. Mutations which can occur in three different central nervous system sodium channel genes split GEFS+ in two subtypes.

GEFS+ type 1 is determined by mutations of SNC1B gene, encoding the β1 subunit and GEFS+ type 2 is caused by mutations of SNC1A (chromosome 2q24-q33) gene encoding the Nav1.1 α-subunit or the SCN2A gene encoding the Nav1.2 α-subunit [24].

Haploinsufficiency of SCN1A determines more severe clinical expression encountered in the most severe forms of GEFS+ and severe myoclonic epilepsy in infancy (SMEI). Missense mutations in the SCN1A sodium channel gene leads to intractable childhood epilepsy with generalized tonic-clonic seizures and are the most common mutations found in GEFS+, as opposed to SMEI where the most common cause is nonsense mutations. Therefore, the severity of epileptic syndrome is suggested to come from the type of SCN1A gene mutation, leading, in the end, to complete loss of sodium channel proteins, as observed in SMEI [25-27].

SCN1A

SCN1A is one of the most causative genes in epilepsy, particularly in GEFS+ and Dravet syndrome, but is also part of genetic causes of hemiplegic migraine and autism spectrum disorder (ASD). It has a high level of expression in the central nervous system and encodes Nav1.1 which is found predominantly in the soma and dendrites of neurons [28]. Functional alterations, which are generally classified in gain of function, loss of function and partial loss of function, further determine the severity of phenotype of GEFS+ spectrum. The prevalence of SCN1A gene mutations in GEFS+ families is approximately 20%, which is the most common mutation encountered in GEFS+ [2,29]. SNC1A has more impact in Dravet syndrome than in GEFS+. The mutation has been identified in more than 80% of Dravet syndrome patients, and a large majority of these patients have de novo mutations that often lead to the syndromic diagnosis. Even so, some authors consider the diagnosis of Dravet syndrome to be based on clinical aspects, rather than the presence of a SCN1A mutation [3].

It is well known that genetic epilepsy with febrile seizures plus is a complex autosomal-dominant disorder, but Brunklaus and Stewart reported rare small families with recessive inheritance, through two novel homozygous missense mutations of the SCN1A gene [30]. De novo mutations or complex inheritance has been found mostly in sporadic cases of exogamic families [31].

A comparison between SCN1A and other frequent genes found in GEFS+, such as SCN1B and GABRG2, revealed that families with SCN1A mutations had the onset of FS and FS+ at an earlier age in the first year of life than families with SCN1B mutation [32].

SCN1B

In a study made by Zhang et al. (2017), SCN1B mutations were identified in 8% of GEFS+ families [2]. The SCN1B (chromosome 19q) gene encodes the voltage-gated sodium channel β-subunit and was the first gene discovered in GEFS+ families with variable expressivity [32]. In another study, it was illustrated that patients with SCN1B gene mutations had later onset of febrile seizures in comparison with individuals with SCN1A gene mutations, 24 months respectively, 12 months [33]. Regarding focal seizures occurring in GEFS+ families and SCN1B gene mutations, the phenotype is suggestive for temporal lobe epilepsy associated or not with febrile seizure [34].

Effects of high temperature on voltage sodium-channels

The actual cause(s) of high temperature sensitivity in sodium channelopathies remain unclear, although it was analyzed from a perspective of the intrinsic nature or kinetics of each channel protein itself [35,36]. In mice studies, it was observed that Nav1.1 haploinsufficiency associated temperature-dependent seizures [37,38], whereas Nav1.2 haploinsufficiency or gain-of-function mutation didn’t associate temperature-dependent phenotypes [39,40].
Therefore, the difference in temperature sensitivity between epilepsies caused by SCN1A and SCN2A mutation consists in their distinct expression sites and functional consequences of mutation [41]. Because Nav1.1 and Nav1.2 are very similar, the electrophysiological properties of sodium channel proteins may not explain the difference in temperature sensitivity [41]. The effect of increased temperature may be decreasing the sodium channel activity [42].

**SCN9A**

SCN9A is a pathogenic gene for epilepsy. This gene encodes the α-subunit of the voltage-gated sodium channel, in particular Nav1.7 and contains 27 exons on chromosome 2q24.3. SCN9A is expressed in the neurons of the dorsal root ganglia [43], but was also described in the brain, particularly in the embryonic hippocampus, suggesting an important role in the central nervous system [44]. Several SCN9A mutations have been identified in febrile seizures-related epilepsies, particularly in GEFS+ and is also considered as a genetic modifier which, in combination with a SCN1A mutation in GEFS+ and Dravet syndrome, when contribute to a more severe phenotype [45,46].

**GABRG2**

GABRG2 is the gene that encodes the GABA-A γ-2 receptor subunit (chromosome 5q34) and mutations have been reported in many GEFS+ families - for the first time in a large French family with GEFS+ phenotypes [47]. The prevalence of GABRG2 is considered to be around 9% in GEFS+ families [2,48]. In individuals within the GEFS+ spectrum, particularly with childhood absence epilepsy and a history of febrile seizures, it is more likely to encounter GABRG2 mutations [12,13,49]. GEFS+ type 3 is determined by mutations of the GABRG2 gene.

