

Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up

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The 2001 classification subcommittee of the International League Against Epilepsy (ILAE) proposed to ‘group JME, juvenile absence epilepsy, and epilepsy with tonic clonic seizures only under the sole heading of idiopathic generalized epilepsies (IGE) with variable phenotype’. The implication is that juvenile myoclonic epilepsy (JME) does not exist as the sole phenotype of family members and that it should no longer be classified by itself or considered a distinct disease entity. Although recognized as a common form of epilepsy and presumed to be a lifelong trait, a long-term follow-up of JME has not been performed. To address these two issues, we studied 257 prospectively ascertained JME patients and encountered four groups: (i) classic JME (72%), (ii) CAE (childhood absence epilepsy) evolving to JME (18%), (iii) JME with adolescent absence (7%), and (iv) JME with astatic seizures (3%). We examined clinical and EEG phenotypes of family members and assessed clinical course over a mean of 11 ± 6 years and as long as 52 years. Forty per cent of JME families had JME as their sole clinical phenotype. Amongst relatives of classic JME families, JME was most common (40%) followed by grand mal (GM) only (35%). In contrast, 66% of families with CAE evolving to JME expressed the various phenotypes of IGE in family members. Absence seizures were more common in family members of CAE evolving to JME than in those of classic JME families ($P < 0.001$). Female preponderance, maternal transmission and poor response to treatment further characterized CAE evolving to JME. Only 7% of those with CAE evolving to JME were seizure-free compared with 58% of those with classic JME ($P < 0.001$), 56% with JME plus adolescent pyknoleptic absence and 62% with JME plus astatic seizures. Long-term follow-up (1–40 years for classic JME; 5–52 years for CAE evolving to JME, 5–26 years for JME with adolescent absence and 3–18 years for JME with astatic seizures) indicates that all subsyndromes are chronic and perhaps lifelong. Seven chromosome loci, three epilepsy-causing mutations and two genes with single nucleotide polymorphisms (SNPs) associating with JME reported in literature provide further evidence for JME as a distinct group of diseases.

Keywords: juvenile myoclonic epilepsy; subtypes; follow-up; classification

Abbreviations: CAE = childhood absence epilepsy; GM = grand mal; IGE = idiopathic generalized epilepsies; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy; SNP = single nucleotide polymorphism

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Introduction

Juvenile myoclonic epilepsy (JME) is a common epilepsy syndrome responsible for 6 to 12% of all epilepsies based on hospital and clinical records (Janz, 1957, 1969, 1985; Tsuboi, 1977; Gooses, 1984; Murthy *et al.*, 1998; Jha *et al.*, 2002; Jain *et al.*, 2003) and 3% based on a door-to-door population study (Nicoletti *et al.*, 1999). Although first described by Herpin (1867) and Rabot (1899), Janz (1957), Delgado-Escueta and Bacsal (1984) and Asconape and Penry (1984) considered myoclonic, generalized clonic-tonic-clonic (grand mal) and absence seizures in JME to be lifelong in duration. However, no prospective long-range studies have documented this concept. Recently, the task force on classification and terminology of the International League Against Epilepsy (ILAE) proposed to 'group JME, juvenile absence epilepsy (JAE), and epilepsy with tonic clonic seizures only under the sole heading of idiopathic generalized epilepsies (IGE) with variable phenotype,' implying that JME does not exist as the sole phenotype of family members and that JME should no longer be classified by itself or considered a distinct disease entity (Engel, 2001).

For these two reasons we re-evaluated the phenotypes of a population of JME prospectively enrolled for genetic studies. We provide data on 257 patients and family members prospectively ascertained through a patient fitting the 1989 ILAE description of JME (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). We divided them into four groups on the basis of their seizure phenotypes and studied their clinical course that ranged from 1 to 52 years (mean 11 ± 6 years). We assessed affectedness of families with two questions. First, can JME families, taken as a whole, be affected with the JME phenotype only or always with the various phenotypes of IGE? Second, looking at individual affected relatives, what are the most common seizure phenotypes?

During this assessment, we also calculated the frequency of JME and the varying IGE phenotypes in relatives from families of the two most common groups, namely, classic JME and childhood absence epilepsy (CAE) persisting and evolving to JME.

Patients and methods

Patients and family ascertainment

Two hundred and fifty-seven families were initially ascertained through a proband with adolescent onset myoclonias and GM seizures by neurologists at the study sites of the international consortium of GENESS (Genetic Epilepsy Studies). A presumed diagnosis of JME was made on the basis of the 1985 and 1989 classification of the ILAE (Commission on Classification and Terminology of the International League Against Epilepsy, 1985, 1989), which defines JME as follows:

'Juvenile myoclonic epilepsy appears around puberty and is characterized by seizures with bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in the arms. Jerks may cause some patients to fall suddenly. No disturbance of

consciousness is noticeable. The disorder may be inherited, and sex distribution is equal. Often, there are generalized tonic-clonic seizures and, less often, infrequent absences. The seizures usually occur shortly after awakening and are often precipitated by sleep deprivation. Interictal and ictal EEGs have rapid, generalized, often irregular spike waves and polyspike waves; there is not close phase correlation between EEG spikes and jerks. Frequently, the patients are photosensitive. Response to appropriate drugs is good.'

Patients with symptoms and signs of progressive myoclonus epilepsies were excluded. An extended pedigree was constructed for each patient's family. Families were classified as simplex (only one member—the proband—affected with epilepsy), multiplex (usually the proband plus one or more siblings) or multigenerational (the proband plus one or more members of separate generations affected). All living affected relatives were interviewed and examined to determine their state of affectedness, clinical and EEG diagnosis. EEGs were also performed on asymptomatic relatives. Asymptomatic relatives with abnormal EEGs were then examined clinically and their histories probed for seizures. We further assessed the seizure types afflicting the proband and clinically affected members, age at onset of seizures, evolution of seizures from infancy through adolescence and adulthood, results of physical and brain imaging examinations and long-term follow-up.

Two hundred and twenty-two out of 257 patients (86%) were available for follow-up from 1978 to 2003 in epilepsy clinics from Los Angeles (California), Mexico City (Mexico), Tegucigalpa (Honduras), Riyadh (Saudi Arabia), San Miguel (El Salvador), Corozal and Belize (Belize), Lima (Peru) and Madrid (Spain). Eleven families are presently residing in the United States and were evaluated in Los Angeles, but were originally from Australia, Iran, and China. Each participating subject or, in the case of minors, the responsible adult signed an informed consent form, as approved by the Human Subjects Protection Committee at the David Geffen School of Medicine at UCLA or at the participating institution of the international consortium, GENESS.

