Epilepsy & Behavior 90 (2019) 122–128

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Psychosocial complications in juvenile myoclonic epilepsy

Marte Syvertsen [a,b,*], Kaja Selmer [c,d], Ulla Enger [a], Karl O. Nakken [d], Deb K. Pal [e,f,g,h], Anna Smith [e,1], Jeanette Koht [a,b,1]

[a] Department of Neurology, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway
[b] Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[c] Department of Medical Genetics, Oslo University Hospital and University of Oslo, Oslo, Norway
[d] National Center for Epilepsy, Division of Clinical Neuroscience, Oslo University Hospital, Oslo, Norway
[e] Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom
[f] MRC Centre for Neurodevelopmental Disorders, King's College London, London, United Kingdom
[g] King's College Hospital, London, United Kingdom
[h] Evelina London Children's Hospital, London, United Kingdom

ARTICLE INFO

Article history:
Received 9 October 2018
Revised 19 November 2018
Accepted 19 November 2018

Keywords:
Epilepsy
Frontal lobe
Executive dysfunction
Levetiracetam
Recreational drugs
ADHD

ABSTRACT

Juvenile myoclonic epilepsy (JME) constitutes about 10% of all epilepsies. Because of executive dysfunction, people with JME may be prone to impulsivity and risk-taking behavior. Our aim was to investigate whether psychosocial issues associated with impulsivity are more prominent in people with JME than in those with other types of genetic generalized epilepsy (GGE). Patients with GGE were recruited retrospectively through the Drammen Hospital records in Buskerud County, Norway, 1999–2013. They were invited to a semi-structured interview, either at the hospital or at home. Ninety-two patients with JME and 45 with other types of GGE were interviewed. Variables were evaluated in terms of their association with JME versus other GGE diagnosis using a logistic regression model. Juvenile myoclonic epilepsy was associated with use of illicit recreational drugs and police charges, although with borderline significance (odds ratio [OR] 3.4, $p = 0.087$ and OR 4.2, $p = 0.095$); JME was also associated with being examined for attention-deficit hyperactivity disorder (ADHD) in females (OR 15.5, $p = 0.015$), a biological parent with challenges like addiction or violent behavior (OR 3.5, $p = 0.032$), and use of levetiracetam (OR 5.1, $p = 0.014$). After controlling for group differences, we found psychosocial complications to be associated with JME, potentially influencing the lives of the individuals and their families to a greater extent than the seizures per se. Thus, JME should be considered a disorder of the brain in a broader sense than a condition with seizures only.

1. Introduction

Juvenile myoclonic epilepsy (JME) constitutes up to 10% of all epilepsies [1,2], making it one of the most common types of epilepsy; JME arises in young people and is hallmarked by myoclonic jerks, often triggered by sleep deprivation [3]. It is most likely a complex genetic disorder and is highly heritable [4–6]; JME was described by Janz and Christian more than 60 years ago [7]. Janz claimed that people with JME tended to have an engaging but emotionally unstable and immature personality [7,8]. However, his statements about behavioral patterns in JME did not receive much attention until nearly 40 years later when Swartz and colleagues compared working memory in frontal lobe epilepsy (FLE) and JME [9]. Test results in the group with JME were similar to those of the group with FLE, a finding that triggered widespread research regarding the neuropsychological profile of people with JME. Several studies conclude that there is a degree of frontal lobe impairment, particularly in relation to executive function [10–13]. A high rate of personality disorders has been noted, with an emphasis on the cluster B group [14,15], comprising features like emotional instability, impulsivity, and lack of discipline. These findings match Janz's description quite well. Accordingly, imaging studies of JME reveal abnormalities within the prefrontal cortex [12,16–18], an area of the brain involved in impulse control and regulation of behavior [19,20].

