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Clinical heterogeneity of juvenile myoclonic epilepsy: Follow-up after an interval of more than 20 years

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ABSTRACT

Purpose: The view that juvenile myoclonic epilepsy (JME) is a uniform and life-long disorder is currently being challenged. The aim of this study was to assess the seizure and psychosocial outcome of JME at least 20 years after onset.

Methods: In 1992, 42 patients with JME were identified. In 2012, 37 agreed to a semi-structured interview. In the remaining five, only medical records were available.

Results: Of 40 patients with known seizure outcome, 21 were in remission for >5 years. Seven were off antiepileptic drugs (AEDs), four being seizure free for >10 years. Myoclonic seizures (MC) evolving to generalized tonic–clonic seizures (GTC) were associated with seizure persistence ($p = 0.013$), whereas >1 year between MC and GTC onset was associated with a trend to GTC remission ($p = 0.069$). Of 19 patients with uncontrolled seizures, eight experienced remission with second generation AEDs.

Favorable psychosocial outcome by interview was found in a third, whereas another third had psychiatric comorbidity, seven with substance or alcohol abuse. Psychosocial and seizure outcome did not correlate.

Conclusion: This study corroborates the heterogeneity of JME in terms of seizure and psychosocial outcome, but without a clear association between the two. It confirms that seizure control may persist after AED withdrawal in some and supports MC evolving to GTC as a predictor of seizure persistence. Moreover, it suggests that newer broad spectrum AEDs may improve the prognosis of JME; their impact should be focus of prospective studies.

1. Introduction

Juvenile myoclonic epilepsy (JME) is the most common type of genetic (idiopathic) generalized epilepsy, comprising 5–10% of all epilepsies.[1] Onset is usually in the second decade, and the cardinal symptom is early-morning myoclonic seizures (MC), often precipitated by sleep deprivation. Approximately 90% of patients have generalized tonic–clonic seizures (GTC), and one third has absence seizures.[2]

Although response to appropriate treatment is good for most patients,[3,4] JME has been considered a lifelong disorder with a high risk of seizure relapse on discontinuation of antiepileptic drugs (AEDs).[5–7] Nevertheless, four long-term follow-up studies have shown that some patients may stop AED treatment and remain seizure free.[8–11]

In contrast to the seemingly positive seizure outcome in the majority, there is expanding evidence of an unfavorable psychosocial outcome in many patients.[9,12] This has been ascribed to a subtle frontal lobe dysfunction in JME.[13,14]

As long-term studies of JME are scarce, there is a need for more clinical research on the course and prognosis of this syndrome. Thus, we aimed to assess the severity of the disorder in a cohort of patients after at least 20 years of follow-up, and to study clinical characteristics in relation to seizure and psychosocial outcome.

2. Methods

In 1992, consecutive patients with JME at Trondheim University Hospital were identified for recruitment in a study on the association with human leukocyte antigens.[15] The clinical diagnosis of JME was based on the 1989 classification of epilepsies and epileptic syndromes by the International League Against

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Table 1
Number of patients included in the various analyses after follow-up >20 years.

	Original cohort (1992)	Seizure outcome	Psychosocial outcome	Disability benefits
Interviewed	37	37	37	37
Unavailable	2	1	0	1
Deceased	3	2	0	2
Total	42	40	37	40

Epilepsy (ILAE).[16] In 2012, we attempted to contact all 42 patients with a request for participation in a follow-up study.

One patient could not be included as he died after only 13 years of follow-up. Two other deceased patients followed for more than 20 years were included based on their medical records. Two patients could not be contacted as they were currently registered with no fixed address; in one medical records were sufficient for inclusion (Table 1).

37 patients (88%) were available for a standardized semi-structured telephone interview, focusing on seizure types, seizure frequency, medication and psychosocial outcome. Medical records were reviewed for background information.

Psychosocial outcome was assessed based on five elements: graduation from high school, disability or unemployment benefits, alcohol or illegal substance abuse causing social problems, need of psychiatric health care and self-reported social network. Social network, as well as perceived satisfaction with health, was simply graded as poor, sufficient or good, as more complex scales were considered less useful for telephone interviews.

Chi-square test and independent *t*-test were used for comparison of categorical and continuous variables, respectively. $p < 0.05$ was considered significant.