Seizure phenotypes

Final seizure phenotype (Commission on Classification and Terminology of the International League Against Epilepsy, 1981) and EEG diagnoses were made in all probands and affected family members by M.T.M. and A.V.D.E., who examined all patients. During field trips, tonic-clonic convulsions, astatic, myoclonic and absence seizures were identified amongst probands and affected family members. In addition, we observed clonic-tonic-clonic convulsions, a category not listed in the 1981 seizure classification. We differentiated absences into pyknoleptic (at least once a day and up to hundreds per day) and spanioleptic or non-pyknoleptic (infrequent, 1–2 per week to 1–2 per month and not daily). When marked and very rapid eyelid jerking occurred during eye closure together with upward deviation of the eyeballs during generalized spike waves, the patient was considered to have eyelid myoclonia with absences (Jeavons, 1996). We identified astatic seizures when patients fell limp to the ground 'like a rag doll' or slumped forwards or backwards while sitting and continued to slide in their chair owing to diminished body tone. Falls as a consequence of a myoclonic jerk propelling patients forward or backwards were distinguished from astatic seizures that caused patients to slump and slide in their chair.

JME subsyndromes

We then determined if subsyndromes were present within the probands and members of the 257 families. First, pyknoleptic absences that started between 3 and 11 years of age were classified as childhood absences. Pyknoleptic absences that started after 11 years of age were grouped as adolescent onset pyknoleptic absences. Then, we identified the subsyndrome of childhood pyknoleptic absence epilepsy evolving to JME. Such patients started pyknoleptic absences with 3–4 Hz spike and wave complexes before 12 years of age (11 years or younger) and then developed myoclonic seizures, clonic-tonic-clonic and tonic-clonic seizures in adolescence together with EEG 4–6 Hz polyspike-wave complexes. Patients with CAE evolving to JME were separated from classic JME; classic JME with or without spanioleptic absences consisted of patients with adolescent onset of myoclonic, tonic-clonic and clonic-tonic-clonic seizures with or without rare-to-infrequent absences (spanioleptic). In contrast to the classic JME with spanioleptic absences, we identified adolescent onset pyknoleptic absences with 3–5 Hz spike and polyspike and wave complexes to be mixed with JME when pyknoleptic absences started at 12 years of age or older. From these three groups, we separated astatic seizures mixed with JME.

Statistical analysis

Phenotype data were stored and analysed in SPSS (version 14.0.0). For calculation of frequency for epileptic seizures, each class of degree relative was examined separately for history of epilepsy. First-degree relatives were parents, siblings (brothers and sisters) and offsprings; second-degree relatives were uncles, aunts, nieces and nephews; and third-degree relatives included cousins. For analysis purposes, offsprings were analysed separately from the other first-degree relatives. χ^2 and Fisher's exact tests were used for group comparisons, for example, all relatives affected with a specific seizure type were compared with all relatives without that specific seizure type in the groups of CAE evolving to JME versus classic JME.

Results

We subdivided 257 patients into four groups (Table 1): (i) 186 patients with classic JME (cJME), (ii) 45 patients with CAE persisting and evolving as JME with GM, myoclonic and absence seizures (CAE/JME), (iii) 18 patients with JME mixed with adolescent onset pyknoleptic absence (JME/aA) and (iv) 8 patients with JME plus astatic seizures (JME/astatic).

Classic JME

Probands

We called the first group 'classic JME' because it corresponds more to the original description of Herpin (1867), Rabot (1899) and Janz (1957, 1969, 1985). Starting in adolescence as isolated awakening myoclonic seizures or generalized clonic-tonic-clonic seizures, spanioleptic absences were rarely present in this group. Myoclonic seizures appeared as the first seizure type in 68%. Grand mal seizures preceded myoclonic seizures in 30% of probands. Although

females were numerically more common than males among probands (103 females and 83 males or 1.25 F : 1 M ratio), the difference was not statistically significant ($\chi^2 = 1.078$; $P = 0.29$). Classic JME accounted for 72% ($n = 186$) of all our cases.

Figure 1 shows that myoclonic (15.1 years 95% CI ± 0.04 ; range 7–28 years) and GM seizures (15.9 years 95% CI ± 0.60 ; range 8–33 years) both appeared for the first time at 15 years of age. Absences, interestingly, appeared a year later at the average age of 16.8 years 95% CI ± 1.19 ; range 11–30 years. Absence seizures, when present, rarely occurred in 33% of the patients. Absences were the first seizure type reported in only one case (onset at 16 years). The most common reasons blamed by patients for breakthrough seizures were sleep deprivation, stress, alcohol, non-compliance and menses. Other reported triggers for seizures were fatigue, hyperventilation, photosensitivity and physical exertion.

Family members (Table 3)

Ninety-two families (49%) of 186 classic JME families reported seizures in family members. Twenty-four families were multiplex, 30 were multigenerational and 38 were both multiplex/multigenerational. Maternal inheritance was slightly more common (46% or 42 out of 92) than paternal inheritance (31% or 29 out of 92), but was not statistically significant ($\chi^2 = 1.2$; $P = 0.3$). Bilineality or epilepsy on both paternal and maternal sides was present in 9% or 8 out of 92. In 13 multiplex families (14%) neither parent had epilepsy and no other relative on either side of the families had seizures or EEG abnormalities.

We first determined if JME families could have JME as the sole phenotype and whether JME families invariably manifested various IGE phenotypes. We were able to validate the affected states of 74 families. We were not able to document if GM only or GM with myoclonias (JME) were present in a few family members of 16 other families. Of these families, 40% (30 out of 74) had members affected with JME only or were asymptomatic but had the EEG polyspike waves, indicating that families can have JME as the sole clinical phenotype. In the other 44 families, genetic pleomorphisms were present with JME and 'grand mal only' as the most common phenotypes and absences rarely. Thirty-five per cent of families (26 out of 74) were affected with either JME or GM only or were clinically asymptomatic but had the EEG polyspike-wave trait only. Febrile seizures were present with JME, GM and the EEG polyspike-wave trait only in another 9 families (12%). Twelve per cent (9 out of 74) of family members combined absence with the phenotypes of JME and GM.