Two studies investigating decision-making concluded that people with JME are prone to make unfavorable and impulsive decisions [21,22], and impulsivity has been shown to affect social adjustment both in JME and in other patient groups [23,24]. However, results from psychosocial studies of people with JME are inconsistent. Issues like unplanned pregnancies, unemployment, and living single are underlined [25,26], while other authors state that a large proportion of patients

* Corresponding author at: Department of Neurology, Drammen Hospital, 3004 Drammen, Norway.
E-mail address: marsyv@vestreviken.no (M. Syvertsen).
[1] These authors contributed equally and are joint last authors.

https://doi.org/10.1016/j.yebeh.2018.11.022
1525-5050/

with JME have a favorable psychosocial outcome [27,28], comparable to those with absence epilepsy [27]. However, the studies are small, conducted at tertiary epilepsy clinics, or they lack control groups.

The aim of the present study was to investigate whether psychosocial issues associated with impulsivity are more prominent in people with JME than in those with other types of genetic generalized epilepsy (GGE).

2. Material and methods

2.1. Study design

The study was cross-sectional and hospital-based, with an internal comparison group. In reporting the study, we have followed the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines [29].

2.2. Study area and population

The study was conducted at Drammen Hospital in Norway. Drammen Hospital serves a population of 477,000 people in Buskerud County and the nearby municipalities of Sande, Svelvik, Asker, and Bærum, i.e., 9.1% of Norway's total population. The hospital has no tertiary or otherwise specialized function in epilepsy care. There is only one department of neurology and one department of pediatrics in this geographical area, both located at Drammen Hospital. The number of private neurologists and pediatricians is low, as Norwegian public healthcare is accessible and well-established, thus utilized by the vast majority of the population. We assume that most patients with epilepsy in our region visit Drammen Hospital at some point [30]. Hence, a hospital-based study of epilepsy in this geographical area would approximate representativeness of the population.

2.3. Definitions

Active epilepsy was defined as ongoing treatment with one or more antiepileptic drugs and/or at least one seizure within the last five years [31]. Included in the definition of GGEs were JME, childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), and epilepsy with generalized tonic–clonic seizures only (EGTCS), as suggested by the International League Against Epilepsy (ILAE) [32]; CAE, JAE, and EGTCS were defined according to the classification of the ILAE [33]. The definition of JME was based on the class II diagnostic criteria of the consensus on diagnosis and management of JME [3]. Occasional myoclonic jerks were allowed in absence epilepsy, but absences had to be the dominating seizure type. In JME, myoclonic jerks had to be the dominating seizure type [1]. Polytherapy was defined as current treatment with two or more antiepileptic drugs. Use of illicit recreational drugs was registered if a subject had used such substances on more than two occasions. When registering history of police charges, speeding fines were excluded.

2.4. Inclusion and exclusion criteria

Patients aged 14–40 years with active GGE were included. Patients with intellectual disability (i.e., intelligence quotient [IQ] <70) were excluded, as were patients with dysmorphic features of face and/or body.

A stricter definition of active epilepsy was applied to patients with CAE, as we wished to include only patients affected by epilepsy in youth. Thus, patients with CAE were excluded if they were not using antiepileptic drugs and were seizure-free for more than one year.

2.5. Participant recruitment

In the period 1999–2013, all consultations and hospital stays containing an International Classification of Diseases, 10th Revision (ICD-10) code of epilepsy (G40) at Drammen Hospital were identified (Fig. 1). A similar search was performed at the National Center for Epilepsy (located 32 km from Drammen Hospital) for the period 2010–2013 to identify subjects from our region possibly receiving follow-up there. The medical records of nearly 3000 people were reviewed to verify diagnosis and identify those with GGE [30]. Patients with GGE aged 14–40 years were contacted and invited to a clinical interview at the outpatient clinic of Neurology at Drammen Hospital. Patients registered with GTCS only, without a focal start and with normal electroencephalograms (EEGs) were classified as epilepsy of unknown etiology [30], and they were not contacted. For the subjects younger than 18 years, the parents were contacted. Those who declined a visit at the hospital were offered a home visit.

After finishing the search limited to Buskerud County, patients with GGE aged 14–40 years were consecutively recruited from the EEG laboratory at Drammen Hospital, including participants from the nearby municipalities of Asker, Bærum, Svelvik, and Sande. Additionally, information about the study and an invitation to participate was published in the magazine of The Norwegian Epilepsy Association. The clinical interviews were conducted between November 2016 and February 2018.