The study was approved by the Regional Committee for Medical Research Ethics, and written informed consent was provided by all interviewed participants.

3. Results

3.1. Patients

Of the 42 patients forming the basis of this study, 25 (60%) were women. Forty patients (95%) had GTC and 12 (29%) had absences. One patient had MC only. In five patients, GTC was the first reported seizure type. The duration of JME, calculated from onset of the first motor seizure (MC or GTC) was 31 ± 9.3 years. Mean age at JME onset was 16 ± 3.2 years (women 15 ± 3.1, men 17 ± 3.0, $p = 0.056$). In three female patients, absences were the first seizure type, with onset at age eight, nine and 12 years, respectively, whereas MC started at age 18 in the two first, and at age 19 in the third.

In the three deceased patients, causes of death were suicide (age 28), cancer (age 59) and dementia (age 81).

3.2. Seizure outcome

In 40 patients seizure outcome was known at least 20 years after JME onset. Median age at follow up was 47 (range 35–81) years.

The five and ten-year seizure remission rates for GTC and MC are shown in Table 2. More than 50% had been completely seizure-free for the last five years, and one-third for at least ten years. Altogether 19 patients had persistent seizures within the last five years; one had GTC only, ten had MC only and eight had both seizure types. Of the 18 interviewed patients with persistent MC, all but two (age 39 and 41) reported a reduced frequency compared to younger years.

Table 2
Terminal seizure remission in 40 patients with JME after follow-up > 20 years.

Seizure remission	Five years	Ten years
Generalized tonic–clonic seizures	31 (78%)	24 (60%)
Myoclonic seizures	22 (55%)	16 (40%)
Both seizure types	21 (53%)	13 (33%)

Table 3
Clinical characteristics in relation to seizure outcome in 40 patients with JME followed >20 years.

	5-year seizure remission	Seizures within last 5 years	*P*-value
Three seizure types	5 (50%)	5 (50%)	0.855
Absence seizures	5 (45%)	6 (55%)	0.583
Myoclonic seizures not strictly confined to awakening	6 (46%)	7 (54%)	0.564
Myoclonic seizures preceding GTC	8 (35%)	15 (65%)	0.013
>1 year between onset of myoclonic seizures and GTC	9 (60%)	6 (40%)	0.464

None of the three patients with absence epilepsy prior to MC onset had experienced seizure remission. All were females. Two had persistent MC and GTC; one had been without GTC for more than ten years, but still had occasional MC without taking AEDs.

The relationship between various clinical characteristics and five-year seizure remission is shown in Table 3. MC habitually or occasionally preceding GTC (clonic–tonic–clonic seizure) was associated with a poorer seizure outcome. Fifteen patients had a delay of more than one year between MC onset and first GTC. At follow-up, 11 of them had not had GTC for more than ten years ($p = 0.069$). However, the longer interval between MC and GTC onsets, did not influence five year complete seizure remission (Table 3). There was no difference in age at JME onset between patients with five-year seizure remission and patients with ongoing seizures (16 ± 3.9 years vs. 16 ± 2.3 years, $p = 0.494$). Eleven women (44%) and ten men (67%) had been seizure-free for more than five years ($p = 0.165$). Seizure persistence was not associated with poor satisfaction with health ($p = 0.506$).

3.3. Psychosocial outcome

Fourteen of the 37 interviewed patients (38%) had a favorable psychosocial outcome, meaning they had graduated from high school, were working, had no history of a psychiatric disorder, had a good or sufficient social network and no substance or alcohol abuse. Altogether 26 (70%) had graduated from high school, and 12 (32%) were college or university graduates, one with a PhD degree. There was no association between these factors and seizure outcome (Table 4).

We were able to obtain information on employment and disability benefits from 40 patients. Twenty-three patients (58%)

Table 4
Unfavorable psychosocial factors in relation to seizure outcome in 37 patients with JME after >20 years.

	5-year seizure remission	Seizures within last 5 years	*P*-value
No high school graduation	4 (36%)	7 (64%)	0.087
Disability benefits/unemployment	7 (50%)	7 (50%)	0.898
Substance abuse	3 (75%)	1 (25%)	0.316
Ever needed psychiatric health care	7 (54%)	6 (46%)	0.823
Poor self-reported social network	2 (40%)	3 (60%)	0.162
No unfavorable psychosocial factors	7 (50%)	7 (50%)	0.699