Next, we determined which specific seizure phenotypes were most common in 128 first-, second- and third-degree relatives of probands. Of the affected relatives, 40% had JME only, while 29% had GM tonic-clonic seizures only. Absences

Table 1 Phenotypes of JME groups

| | Classic JME (<i>n</i> = 186) | CAE persisting as JME with grand mal, myoclonic and absence seizures (<i>n</i> = 5) | JME with adolescent onset pyknoleptic absences (<i>n</i> = 18) | JME with atstatic seizures (<i>n</i> = 8) |
|-------------------------------|--|--|--|--|
| Probands | | | | |
| Age at onset of first seizure | 15.1 years (7–28 years) | 5 years (1–10 years) | 16 years (11–32 years) | 14.2 years (8–19 years) |
| Gender | 1.25 F : 1 M | 1.8 F : 1 M | 2.6 F : 1 M | 1.2 F : 1 M |
| Seizure type | Adolescent myoclonias, grand mal and rare absences | Childhood pyknoleptic absences, followed by myoclonic and grand mal seizures 30% eyelid myoclonias + absences | Adolescent pyknoleptic absences, myoclonias and grand mal | Myoclonias, grand mal, rare absences and infrequent atstatic seizures |
| EEG | 4–6 Hz polyspike and slow wave complexes in 61% 3 Hz spike and slow waves complexes in 14% Photoparoxysmal response in 13% | 3 Hz spike and slow wave complexes in 100%; 54% also had 4–6 Hz polyspike and slow wave complexes Low amplitude 15–25 Hz fast rhythms in 22% Photoparoxysmal response in 22% | 4–6 Hz polyspike and slow wave complexes in 50%; 11% had 4–6 Hz polyspike and slow waves mixed with 3 Hz spike and slow wave complexes; 5% had 3 Hz spike and slow waves complexes. Photoparoxysmal response in 15% | 4–6 Hz polyspike and slow wave complexes in 60%; 12% had combined 4–6 Hz polyspike and slow waves mixed with 3 Hz spike and slow wave complexes. Photoparoxysmal response in 1/4. |
| Family members | | | | |
| Epilepsy in families | 49% (92/186) | 71% (32/45) | 61% (11/18) | 3/8 probands |
| Main seizure | JME in 40% and tonic-clonic only in 29% | Absence alone or with tonic-clonic and/or myoclonic seizures in 42%. Tonic-clonic only in 32% | JME and tonic-clonic | JME and tonic-clonic |
| EEG | —297 had normal EEGs —33 had abnormal EEGs: 9 symptomatic members had 4–6 Hz polyspike, 15 asymptomatic had 4–6 Hz polyspike wave complexes, 4 asymptomatic had bursts of focal or diffuse slowing, 3 asymptomatic had 3 Hz spike and wave complexes and 2 asymptomatic had bursts of focal or diffuse sharp waves | —276 normal EEGs —30 had abnormal EEGs: 8 symptomatic had: —22 asymptomatic and 8 symptomatic had abnormal EEGs: 16 had 3 Hz spike and wave complexes, 6 had 4–6 Hz polyspike wave complexes, 6 had focal spikes or sharps and 6 had focal or diffuse slowing | —49 had normal EEGs —7 had abnormal EEGs: 3 symptomatic had 4–6 Hz polyspike and wave complexes, 1 symptomatic had 3 Hz spike and wave complexes and 3 asymptomatic had 4–6 Hz polyspike and wave complexes | —17 had normal EEGs —1 asymptomatic member had an abnormal EEG with 4–6 Hz polyspike and slow wave complexes |
| Transmission | Maternal > Paternal | Maternal > Paternal | Maternal = Paternal | Maternal = Paternal |

as the sole phenotypes were present rarely (4%). Abnormal EEGs with 3.5–6 Hz polyspike waves were found in 24 clinically asymptomatic relatives (see Table 1). Most asymptomatic family members with EEG spike and slow wave and polyspike waves were females (16 F : 8 M).

Long-term follow-up

We followed 161 of these 186 classic JME patients for a mean period of 12.4 years (range 1–41 years) (Table 2). During follow-up, 58% (93/161) were free from all seizure types

(tonic-clonic, myoclonic and absence seizures) during anti-epileptic drug treatment. Of these patients without seizures, 65% were on valproate monotherapy, 11% on valproate plus one or more other antiepileptic drugs and 15% on anti-epileptic drugs other than valproate either in monotherapy or polytherapy.

Seizures continued in 68 of 161 (42%) patients despite antiepileptic drug treatment. Seizures in these 68 patients provide evidence of a chronic epilepsy syndrome that lasted up to at least 41 years of age. Figures 2 and 3 show 53 patients amongst 68 classic JME patients who continued to have