2.6. EEG recordings

All EEGs were conventional 20-min recordings, including hyperventilation and photostimulation. In some subjects, sleep-deprived EEG studies and records from long-term monitoring (LTM) were available as well. Electrodes were placed according to the international 10–20 system. All available EEG recordings and reports of the included subjects were reviewed by the first author.

2.7. Clinical interview

All included patients were interviewed by the first author according to a semi-structured questionnaire designed for the purpose of this study. A semi-structured approach was chosen to allow patients to expand on their experiences. The questionnaire included sections regarding background and family history, clinical information about epilepsy history and medication, and a section regarding social factors. Based on insight into the histories of nearly 100 people with JME [1,28] and the previous studies showing that they are prone to impulsive decision making [21,22], we included questions that could illuminate potential consequences of risk-taking behavior. Among the issues included were use of illicit recreational drugs, being charged by the police, and smoking prior to the age of 18 years, all self-reported. Eighteen years is the minimum age to lawfully purchase cigarettes in Norway. Participants were also asked whether one or both biological parents ever had severe psychosocial challenges, like addiction or violent behavior, including abuse of alcohol, abuse of recreational drugs, gambling, or domestic violence. One hour was scheduled for the interview, which was organized for research purpose only, independent of regular clinical follow-up. Sensitive questions were always asked in private.

2.8. Statistical methods

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 23. For univariate analyses, Chi-Square tests (with Yate's Continuity Correction for 2×2 tables) were used for comparison of categorical variables. When expected cell count was less than five in any cell, Fisher's Exact Probability test was used. Independent *t*-tests were used for comparison of continuous variables. Clinical and background variables with p-values <0.20 and psychosocial factors potentially associated with a diagnosis of JME were analyzed in a logistic regression model. Impulsive behavioral patterns are more prominent in men [34]. Thus, interaction terms were entered one at a time for gender and all independent variables. As our sample size was larger than that of previous studies of

