

# Possible genetic anticipation in families with idiopathic generalised epilepsy

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**ABSTRACT** – Idiopathic generalised epilepsies (IGE) constitute nearly one third of all epilepsies. IGEs manifest with absences, myoclonic jerks and generalised tonic-clonic seizures (GTCS), either alone or in varying combinations, and have a strong genetic background. We present two three-generation families with juvenile myoclonic epilepsy (JME) probands and other affected family members with different forms of IGE in whom genetic anticipation was possible, *i.e.* the progressive decrease in age at onset with each successive generation. In the first family, the proband presented with JME with all three seizure types with an age at onset of eight years. Her cousin presented with both absence seizures and myoclonic jerks simultaneously at age 14 years, and GTCS occurred one year later. The proband's mother had her first seizures at the age of 39 years (brief myoclonic jerks and subtle absences predated GTCS by a few months). In the second family, the proband and his younger brother presented with JME at the age of 13 years, their mother experienced a single GTCS at the age of 38 years, while the grand-mother died during *de novo* generalised status at the age of 62 years. To our knowledge, this is one of the few reports to describe the occurrence of possible genetic anticipation in IGE which should be further investigated in larger cohorts of patients.

**Key words:** idiopathic generalized epilepsy, juvenile myoclonic epilepsy, genetic anticipation

Idiopathic generalised epilepsies (IGEs) constitute nearly one third of all epilepsies. They manifest with absences, myoclonic jerks and generalised tonic-clonic seizures (GTCS), either alone or in varying combinations and severity. There are several IGE syndromes recognized by the International League Against Epilepsy (ILAE), of which the four main syndromes are: child-

hood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and epilepsy with generalized tonic-clonic seizures alone (EGTCSA).

Of all patients with IGE, JME accounts for 20-27% cases (Thomas *et al.*, 2002), *i.e.* 5-10% of all epilepsies (Hauser, 1994). The syndrome is characterized by myoclonic jerks on awakening, GTCS and typical

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absences in more than one third of the patients (Panayiotopoulos, 2002). The essential diagnostic procedure is EEG monitoring. Other examinations are normal, although there is increasing evidence of more prominent focal, predominantly frontal involvement rather than involvement of other cortical structures. Seizures are life-long in most of the cases, but well controlled with adequate antiepileptic drugs in about 90% of patients. A family history of JME or other seizure disorder is common in patients with JME (Panayiotopoulos *et al.*, 1994; Murthy *et al.*, 1998). While it is generally accepted that JME is genetically determined, the observed inheritance pattern differs greatly among the studies, varying from autosomal recessive, autosomal dominant, polygenic to no known mode of transmission (Delgado-Escueta, 2007). Mutations in several genes have been found in JME patients and most of them encode for ion channels. Thus far, the most obvious association (albeit with low penetrance) was described between JME and mutations in the *EFHC1* gene (Suzuki *et al.*, 2004; Annesi *et al.*, 2007). Some clinical and genetic studies also suggest an association with mutations in the *GABRA1*, *CACNB4*, *CLCN2*, *GABRD* genes and other genes have also been described in cases of JME (Haug *et al.*, 2003; Ma *et al.*, 2006; Delgado-Escueta, 2007).

## Materials and methods

The families described in this paper were identified during a genetic study of 60 patients with JME and included molecular screening for *EFHC1* gene mutations. Patients were evaluated at the University Clinic for Neurology in Skopje between 2007 and 2010. The diagnosis of JME was established following the ILAE classification and diagnostic scheme (Commission on Classification and Terminology of the ILAE, 1989). More precisely, the diagnosis was determined by history, clinical features, EEG and MRI data. Detailed family history was obtained and other affected members with seizures were included in the study. Pedigree analyses were undertaken. After approval from the ethics committee with a detailed explanation of the study, written consent was obtained along with venous blood samples for molecular analyses from each patient and family member.

## Results

Sixty patients with JME (42 females and 18 males) and 19 family members with seizures (10 females and 9 males) were analyzed. The onset of seizures in JME patients was between 7 and 19 years, with a mean age of 14.2 years.

Myoclonic jerks were the dominant seizure type in all patients, typically occurring early in the morning during the first half hour after awakening. They appeared in the upper and lower extremities, involving more frequently the arms than the legs. Myoclonic jerks were reported to be bilateral by most of our patients, but 13 patients (22%) described predominantly unilateral myoclonus. Fifty-seven patients (95%) had GTCS and absences were reported in 26 patients (43%). Of the precipitating factors, sleep deprivation was the most common, photic stimulation in daily life induced seizures in six (10%) patients and mental (cognitive) effort in only a few.