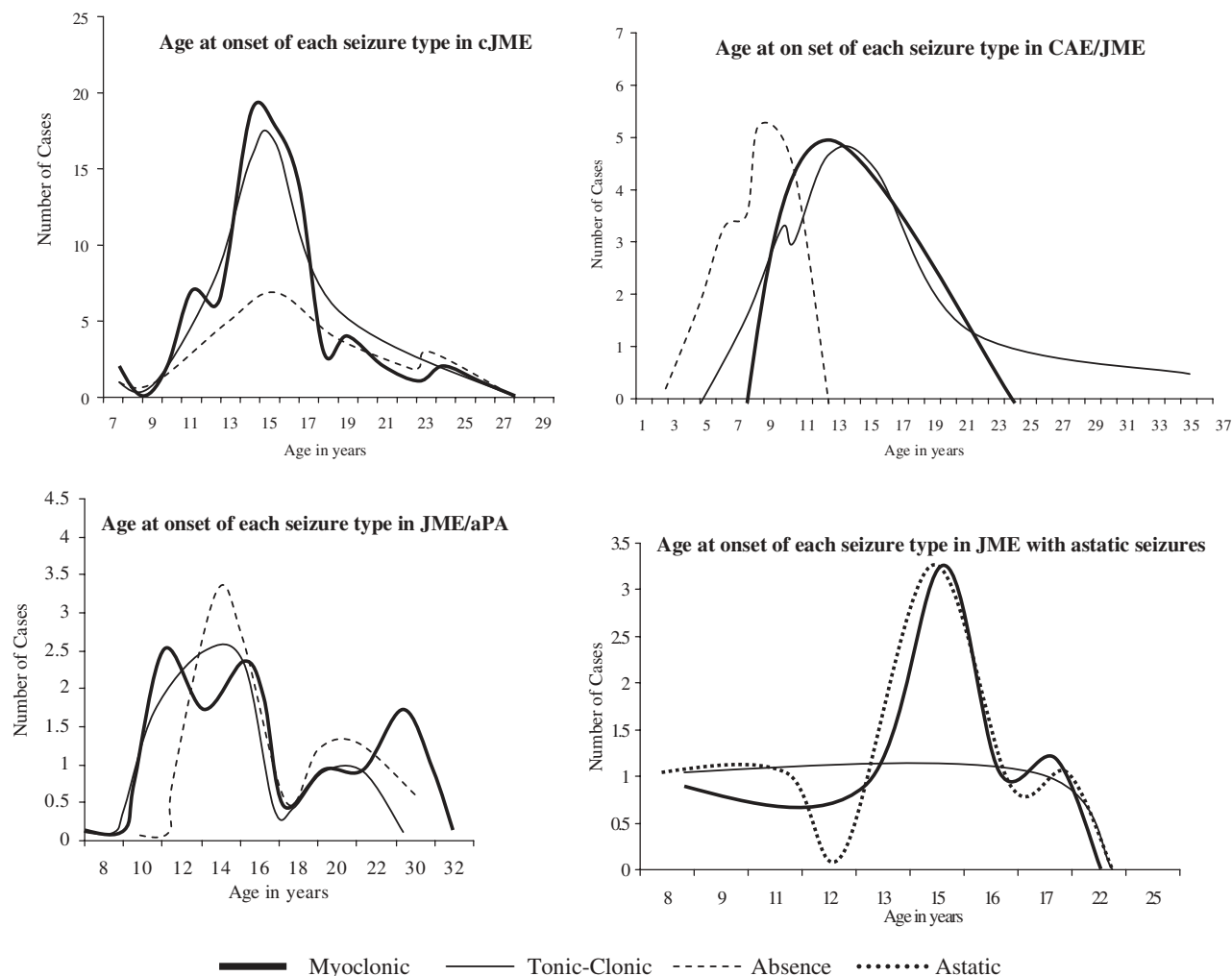


Fig. 1 Age at onset of each seizure type in the four subtypes of JME. cJME, classic JME; CAE/JME, childhood absence epilepsy evolving to JME; JME/aPA, JME with adolescent onset pyknoleptic absence.

seizures between 21 and 41 years of age. In 40 out of these 68 patients, seizures continued from 11 to 40 years of follow-up. Myoclonic seizures with or without GM and absence seizures persisted in 59 out of 68, GM only in 8 out of 68 and absence only in 1 out of 68 patients. In 8 patients (9%) JME may not be lifelong. These 8 patients have been free from seizures without medication for 1–11 years, 4 of them from 5 to 11 years.

CAE persisting and evolving into JME

Probands

We called the second group of 45 patients 'CAE/JME' because absence epilepsy started in childhood and persisted as JME with myoclonic, tonic-clonic GM and absence seizures into adulthood. Females were also numerically preponderant among probands (29 females and 16 males or 1.8 F : 1 M ratio), but again this was not statistically significant ($\chi^2 = 1.91$; $P = 0.166$) because of the small number of cases. Moore *et al.* (2001) and Wirrell *et al.* (1996) called

this group CAE evolving to JME. This group accounted for 18% of our idiopathic adolescent myoclonic epilepsies (Table 1).

This group is easily separated from classic JME because pyknoleptic absence seizures are the first seizures that appear in 41 probands, starting at the average age of 6.9 years 95% CI ± 0.08 ; range 1–11 years (Fig. 1). Absence seizures occurred at least once a day (range 1–200 per day) In four probands, parents could only describe absences as starting during or before elementary school.

Adolescent onset myoclonias (average age 14.2 years 95% CI ± 2.14 ; range 8–47 years) and tonic-clonic GM seizures start earlier (average age 13.4 years 95% CI ± 1.22 ; range 2–37 years) than myoclonic seizures and GM of classic JME (Fig. 1). Myoclonic seizures preceded GM seizures in 18%, but more often they started in adolescence simultaneously with tonic-clonic seizures (40% of patients).

All probands had the classic 3 Hz single spike- and slow-wave complexes (see Table 1). Seventy-eight per cent (29 probands) also had 2–5 Hz single spike- and

Table 2 Long-term follow-up and outcome of JME subsyndromes in 222 patients

| Response to treatment | Classic JME (<i>n</i> = 161) | CAE/ JME (<i>n</i> = 35) | JME with adolescent onset pyknoleptic absence (JME/aPA) (<i>n</i> = 18) | JME with astatic seizures (<i>n</i> = 8) |
|--|----------------------------------|------------------------------|--|--|
| Free of seizures | | | | |
| All seizure types controlled ^a | 93 (58%) | 3 (7%) | 10 (56%) | 5 (63%) |
| In remission from all seizure types (>5 years without medication) | 4 (2.5%) | – | – | – |
| Persisting seizures | 64 (39.8%) | 32 (93%) | 8 (46%) | 3 (37%) |
| Types of persisting seizures | | | | |
| GM controlled but myoclonias or absences persist | 39 (24%) | 23 (66%) | 7 (38%) | 1 (12.5%) |
| Myoclonic seizures only | 33 (20%) | 5 (15%) | 2 (11%) | – |
| GM only | 8 (5%) | 5 (15%) | 1 (5%) | 1 (12.5%) |
| Absences only | 1 (1%) | 16 (46%) | – | – |
| Myoclonic astatic only | – | – | – | 1 (12.5%) |
| Myoclonic and GM seizures | 18 (11%) | – | – | – |
| Myoclonic and absence seizures | 5 (3%) | 2 (6%) | 5 (28%) | – |
| Absences and GM seizures | – | 4 (11%) | – | – |
| Myoclonic, absences and GM seizures | 3 (2%) | – | – | – |

^aAntiepileptic drugs taken by seizure-free patients.