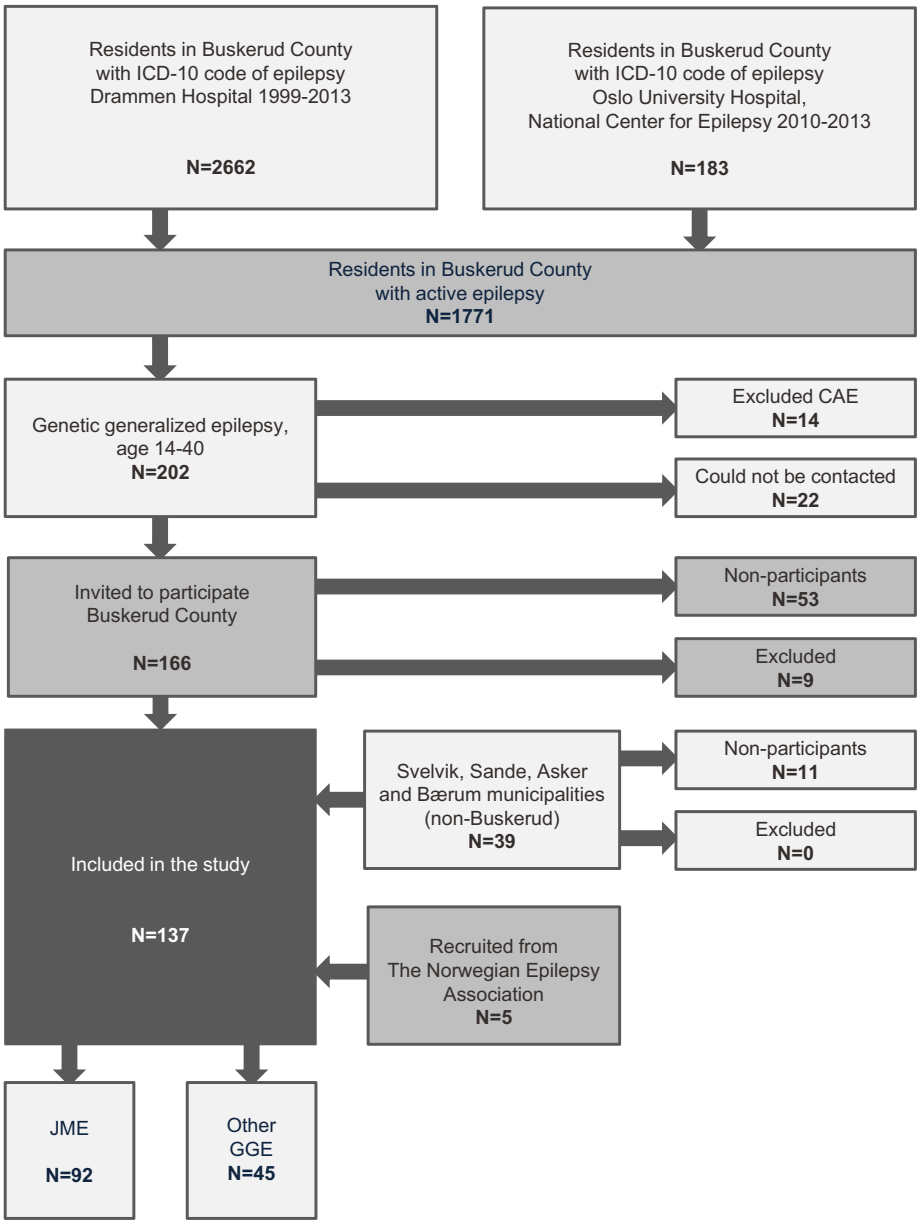

Fig. 1. Identification and inclusion of study participants. GGE = Genetic generalized epilepsy. JME = Juvenile myoclonic epilepsy. CAE = Childhood absence epilepsy.

the psychosocial complications of JME [14,15,25–28] and considered representative of the population of interest, we chose an exploratory approach by means of a stepwise backwards conditional regression procedure, in order to identify the subset of variables best predicting outcome (i.e., a diagnosis of JME or not) [35] ($p < 0.05$ [predictor included], $p < 0.10$ [predictor excluded]; iteration 20; cut-off set at 0.5; constant included). Outcome odds ratios (ORs) were converted to Cohen's d in order to facilitate interpretation of effect size [36]. p-Values ≤0.05 were considered statistically significant. As we were not able to include more participants than the given number of consenting patients with JME/GGE in our region, a posthoc power analysis was carried out [37], determining the power that we would have to detect significant differences between cases and controls.

2.9. Ethics

The study was approved by the Regional Committee for Medical Research Ethics, South East Norway (ethical agreement no. 2013/1027) and by the data protection officer of Drammen Hospital. Written informed consent was obtained from all study participants.

3. Results

3.1. Participation rate

Of 202 patients aged 14–40 years with GGE diagnoses in Buskerud County, 14 individuals with CAE were excluded because they were without antiepileptic drugs and had been seizure-free for more than one year. Of the remaining 188, we were able to contact 166 and invited them to participate. Additionally, 39 patients from the neighboring municipalities were invited. Of the 205 patients that we contacted, 64 (31%) declined participation. The mean age of nonparticipants was 25.8 ± 7.0 years, and 35 (55%) of them were female. Five patients were recruited from The Norwegian Epilepsy Association. All in all, nine were excluded; three had intellectual disability; one had suspected monogenetic disorder; two no longer had active epilepsy; one had

epilepsy with myoclonic atonic seizures, and two had focal epilepsy (Fig. 1).

3.2. Clinical and background characteristics

One hundred and thirty-seven patients were included in the study, 92 with JME and 45 with other types of GGE (Fig. 1). Univariate analyses of clinical characteristics and psychosocial complications are summarized in Table 1. In the group with JME, 31 patients (34%) reported absence seizures and seven (8%) never had a generalized tonic–clonic seizure (GTCS). In the group with other types of GGE, 12 (27%) reported myoclonic jerks, and six (13%) never had a GTCS. All patients had generalized spike–wave discharges in at least one EEG recording, except for two patients with EGTCS. Both had a typical clinical history, with GTCSs facilitated by stress and lack of sleep, one on awakening and one mostly in the afternoon. None of them had symptoms indicating focal seizure onset. The rates of polyspike and wave activity and photoparoxysmal responses are presented in Table 1. The EEG background activity was normal in all. Of the patients classified as JME, 32 (35%) did not report a clear cut morning predominance of seizures. However, they were confident that myoclonic jerks was the dominant seizure type. Thus, they were kept in the group with JME.