EEG abnormalities consisted mainly of bilateral spike-polyspike-wave (SPSW) discharges with a frequency of 3-5 Hz. Asymmetry, regional accentuation and focal abnormalities were recorded in 19 (32%) patients. Photoparoxysmal responses were evoked in 35 (58%) patients. Detailed visual inspection of all magnetic resonance images revealed no abnormalities.

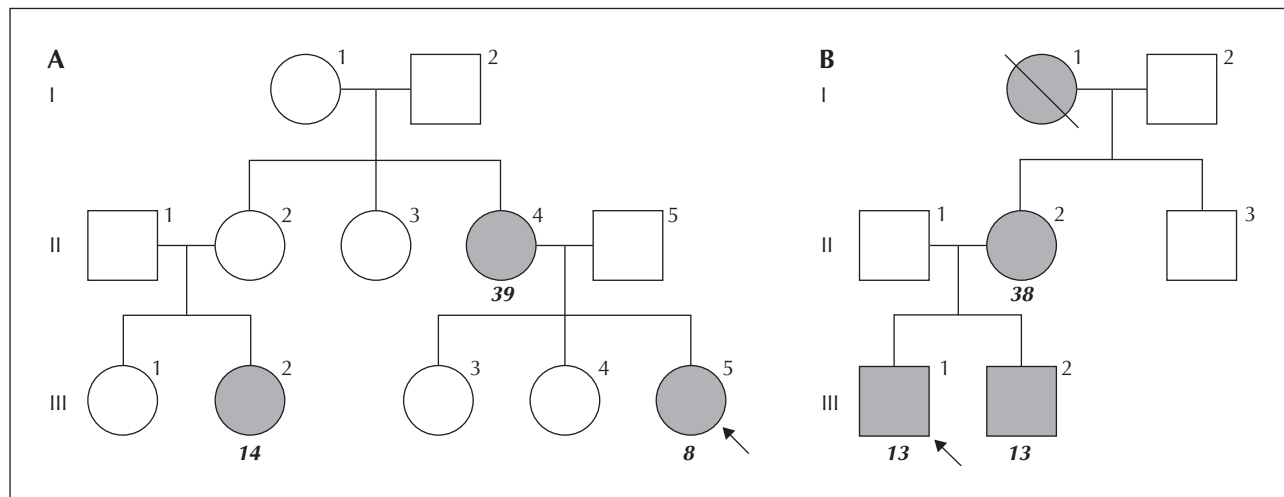
A positive family history of seizures was obtained for 22 (37%) patients. In total, ten families with a JME proband were further analyzed. The mean number of affected individuals per family was three. In half of the families, JME was the only clinical feature, while the others included members with other forms of IGE (five with EGTCSA, three with JAE and one with adult-onset myoclonic epilepsy).

Seizures were well controlled in more than 90% of patients with appropriate antiepileptic drugs (the most commonly used drugs were valproic acid, followed by lamotrigine, topiramate and levetiracetam).

The results of the molecular genetic screening for mutations or polymorphisms in all 11 exons of the *EFHC1* gene will be published elsewhere.

During pedigree analysis, we observed that the onset of disease in the two three-generation families had a tendency to decrease in age with each successive generation.

In the first family, all affected members had myoclonic jerks, absences and GTCS (*figure 1A*). The proband of this family was a 19-year-old girl (pedigree member: III-5), with absences which started at age eight years, followed by myoclonic jerks and GTCS several years later. Interictal EEG showed bilateral SPSW spontaneously and during intermittent photic stimulation. Her cousin (III-2) had simultaneous onset of absence seizures and myoclonic jerks at age 14 years and GTCS which occurred a year later. Her EEG also showed typical 3-5 Hz paroxysms of SPSW complexes and photoparoxysmal responses. The proband's mother (II-4) had her first seizures at age 39 years (brief myoclonic jerks and subtle absences predated GTCS by a few months). The EEG recorded interictal bursts of polyspike waves.



**Figure 1.** Pedigree analysis of two families.

**A)** Family 1 with JME and adult-onset myoclonic epilepsy individuals.

**B)** Family 2 with mixed JME and GTCS members. Numbers in italic below the symbol of each affected member represents the age when first seizures occurred. Circles and squares indicate female and male family members, respectively. Filled symbols refer to affected members, arrows to proband (propositus) and crossed symbol indicates deceased individual.

In the second family (figure 1B), onset of JME in the proband (pedigree member: III-1) occurred with morning myoclonic jerks at the age of 13 years. He was not diagnosed until GTCS occurred a year later. His younger brother (III-2) also experienced first myoclonic seizures at the same age. Valproic acid (VPA) was immediately introduced and he no longer had GTCS. The EEGs of both brothers recorded normal background activity with intermittent PSW. Their mother (II-2) had a single unprovoked GTCS at the age of 38 years. Her EEG also showed bursts of bilateral PSW complexes. With low doses of VPA, she no longer had any seizures. Retrospectively, the medical history revealed that the grandmother (I-1) was referred to the clinic at age 62 years after recurrent GTCS which evolved into generalised status, and she died within 24 hours of admission. There was no evidence of intercurrent neurological or other medical illness, and no evidence of misuse of drugs, or of any precipitants.