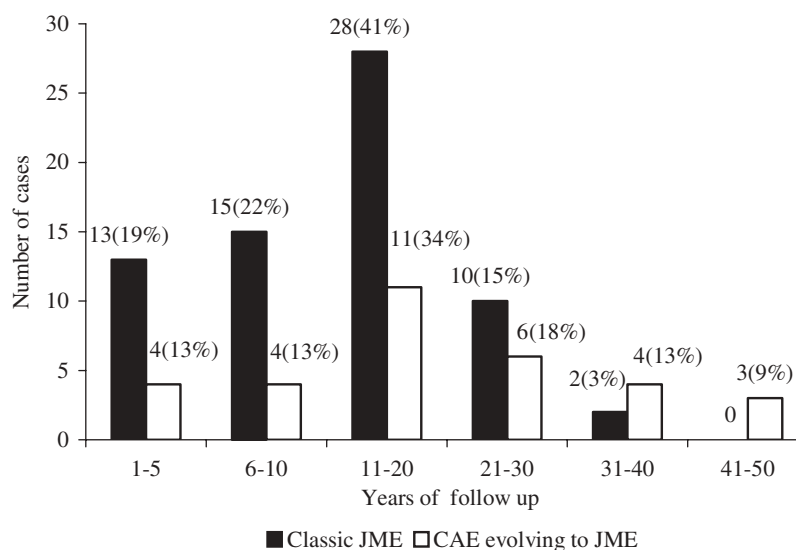
Long-term follow-up and outcome of JME subsyndromes in 222 patients

Classic JME: Sixty-one patients were seizure-free on valproate (VPA) alone. Eleven patients were seizure-free in monotherapy with the following antiepileptic drugs: three patients were seizure-free on carbamazepine (CBZ), two patients on lamotrigine (LTG), two patients on phenobarbital (PB), two patients on levetiracetam (LEV), one patient on topiramate (TP) and one patient on primidone. Ten patients were seizure-free on VPA plus another antiepileptic drug: five patients were seizure-free on VPA + LTG, one patient on VPA + CBZ, one patient on VPA + phenytoin (PHT), one patient on VPA + CLZ, one patient on VPA + TP and one patient on VPA + lorazepam. One patient was seizure-free on TP + LTG and one patient on PG + clonazepam. Eight patients were seizure-free without medication.

CAE/JME: Of three patients who were completely free of seizures, one was taking PB and mephentyoin, one was on LEV + TP and one was on VPA monotherapy.

JME/aPA: Seven patients were seizure-free on VPA monotherapy. One was seizure-free on VPA + LTG, one on VPA + TP and one on VPA + LEV.

JME with astatic seizures: Three patients were seizure-free on VPA monotherapy. One patient was on VPA + LTG and one patient on VPA + CBZ.

**Fig. 2** Years of follow-up in 68 classic JME patients and 35 patients with CAE evolving to JME who had persisting seizures.

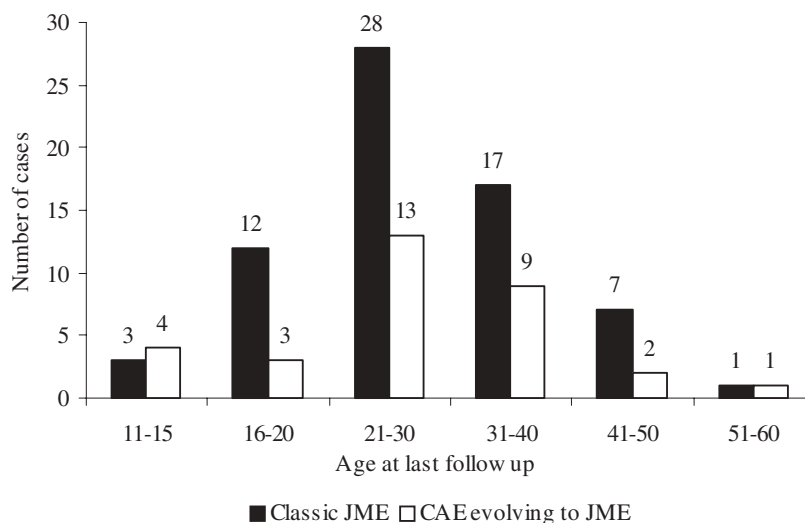


Fig. 3 Evidence of a lifelong trait: persisting seizures and age at last follow-up in 68 patients with classic JME and 35 patients with CAE evolving to JME.

slow-wave complexes. Bursts of 3–5 Hz single spike wave and/or 4–6 Hz polyspike wave were induced during hyperventilation in 29% of probands and during photic stimulation in 22%. Background activity was normal in all cases.

Family members

Epileptic seizures were present in 32 (71%) families. Thirteen families (29%) were simplex, seven families (16%) were multiplex, 12 (27%) were multigenerational and 13 (29%) were both multiplex/multigenerational. In contrast to classic JME, two-thirds of the families (21 out of 32) expressed combinations of various phenotypes in the same family, namely, CAE/JME, CAE only, GM only, JME only, CAE with GM, CAE with GM and febrile seizures. Rarely CAE/JME was the sole phenotype in the same family (2 out of 32). Also rare were CAE/JME, CAE only and CAE plus GM in the same family (6 of 32). In two families, CAE/JME and JME only were the two phenotypes. In one family, CAE/JME and the EEG polyspike-wave trait were the two phenotypes.

Looking at seizure phenotypes in individual family members, absence seizures alone or in combination with other seizure types were most common, affecting 32 non-proband family members. In contrast, myoclonias only or myoclonias plus GM were rare and affected only three persons (3.9%). Sixteen families (306 non-proband members) had EEGs. Ten per cent (30 members) had single spike-wave or polyspike-wave complexes; 11 of these persons were asymptomatic. Again, more asymptomatic members with the polyspike-wave trait were females (8 F : 3 M). Maternal transmission occurred in 57% while epilepsy appeared to pass through the father in 31%. The small number of cases prevented statistical significance ($\chi^2 = 1.17$; $P = 0.3$). There was no sex preponderance among non-proband

clinically affected members (10.6% of females versus 9.8% males).

Long-term follow-up

Thirty-five of 45 patients were followed from 5 to 52 years (Fig. 2). In contrast to classic JME, only 3 of 35 patients achieved complete freedom from seizures. Although tonic-clonic seizures were suppressed by antiepileptic drugs in 66% (23 out of 35), absence seizures alone or in combination persisted in 22 of these 35 patients. Rarely did tonic-clonic only (5 out of 35) or myoclonic seizures only (5 out of 35) break through. Seizures persisted for as long as 11–50 years in 25 patients who were 21–52 years of age (Fig. 3).