3.3. Regression analysis

In addition to gender, the following variables were entered into a binary logistic regression model as covariates to control for group differences identified in the univariate analyses (Table 1); age at inclusion in study; previous or present levetiracetam use; and whether a biological parent ever had challenges like addiction or violent behavior. Predictor variables included whether the participant was currently employed or studying; smoking prior to the age of 18 years; use of illicit recreational drugs; being examined for ADHD; being a victim of violence or abuse; and being charged by the police. Being examined for ADHD (self-reported, N = 29) was used rather than being with diagnosed ADHD (N = 9), as several subjects stated that they fulfilled the criteria of ADHD when examined, but were nevertheless not diagnosed because the psychiatrist related the symptoms to epilepsy. Independent variables were checked for collinearity, and all had tolerance values exceeding 0.5. In the analysis of residuals, three outlier cases were discovered (ZResid −3.94, −3.17, and − 3.08). These cases were removed, and the logistic regression analysis was repeated. The final model was statistically significant (Chi-Square 43.04, $p < 0.001$), explaining between 28% (Cox & Snell R square) and 39% (Nagelkerke R square) of the variance in JME status, i.e., whether a patient was with diagnosed JME or another type of GGE. The variables significantly predicting diagnosis of JME were as follows: being examined for ADHD in females; parent with psychosocial challenges; age at inclusion in study; and previous or present use of levetiracetam. Being charged by the police and use of illicit recreational drugs increased the likelihood of belonging to the group with JME, but not at a statistically significant level (Table 2). In a posthoc power analysis, the power to detect a significant difference in police charges ($\alpha = 0.05$) between 92 cases of JME and 45 controls was 79%, with a rate of police charges at 26% in the group with JME, and 7% in the control group. The power to detect a significant difference in use of illicit recreational drugs was 83%, with a rate of illicit recreational drug use of 33% in the group with JME, and 11% in the control group.

Table 1
Univariate analyses of clinical characteristics and psychosocial complications.

	JME N = 92	Other GGE N = 45[a]	p-Value
Female	55 (59.8%)	26 (57.8%)	0.969
Age at inclusion (years)	25.8 ± 6.9	23.5 ± 6.7	0.066[b]
Epilepsy duration (years)	11.1 ± 6.5	11.3 ± 8.1	0.875
Photoparoxysmal response in EEG	35 (38.0%)	14 (31.1%)	0.545
Polyspikes in EEG	45 (48.9%)	21 (46.7%)	0.948
No GCTS within the last year	72 (78.3%)	37 (82.2%)	0.753
No myoclonic jerks within the last year	29 (31.5%)	6 (50.0%)[c]	0.212[d]
Polytherapy	16 (17.4%)	4 (8.9%)	0.286
Antiepileptic drugs, previous or present			
Valproate	56 (60.9%)	27 (60.0%)	1.000
Levetiracetam	42 (45.7%)	11 (24.4%)	**0.027**[b]
Lamotrigine	61 (66.3%)	29 (64.4%)	0.981
Topiramate	13 (14.1%)	4 (8.9%)	0.550
Zonisamide	10 (10.9%)	2 (4.4%)	0.336[d]
Off antiepileptic drugs >1 year	18 (19.6%)	7 (15.6%)	0.737
1st degree relative with epilepsy	30 (32.6%)	12 (26.7%)	0.609
Currently employed or studying	72 (78.3%)	41 (91.1%)	0.105[b]
High school degree	57 (62.0%)	31 (68.9%)	0.545
Ever in need of psychiatric healthcare	50 (54.3%)	19 (42.2%)	0.250
Being examined for ADHD	23 (25.0%)	6 (13.3%)	0.178[b]
Being charged by the police	24 (26.1%)	3 (6.7%)	**0.014**[b]
Use of illicit recreational drugs	30 (32.6%)	5 (11.1%)	**0.012**[b]
Victim of violence or abuse	36 (39.1%)	7 (15.6%)	**0.009**[b]
Smoking prior to the age of 18 years	37 (40.2%)	9 (20.0%)	**0.031**[b]
Parent with psychosocial challenges	32 (34.8%)	8 (17.8%)	0.063[b]