**GABRD**

GABRD is one of the genes that encode the δ-subunit of the GABA-A receptor. The mechanism consists in exhibition of preferential sensitivity of δ-containing GABA-A receptors to extracellular GABA concentration, mediating tonic inhibition. Thus, mutations of this gene lead to uncontrolled excitation of neurons, leading to epileptic manifestations. This type of mutations has been described in GEFS+ patients as well as in juvenile myoclonic epilepsy patients [50,51].

**FGF13**

A gene that encodes an auxiliary protein of voltage-gated sodium channels has been described - fibroblast growth factor 13 (FGF13). The discovery was made by Puranam et al. (2015), who has described a maternally transmitted balanced translocation between chromosomes X and 14. The further cellular electrophysiological studies made on mice revealed an imbalance of excitatory and inhibitory synaptic input activity, resulting in decreased inhibitory and increased excitatory synaptic inputs located in hippocampal neurons, through the deletion of one of FGF13 allele by exhibited hyperthermia [52]. FGF13 belongs to a subset of FGFs (fibroblast growth factor homologous factors) and is primarily expressed in the nervous system. The frequency of FGF13 mutations in GEFS+ is yet unknown [53,54].

**STX1B**

The syntaxin 1B protein is encoded by STX1B gene and plays an important role in neuronal excitability and presynaptic function through its complex implication in regulation of synaptic vesicles fusion to the presynaptic membrane. A study made on two large German families has shown that STX1B mutations may lead to a wide phenotypic spectrum, which includes febrile seizures, genetic epilepsies with febrile seizures plus and also epileptic encephalopathies. Therefore, there is a link between STX1B and fever-associated epilepsy syndromes [55,56].

**DIAGNOSIS**

Genetic epilepsy with febrile seizures plus has a wide variety of clinical manifestations. Phenotypes described in GEFS+ have a core represented by febrile seizures or febrile seizures plus. One of the most important characteristics of GEFS+ is the inheritance. Therefore, when we face a child with febrile seizures, generalized or focal, we must carefully examine the family history and look for
this type of seizures in family members. To confirm the diagnosis of GEFS+, it’s necessary to test the patients and family for genetic mutations.

Genotype-phenotype correlation is unclear if a SCN1A missense mutation is identified. As a result, as said above, interpretation depends on the clinical history to determine if the patient has a phenotype that lies at the benign end of the GEFS+ spectrum or a severe phenotype such as Dravet syndrome [15].

**PROGNOSIS AND OUTCOME**

The outcome of children diagnosed with genetic epilepsy with febrile seizures plus varies depending on the severity of their phenotypes found within GEFS+ spectrum. The mild end of the GEFS+ spectrum represented by febrile seizures or febrile seizures plus generally has a good prognosis, a good seizure control with antiepileptic drugs. The seizures may stop in late childhood or early teenage years and no intellectual disability is present. However, detailed information on seizure course, medication use, comorbidities and seizure freedom is lacking for this group of phenotypes [57]. The severe end of GEFS+ spectrum was more thoroughly analyzed. Dravet syndrome is characterized by intractable epileptic seizures and there have been numerous studies on outcome and comorbidities that showed that walking disabilities and severe behavioral problems affect most Dravet syndrome patients. These comorbidities correlate strongly with lower quality of life scores [57-59].

**CONCLUSIONS AND PERSPECTIVES**

Genetic epilepsy with febrile seizures plus is mainly an autosomal dominant group of epilepsy disorders with heterogeneous and complex clinical phenotypes.

The discovery of the disease-associated genes affecting the sodium channel subunits, such as SCN1A, SCN1B, SCN2A, SCN9A and the genes altering GABA receptor subunits as GABRG2, GABRGD suggest that genetic inheritance is pivotal in GEFS+. As a consequence of progress of genetic findings, GEFS+ has been divided in GEFS+ type 1, determined by SCN1B gene mutation, GEFS+ type 2, caused by mutations of SCN2A, and GEFS+ type 3, determined by GABRG2. Ion channels and neurotransmitter receptors are responsible for the seizure-causing alleles. The heterogeneous expression in GEFS+ increases the difficulty of identifying disease genes. SCN1A encodes Nav1.1 and the prevalence of SCN1A gene mutations in GEFS+ families is approximately 20% which determines the severity of phenotype of GEFS+ spectrum. Also, SCN9A is considered as a genetic modifier which causes a more severe phenotype when associated with a SCN1A mutation. SCN1B gene encodes the voltage-gated sodium channel β-subunit and it was illustrated that patients with SCN1B gene mutations had later onset of febrile seizures.

Elevated temperature sensitivity between epilepsies caused by SCN1A and SCN2A mutation may enhance synaptic transmission. The effect of increased temperature may be decreasing the sodium channel activity. GABRG2 and GABRD encode different subunits of the GABA-A receptor, mediating inhibition. Thus, mutations of these genes led to uncontrolled excitation of neurons, which results in epileptic manifestations and presentation of febrile seizures.

Given the fact that cases with de novo and autosomal-recessive inheritance of SCN1A gene mutations were described, genetic epilepsy with febrile seizures plus should not be forgotten when we are facing a child with febrile seizures and no family history of GEFS+, Dravet syndrome or other epilepsies associated with febrile seizures.

The outcome of children diagnosed with genetic epilepsy with febrile seizures plus varies depending on the severity of the phenotypes found within the GEFS+ spectrum. The cause of the high variability of GEFS+ phenotypes among family members is yet to be established. The hypothesis is that other genes and environmental factors help determine the severity of the phenotype, with room to spare for more discoveries in GEFS+ genotype.
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