JME with adolescent onset pyknoleptic absence or JME/apA

Probands

This group accounted for 7% of all JME cases (18 families). Myoclonic (mean 14 years, range 8–30 years) and clonic-tonic-clonic GM seizures (mean 14 years, range 11–20 years) started earlier than pyknoleptic absences. Myoclonic seizures were the first seizure type in 61%. There was a female preponderance in probands (2.6 F : 1 M ratio, $\chi^2 = 1.87$ $P = 0.171$). Myoclonic seizures were the main seizure type in 72% of the probands who had persisting seizures, but in eight cases with persistent seizures, absences with or without myoclonic seizures were predominant (5 out of 8). Interictal EEG of 14 probands was available for analysis. Seven of 14 (50%) had normal 4–5 Hz spike wave or polyspike waves. Two showed 4–6 Hz polyspike-wave complexes mixed with 3 Hz spike-wave complexes. One had generalized bursts of slow waves and one had 3 Hz spike-wave complexes. Photoparoxysmal response was found in 2 of 14. Three probands had normal EEGs. Neurological exam was normal

Table 3 Epileptic seizures among first-, second- and third-degree relatives of probands with classic JME and CAE/JME

| Epilepsy syndrome and seizure types in relatives | First-degree affected | | Second-degree affected ^a | Third-degree affected ^b | Total |
|---|-----------------------|-------------|-------------------------------------|------------------------------------|-----------------|
| | Parents and sibs | Offspring | | | |
| Classic JME (92 families) | | | | | |
| Myoclonic with/without tonic-clonic seizures | 26 | 2 | 11 | 11 | 50 |
| Tonic-clonic only | 11 | — | 13 | 12 | 36 |
| Absence seizures alone | 3 | 2 | 2 | — | 7 |
| Absence with tonic-clonic seizures | 1 | — | — | 2 | 3 |
| Febrile | 7 | 3 | 3 | 4 | 17 |
| Symptomatic localization related | 2 | 1 | 2 | 3 | 8 |
| Not validated seizure/epilepsy type | — | — | 4 | 3 | 7 |
| Total number of affected relatives by degree | 50 | 8 | 35 | 35 | 128 |
| Number of affected relatives over total number of relatives by degree | 50 out of 480 | 8 out of 58 | 35 out of 705 | 35 out of 171 | 128 out of 1414 |
| CAE evolving to JME (32 families) | | | | | |
| Myoclonias with/without tonic-clonic | 1 | — | 1 | 1 | 3 |
| Tonic-clonic only | 8 | 1 | 8 | 8 | 25 |
| Absence seizures alone | 7 | — | 2 | 3 | 12 |
| Absence with tonic-clonic seizures | 3 | — | 5 | 1 | 9 |
| Absence with tonic-clonic and myoclonic seizures | 7 | 1 | 2 | 1 | 11 |
| Febrile | 5 | — | 4 | 4 | 13 |
| Symptomatic localization related | — | — | — | — | — |
| Not validated seizure/epilepsy type | 1 | — | — | 3 | 4 |
| Total number of affected relatives by degree | 32 | 2 | 22 | 21 | 77 |
| Number of affected relatives over total number of relatives by degree | 32 out of 161 | 2 out of 12 | 22 out of 101 | 21 out of 141 | 77 out of 415 |

Pyknoleptic absences are more common in relatives of CAE/JME than in relatives of classic JME ($P < 0.001$); in contrast, myoclonias are less frequent in relatives of CAE/JME versus classic JME ($P < 0.01$). There was a higher frequency of any seizure types ($P < 0.001$) including febrile convulsions ($P < 0.01$) in CAE/JME compared with classic JME. ^aAunts, uncles, nieces, nephews; ^bcousins.

in all patients. Neuroimaging studies were normal in the 16 who had one or more of the following tests performed: CT scan (8), MRI (6) and 2FDG-PET scan (2).

Family members

Of 18 probands, 61% (10 out of 18) had a family history of epilepsy. One family was multiplex, five were multigenerational and five were both multiplex/multigenerational. Maternal transmission was as common (4 out of 11) as paternal transmission (5 out of 11) and two families were bilineal. Source of transmission could not be determined in one family with affected monozygotic twins. Like families with classic JME, JME (30%) and GM (30%) most commonly affected the individual members. Individuals rarely had absences as the sole phenotype (two persons). Four non-probands were asymptomatic but were affected by EEG 4–6 Hz polyspike-wave traits. All were females. Two non-probands had absences only, three had febrile seizures and one had partial seizures.

Long-term follow-up

We followed this group of patients for a mean period of 13.4 years (range 5–26). Under antiepileptic drug treatment, 10 patients (56%) were free of all seizures while 8 (44%) still had some type of seizures. However, seven of these eight patients were free of tonic-clonic seizures. But absences with

myoclonic seizures persisted in five of eight, myoclonic seizures in two of eight and tonic-clonic seizures in one.

JME with astatic seizures or JME/astatic Probands

This group identified as ‘JME/astatic’ accounted for 3% of all JME cases. Eight patients exhibited astatic seizures at a mean age of 14.3 years (range 8–17 years), preceding myoclonic seizures at a mean age of 16 years (range 11–30 years) and GM seizures at a mean age of 16 years (range 8–28 years). No gender predominance was found (four females and four males). EEGs of three patients showed 4–6 Hz spike-wave or polyspike- and slow-wave complexes. One patient had the same pattern but polyspike waves were combined with 3 Hz spike-wave complexes. One patient’s EEG consisted of generalized bursts of slow waves. General and neurological examination was normal in all patients. Four probands had normal CT scans, and one had normal 2FDG-PET brain scan. One patient had bilateral hippocampal atrophy on MRI.

Family members

Five families were simplex and only three were multiplex/multigenerational. Maternal and paternal transmission was equally common in multiplex/multigenerational families. Bilineality was not present in this group. Among non-proband family members, three were affected. One had JME

and astatic seizures, while two had GM only. EEG polyspike and slow waves affected one asymptomatic family member.

Long-term follow-up

Eight patients who had astatic seizures during adolescence were followed for a mean period of 11.1 years (range 3–18). Five of these patients were seizure-free. One had persisting astatic seizures while another one had breakthrough tonic-clonic seizures.

Frequency of seizures in classic JME and CAE evolving to JME

We initially asked how frequent specific epilepsy phenotypes were among relatives of classic JME probands. Almost 11% of first-degree relatives had seizures. Amongst all affected first-, second- and third-degree family members, myoclonic seizures with or without GM were the most common (40%). Absence seizures were rarely present in relatives. Only 5% of second-degree relatives had seizures. Amongst the second-degree relatives, tonic-clonic or GM seizures only (37.2%) were the most common followed by myoclonic seizures (31.4%). Because many probands were adolescent or young adults who did not have children, we only had 58 offsprings to study.

Frequency of myoclonic seizures in non-proband affected members was higher in classic JME families when compared with families with CAE evolving to JME (39.7% versus 3.9%; $P < 0.01$; see Table 3). In contrast to this, the frequency of absence (mainly pyknoleptic) with or without tonic-clonic seizures in non-proband affected members was higher in CAE evolving to JME compared with classic JME families (27.3% versus 6.5%; $P < 0.001$; see Table 3). The relative frequencies of having tonic-clonic seizures ($P < 0.001$), febrile seizures ($P < 0.01$) and all idiopathic seizure types ($P < 0.001$) were more common in CAE evolving to JME than in classic JME.