Statistically significant findings are marked in bold.
[a] 8 childhood absence epilepsy, 22 juvenile absence epilepsy, 15 epilepsy with GTCS only.
[b] Variable included in regression model.
[c] Of 12 patients with other types of GGE who had experienced occasional myoclonic jerks.
[d] Fisher's Exact Test.

4. Discussion

In the present study, negative psychosocial outcomes like police charges and use of illicit recreational drugs were highly prevalent in people with JME. Additionally, a diagnosis of JME was associated with being examined for ADHD in females, use of levetiracetam, and a familial background of addiction and/or violent behavior.

Police charges and use of illicit recreational drugs are factors that may represent major challenges to the individuals and their families. Such psychosocial difficulties are linked to impulsivity and executive dysfunction [19,38,39], but received little attention in previous research of JME. In a small population-based study from Canada, three out of 23 participants (13%) with JME were arrested for criminal offense, but none admitted to use of recreational drugs [25]. A German study found use of recreational drugs in one out of 33 patients with JME (3%) [26], and polysubstance abuse was registered in one of 43 (2%) in an Austrian study of people with JME [15]. A Norwegian study found a higher rate of substance abuse in those with JME, 17% (7/42), but also included abuse of alcohol. In the same study, four patients (10%) were convicted of criminal offense [28]. The rates of police charges and recreational drug use were considerably higher in the present study, with nearly one-third of the patients with JME admitting to use such drugs and one-fourth reporting police charges. Three of the previous studies referring to substance abuse and/or criminal offense in JME used a similar approach to ours, i.e., a semi-structured interview by telephone or in person. The sample sizes were small, however (N = 24–42) [25,26,28]. Moreover, recall bias must be considered, as use of recreational drugs is more common in youth [40], and the mentioned studies were conducted after more than 20 years of follow-up, with mean age at inclusion at 36–52 years [25,26,28]. The Austrian study reported polysubstance abuse according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) [15], including only those with severe drug-related problems. Selection bias is another possible explanation of why drug use and police charges were more common in the present study, which achieved a higher participation rate (69%) than some of the previous studies addressing psychosocial issues of JME (37–50%) [15,26,27]. People with psychosocial challenges are most likely hard to recruit for clinical studies. We know from our review of medical records that some of the patients that we were unable to include had very disorganized lives, often including drug abuse and severe

Table 2
Logistic regression predicting likelihood of belonging to the group with JME.

	β	SE	Wald	df	p	Odds ratio	95% CI for OR	Cohen's d
Being examined for ADHD * gender	2.742	1.128	5.905	1	**0.015**	15.517	1.700–141.672	0.656
Being charged by the police	1.433	0.859	2.782	1	0.095	4.190	0.778–22.553	0.364
Use of illicit recreational drugs	1.230	0.720	2.921	1	0.087	3.422	0.835–14.032	0.294
Parent with psychosocial challenges	1.260	0.588	4.594	1	**0.032**	3.525	1.114–11.153	0.302
Age at inclusion in the study	0.064	0.032	3.888	1	**0.049**	1.066	1.000–1.136	0.015
Previous or present use of levetiracetam	1.633	0.505	10.459	1	**0.014**	5.120	1.903–13.777	0.391

Statistically significant findings are marked in bold.

psychiatric difficulties. Hypothesizing that psychosocial difficulties are more prominent in JME, and that the most severely affected individuals are among the nonparticipants, low participation rate would represent a bias towards no difference in psychosocial difficulties between those with JME and controls. Moreover, some of the previous studies were conducted at tertiary care epilepsy centers [26,27]. As stated by a German JME research group, long and stable follow-up by a dedicated doctor at a specialized center may represent a protective factor when it comes to psychosocial complications [27]. Our population-based approach [1,30] and offering home visits represent strengths of the study design and probably contributed to a lower selection bias.