## Discussion

Based on a pedigree analysis of ten families with a JME proband, a progressive decrease in age at onset with each successive generation was identified in two families. By definition, genetic anticipation is a phenomenon in which the symptoms of a disease become more severe and/or appear at an earlier age, as the disorder is passed from one generation to the next. To our knowledge, this is one of the few reports to describe the occurrence of possible genetic anticipation in IGE. The possibility that the reported correlation of age at

onset in the families was purely coincidental, however, cannot obviously be excluded.

For the majority of reports, the age at onset was reported to be roughly uniform in families with IGE (Kinirons *et al.*, 2008). Moreover, in cases of late-onset IGE, initial seizures occurred after the age of 30 years in all affected family members (Gilliam *et al.*, 2000). However, genetic anticipation has previously been described in some forms of IGE (Arcos-Burgos *et al.*, 1999; Ikeda *et al.*, 2005). A comparison of age at seizure onset among 84 pairs of relatives with IGE (parents/children, grandfathers/grandsons and nephews/uncles) from 72 multi-generational pedigrees showed significant inter-generational differences in the age at onset which decreased with each successive generation (Arcos-Burgos *et al.*, 1999). By analyzing the neurological and clinical findings in a three-generation family with BAFME (benign adult familiar myoclonic epilepsy), Ikeda *et al.* (2005) suggested that this entity has autosomal dominant inheritance and identified a genetic anticipation in this pedigree. In addition, in the study by Marini *et al.* (2003) on adult-onset epilepsies, the proband was a 45-year-old woman with adult-onset absence epilepsy who had a daughter with childhood-onset absence epilepsy, however, the authors did not recognize the possibility of genetic anticipation in their study.

As well as the JME probands, there were also family members with typical JME and adult-onset IGE in both families. This phenotypic heterogeneity is well known since numerous studies have revealed that for about 60% of the families with JME probands, the other affected family members have different forms

of IGE (Martínez-Juárez *et al.*, 2006; Kinirons *et al.*, 2008; Jayalakshmi *et al.*, 2006). In fact, different epileptic syndromes such as CAE, JAE, or EGTCSA may be observed in members of the same family, thus suggesting that they are genetically related to JME and that the genetic mutation responsible for JME may also underlie these non-JME forms of IGEs (Jayalakshmi *et al.*, 2006; Kinirons *et al.*, 2008).

In our second family, the proband's mother presented with clinical and EEG features typical of JME, although the age at onset was beyond the upper range usually reported in prior descriptions of the syndrome. It is unclear whether this may represent a late-onset variation of JME or a distinct syndrome of adult myoclonic epilepsy (AME), as previously described (Gilliam *et al.*, 2000). IGE syndromes usually start in childhood and adolescence, although a number of studies suggest that adult onset is more common than generally realized (Marini *et al.*, 2003; Cutting *et al.*, 2001; Gilliam *et al.*, 2000; Reichsoellner *et al.*, 2010). In the report of Marini *et al.* (2003) on late-onset IGE, onset occurred at 20 years or later for 28% of IGE cases (Marini *et al.*, 2003). Although childhood or juvenile onset is commonly documented, the international classification does not define the age at onset as a limit for IGE subsyndromes. Some studies suggested that related genetic abnormalities are associated with classic, late-onset IGE and different IGE subsyndromes (Berkovic, 1997; Marini *et al.*, 2003).

Other than epilepsies, genetic anticipation is a characteristic of some neurological and neurodegenerative disorders, including spinocerebellar ataxias, Huntington's disease, myotonic dystrophy, fragile X syndrome and dentatorubral-pallidoluysian atrophy (DRPLA). In most of these entities, dynamic mutation leads to expansion of the trinucleotide repeats. For example, in DRPLA an inversely proportional correlation between the number of CAG repeats and the age at onset has been reported (Ikeda *et al.*, 2005). Generally, in the normal population, the number of repeats within the implicated genes is polymorphic, and the disease phenotype is not expressed until a threshold length of repeats is reached making the mutations pathogenic, according to the characteristics of each gene.

Since nucleotide expansion mutations are implicated in all disorders in which genetic anticipation has been observed, single nucleotide (point) mutations in the JME candidate genes do not provide a rational molecular mechanism for this phenomenon. This raises the necessity for further research in an attempt to describe the precise mutations in JME families with genetic anticipation. One could hypothesize that the affected members in those families presenting genetic anticipation have a molecular subtype of JME which is different from family members with no apparent genetic anticipation. □

## Disclosure.

None of the authors has any conflict of interest or financial support to disclose.

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