Discussion

Our present cohort and similarities with recent published literature

The method of data collection and ascertainment of a disease trait can influence how investigators view distribution of the disease trait(s) across patients and families, the apparent clinical course of the disease within a lifespan and even the clinical signs that are used to separate disease or syndromic entities. Our present cohort consisted of prospectively collected and consecutively ascertained sporadic and familial cases of JME from the clinics for genetic segregation and linkage analyses. Winawer *et al.* (2005) collected families for a family aggregation study, examining genetic relationships amongst epilepsies with different seizure types. For studies of IGE syndromes analyses were restricted to families with two or more individuals with defined CAE, JAE and JME. Trinka *et al.* (2004) retrospectively analysed a hospital

cohort of absence epilepsy. Although collected by different methodologies, these three data sets show similarities. Winawer *et al.* (2005) in their ‘familial aggregation study’ defined JME/JAE as individuals with absence seizures that began at 12 years or older. These patients with JME/JAE correspond to our subsyndrome of JME with adolescent pyknoleptic absences. In addition, their analyses of concordance amongst families (families were considered concordant if all affected relatives had the same seizure type or syndrome of interest; e.g. JME is present in all affected members) agree with our observations that JME can exist as the sole and distinct entity in 40% of our multiplex and multigeneration families. Winawer *et al.* (2005) observed concordance amongst families of JME versus JAE versus CAE ($P < 0.0001$) and concordance amongst families of JME versus CAE ($P < 0.0001$).

Trinka *et al.* (2004) in looking for prognostic factors for absences identified an overlap group between CAE and JAE that developed myoclonic attacks and was predictive for long-term lack of remission (66%). The overlap group consisted of both pyknoleptic absences that started after 10 years and non-pyknoleptic absences that started at 10 years or before 10 years. In our present data set, the subsyndrome of JME with adolescent pyknoleptic absences is likely to be the same group as the pyknoleptic absence patients that started after 10 years of age who later developed myoclonic seizures. Trinka *et al.* (2004) also classified as JME those patients who were initially classified as CAE and who developed ‘additional myoclonic attacks in association with the characteristic EEG changes of fast generalized spike wave or polyspike wave discharges’. These CAE patients of Trinka *et al.* are identical to our subsyndrome of CAE evolving to JME. In the studies of Trinka *et al.* (2004) and Wirrell *et al.* (1996), the development of myoclonic seizures or tonic-clonic convulsions in absence epilepsies had an adverse influence on the rate of seizure-free patients and their remission, thus agreeing with our observation that CAE evolving to JME is difficult to control with antiepileptic drugs.

Which subsyndromes belong to JME or CAE?

The higher frequency of pyknoleptic childhood absences in relatives of probands with CAE/JME compared with classic JME ($P < 0.001$) where ‘absence only’ rarely occur, the rarity of myoclonic seizures in relatives of CAE/JME compared with JME ($P > 0.01$), the relatively higher frequency of any seizure types ($P < 0.001$) including febrile convulsions ($P < 0.01$) in CAE/JME compared with classic JME support the separation of our data set into classic JME and CAE/JME. Myoclonic, GM and rare or spanioleptic absence seizures all peaked at 15 years of age in classic JME. Pyknoleptic absences peaked at seven years and preceded adolescent GM and myoclonic seizures in CAE/JME. Myoclonias and GM preceded absence seizures that appeared at 16 years of age in a smaller subset of JME with adolescent pyknoleptic absences. Astatic

seizures appearing at 14 years of age and preceding myoclonic and GM seizures that started at 16 years further define the smaller group of JME with astatic seizures.

The concept of adolescent absence in JME may not appear to be new since Janz (1985), Tsuboi (1977) and Mai *et al.* (1990) reported 10, 14 and 5%, respectively. However, these JME patients had juvenile absences with infrequent occurrence or spasioleptic absences. In our subsyndrome of JME with adolescent absences, petit mal seizures were pyknoleptic. Our subsyndrome of JME with adolescent pyknoleptic absences is similar to the JME/JAE group of patients described by Winawer *et al.* (2005) and the overlap group with pyknoleptic absences that started after 10 years of age who later developed myoclonic seizures described by Trinka *et al.* (2004).

Pure atonic or astatic seizures have been rarely observed in JME (Janz and Christian, 1957; Asconapé and Penry, 1984; Manon Espaillet *et al.*, 1987). We separated these groups of patients because physicians or responsible family members witnessed them to slump in their chair or fall 'like a rag doll', suggesting a sudden loss of muscle tone. EEG and EMG polygraphic studies as well as back-averaging are needed to determine origin of myoclonic seizures and substantiate EMG inhibition or silent periods during astatic drop (Oguni *et al.*, 2001; Guerrini *et al.*, 2005).

We originally reported the concept of CAE evolving into JME in 1995 (Medina *et al.*, 1995). Wirrell *et al.* (1996) then described about 15% of their cohort of CAE progressing to JME. This group of CAE/JME patients can also be deduced from the JME cohorts of Janz (4.6% in 1985 manuscript), Whitehouse *et al.* (1993), Elmslie *et al.* (1997), Panayiotopolous *et al.* (1989), Jain *et al.* (2003), and, as discussed above, in Trinka *et al.* (2004) and Winawer *et al.* (2005). What further new observations our data set emphasize are the poor results of long-term treatment and follow-up and the tendency for female preponderance in CAE/JME (1.8 F : 1 M). We observed similar female preponderance in probands with JME that associate with adolescent onset pyknoleptic absences (2.6 F : 1 M). Female preponderance is reported in literature in typical CAE (Currier *et al.*, 1963; Doose and Neubauer, 2001; Loiseau *et al.*, 2002). Our data set also suggests that maternal transmission of the epilepsy phenotype is more common than paternal transmission in the subsyndrome of CAE/JME. Most important, perhaps for the patients, is the poor response to treatment in CAE/JME during follow-up. Absence and absence with tonic-clonic seizures are the most common persisting complaints of patients with CAE/JME and are the most common seizure types in non-proband affected family members. Absences together with tonic-clonic or myoclonic seizures respond poorly to treatment in CAE/JME in agreement with Trinka *et al.* (2004) and Wirrell *et al.* (2001). In contrast, almost all seizure types in classic JME, JME with adolescent pyknoleptic absences and JME with astatic seizures respond well to valproate monotherapy (Table 2).