Regarding illicit recreational drugs in the general population, The Norwegian Institute of Public Health conduct regular surveys, inviting 3700 randomly selected Norwegians aged 16–64 years to a telephone interview. In the latest survey (2016, participation rate 47%), 21% of 897 individuals aged 16–40 years confirmed use of cannabis at least once [40], which is lower than among patients with JME. Our definition was stricter, i.e., use at least twice, but included all recreational drugs, not just cannabis. It is likely however, that those who used other types of drugs also tried cannabis at some point, as it is the recreational drug most commonly used [40]. As for police charges, 8% of the general Norwegian population aged 15–39 years were registered with sanctions for any type of criminal offense during 2015, including speeding fines [41], which is similar to the proportion of police charges noted in the group with other types of GGE in the present study (7%). Considering that 26% of the patients with JME reported police charges (excluding speeding fines) and expecting self-reported police charges to be lower than the registered ones, the difference is noteworthy. All in all, psychosocial difficulties like use of recreational drugs and incriminating behavior seem to be more prominent in people with JME than previously thought, possibly due to inadequate reporting and inattention to these rather serious issues. By mapping individuals at risk for impulsive behavioral traits at an early stage, it might be possible to prevent some of these unfortunate consequences.

We found that being examined for ADHD was associated with a diagnosis of JME, but only in females. High prevalence of ADHD in children and youths with epilepsy is well-documented [42], but to the best of our knowledge, an excess of ADHD in females with JME has not been demonstrated. There are parallels between the neuropsychological and behavioral traits now described in JME and those described in ADHD, including executive dysfunction, impulsivity, and risk-taking behavior [43]. Thus, it is not surprising that ADHD was suspected in some of the subjects with JME. That it was evident only in females could in part be explained by a higher general prevalence of ADHD in males [44]. The finding needs to be confirmed by formal clinical assessment; however, as it was based on self-reporting as opposed to standard instruments for diagnosing ADHD.

The high proportion of patients with JME confirming a biological parent with challenges like addiction or violent behavior has not been reported earlier. Two previous studies revealed that the neuropsychological deficits described in JME could also be detected in otherwise healthy siblings [45,46]. Hence, one might speculate whether the behavioral patterns of JME show heritable traits as well, perhaps representing an endophenotype with few or no apparent seizures in some cases. Moreover, myoclonic jerks are often subtle and go undetected by patients and even neurologists, unless they ask specifically, which they often forget to do [1]. When it comes to the psychosocial difficulties of JME, telling the difference between shared environmental factors and shared heredity is problematic, however.

The differences in use of levetiracetam between JMEs and controls could reflect that in regular clinical practice, levetiracetam is a less preferred or known drug when treating absences, while it is a better established treatment for JME [47]. The majority of the patients without JME in the present study had absence epilepsy. Higher mean age at inclusion in those with JME could also help explaining this finding, as females with GGE reaching fertile age are often switched from valproate, due to its teratogenic effects [48], to for instance levetiracetam. Given the adverse-effect profile of levetiracetam, we found that it is important to include this variable in the multivariate analysis. Levetiracetam is associated with psychiatric and behavioral issues like depression, irritability, and aggression [49–51], and the univariate analyses revealed a significantly higher rate of levetiracetam use in the group with JME. Consequently, this factor could have explained why psychosocial difficulties like police charges were more common in people with JME. However, even when controlling for use of levetiracetam, police charges remained in the regression model as a potential predictor of a diagnosis of JME.

A limitation of the present study is that it was based on a semi-structured questionnaire and self-reporting, as opposed to standardized instruments and validated tools. Hence, our findings must be considered hypothesis-generating and in need of confirmation and elaboration by further studies. Furthermore, the results were not compared to a healthy control group or a different type of epilepsy than GGE. We did not have the possibility to include more than one control group, however, and our aim was to investigate whether psychosocial complications were specific to JME, and not for instance, related to the stigma and social exclusion people with epilepsy may be exposed to [52]. Thus, except for not having JME, we attempted to include a control group as similar to the case group as possible (i.e., comparable EEG findings, disease duration, medication etc.) That we still found notable differences in psychosocial outcome between the two groups strengthens the hypothesis of a JME specific deficit in social functioning.