For all the above reasons, CAE/JME is more likely a separate disorder from JME. It probably rightfully belongs to the absence epilepsy subsyndromes rather than a JME subsyndrome. CAE/JME has the 'typical 3 Hz spike wave' as the predominant EEG pattern. Low-amplitude 15–25 Hz rhythms or runs or rapid spikes that we find in CAE/JME have also been observed in typical absence epilepsies by Sato *et al.* (1976), Gastaut *et al.* (1986), Fakhoury and Abou-Khalil (1999) and Michelucci *et al.* (1996). Regardless of whether it belongs under absence or JME, the group of CAE evolving to JME is a true entity and should be included under the IGEs.

Are all four groups lifelong epilepsies?

Perhaps they are all lifelong epilepsies, but the best information is in classic JME and CAE/JME. Only 8 of 161 (5%) patients with classic JME are in remission from all seizures without treatment, 4 of them from 5 to 11 years. In the remaining 153 patients, epilepsy is clearly chronic as shown by recurrence of seizures when medications are stopped or missed or when trigger factors precipitate seizures. Thus, with rare exceptions, classic JME is not a remitting form of epilepsy but rather chronic and long in duration. In CAE/JME, only 3 of 35 patients achieved complete seizure control with medication during a mean follow-up period of 19.4 years. From Fig. 2, we know that 28 patients had seizures for a long duration (6–50 years). We did not stop treatment in the three patients with complete seizure control for ethical reasons.

Even the 18 patients with 'JME with adolescent pyknoleptic absence' and the 8 patients with 'JME with astatic seizures' have received continuing treatment for as long as 5–26 years and 3–18 years, respectively. These patients are expecting to continue treatment for their lifespan because they experience seizures when they forget to take medication or when sleep deprivation, alcohol or fatigue trigger a breakthrough seizure.

Unequivocal evidence for a lifelong trait can only be obtained by stopping treatment randomly in all the four groups. Ethical reasons constrain such a study. Moreover, it can be argued that each of these groups may have subgroups that have limited expression in adolescence or early childhood and that we do not see those patients who could be seizure-free and who are in their community clinics under the care of general medical and pediatric practitioners. These suggestions are possible but they do not negate the existence of these four groups of patients with chronic long-standing epilepsies (Canevini *et al.*, 1992; Genton *et al.*, 2000; Wirrell *et al.*, 2001).

In the small number of patients with CAE/JME, we have not observed any patient in remission without antiepileptic drug treatment. For reasons presently unknown, CAE/JME has been the hardest group to treat. Only 7% are seizure-free on valproate. Satisfaction with reduction of GM seizures by valproate was reported by 72% but 93% have frequent breakthrough absences that combine with myoclonic or GM and that trouble the patients weekly, monthly or at least every

three months. In classic JME, 58% of patients are completely free of seizures and when breakthrough GM seizures occur, they occur once a year to once every 5 years.

The International League Against Epilepsy classification of epilepsies and epileptic syndromes

Recently, the 2001 ILAE Task Force on Classification and Terminology ‘proposed to group JME, Juvenile Absence Epilepsy and Epilepsy with Tonic Clonic Seizures only, under the sole heading of idiopathic generalized epilepsies (IGE) with variable phenotypes’ (Engel, 2001), implying one disease with variable manifestations, implying that JME cannot exist as the sole phenotype in JME families and that JME should no longer be considered a disease entity or syndrome.

In the proposed diagnostic scheme, Engel (2001) wrote ‘It is important to stress that the list shown in Table 4 contains syndromes that are still under discussion, such as the new concept of generalized epilepsies with variable phenotypes,’ which Engel acknowledged was introduced by Anderman and Berkovic. Our present data show that 40% of typical JME families have JME as their sole phenotype, indicating that JME can be a distinct and separate entity in families and not have other IGE phenotypes amongst their family members. Our present data agrees with Wirrell *et al.* (2005), as discussed above. Our present results also show that 66% of families with CAE/JME express the various phenotypes of IGEs, suggesting genetic pleiotropism as an action of gene or genes. Our data further show that 44% of families with CAE/JME can have CAE/JME as the sole phenotype of families.

Thus, on the basis of our data, we would suggest four syndromes under IGE, namely, (i) the more frequent classic JME with or without spatioleptic absences; (ii) pyknoleptic CAE evolving to JME; (iii) JME with adolescent onset pyknoleptic absences; and (iv) the rare JME with astatic seizures. These syndromes should be added to the IGE syndromes of childhood absence and juvenile absence (both do not develop myoclonic seizures). In other words, juvenile absence with myoclonic seizures is a form of JME and should be separated with juvenile absence without myoclonic seizures. Similarly, CAE that evolves into JME should be separated from CAE that remits during adolescence and does not develop myoclonic seizures. Our data do not eliminate the concept of generalized epilepsies with variable phenotypes, which can be observed in many families. Our data merely emphasize that JME syndromes such as classic JME and CAE evolving to JME can also appear as the sole phenotypes of probands and affected members of families and deserve to be considered as disease entities.

In addition to our present data, there are new and past published clinical evidence (Liu *et al.*, 1995, 1996; Serratosa *et al.*, 1996; Trinka *et al.*, 2004; Winawer *et al.*, 2005) and published genetic linkage studies from independent laboratories that argue in favour of JME as specific disease

entities. JME is genetically heterogeneous and hence a disease with various molecular causes. Seven chromosome loci are currently genetically linked to JME, namely, chromosomes 6p12 (Bai *et al.*, 2003; Serratosa *et al.*, 1996), 6p21.3 (Greenberg *et al.*, 2000), 15q14 (Whitehouse *et al.*, 1993; Elmslie *et al.*, 1997), 5q (Cossette *et al.*, 2002), 3q26 (Haug *et al.*, 2003), 16p13 and 7q32 (Pinto *et al.*, 2005). Of these chromosome loci, three disease-causing mutations, namely, *GABRA1* in 5q34–q35 (Cossette *et al.*, 2002), *CLCN2* in 3q26 (Haug *et al.*, 2003) and Myoclonin/EFHC1 in 6p12 (Suzuki *et al.*, 2004) and two genes with single nucleotide polymorphism (SNP) variants, namely, *BRD2* *RING3* in 6p21 (Pal *et al.*, 2003), and connexin 36 in 15q14 (Mas *et al.*, 2004) have been associated with JME.

Finding more chromosome loci and more epilepsy-causing mutations for JME and for each of the four sub-syndromes will continue to provide definitive evidence of the existence of specific diseases within JME.

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