Another challenge to consider was recall bias. Self-reporting of seizures can be unreliable [53], especially when it comes to subtle seizures like absences and myoclonic jerks that happened years ago. Correct classification of JME was highly important in the present study and was aided by information from medical charts. However, the charts rarely contained information about myoclonic jerks, and we had to rely on self-reporting when it came to both frequency and chronodependency of such seizures. A prospective study with inclusion of patients at seizure onset would have resolved this issue, but was not compatible with the time frame and resources of the present study. The same limitations apply to our sample size, which was restricted to the maximum number of participants who we were able to identify within our particular region of Norway. Fourteen patients with CAE who were seizure-free >1 year and off antiepileptic drugs were excluded. We did so, assuming that patients who were seizure-free and off antiepileptic drugs when reaching youth would have an improved psychosocial prognosis

and could contribute to biased findings, i.e., exaggerating the association between psychosocial complications and JME. Excluding the 14 patients with CAE does not entirely explain that the case group was larger than the control group, however. As we included the maximum number of patients with GGE who we were able to identify and recruit, the imbalance probably illustrates that JME simply is more common than other types of GGE. Nevertheless, police charges and use of illicit recreational drugs did not completely reach statistical significance as predictors of belonging to the group with JME, even with 79% power to detect a significant difference in police charges, and 83% power to detect a significant difference in use of illicit recreational drugs. The effect size (Cohen's d) of both of these variables was modest, however. Collaboration across regions, or even across countries in order to achieve larger sample sizes, would greatly improve the quality of future JME research.

We did note, however, that the number of patients with EGTCS was lower than expected. The Osservatorio Regionale per l'Epilessia (OREp) group in Italy found 17% of all idiopathic generalized epilepsy to be JME, and 12% to be epilepsy with grand mal on awakening (i.e., EGTCS, but with a strict chronodependency of seizures). Eleven percent had JAE, and 25% had CAE [54]. The Coordination Active du Réseau Observatoire Longitudinal de l'Epilepsie (CAROLE) study from France found 19% of all idiopathic generalized epilepsy to be JME; 11% was JAE, and 33% was CAE. Only 2% was epilepsy with GTCS on awakening [55]. Both of the studies had a large group of "other idiopathic generalized epilepsy", which could comprise patients with GTCS only, but without morning predominance of seizures [54,55]. In the present study, the percentage of CAE was low, as people <14 years of age were excluded, in addition to people with CAE who were seizure-free >1 year and off antiepileptic drugs. The identification of just 15 patients with EGTCS in our study could be explained by the fact that we did not contact patients with GTCS only if their EEGs were normal, as this group could comprise both EGTCS and focal epilepsy. Without EEG findings, it would be difficult to differentiate them from each other. Consequently, they were classified as epilepsy of unknown etiology and not included in the group with GGE [30]. Moreover, absence of EEG findings could denote a milder type of epilepsy, and including these patients could have biased our results towards more complications in the group with JME. Another reason why previous studies found a larger proportion of epilepsy with GTCS only could be that myoclonic jerks were not inquired about specifically. When doing so, we found that several patients with GTCS as their only seizure type according to medical records in fact had JME [1].

In conclusion, to the best of our knowledge we present the most extensive study on the psychosocial issues of JME to date, adding weight to Dieter Janz's initial remarks about a JME-specific behavioral pattern [7,8]. Even though initially called a benign type of epilepsy [56], with intelligence within the normal range [3,11], reports of a satisfactory social life [25–28] and financial situation [27], potentially severe consequences of risk-taking behavior are associated with the diagnosis of JME. Thus, we believe that JME should be seen as a disorder of the brain in a broader sense than a "pure" epilepsy.

Acknowledgments

This work was supported by grants from Vestre Viken Hospital Trust, Norway (MS); the Canadian Institutes of Health Research: Biology of Juvenile Myoclonic Epilepsy (BIOJUME) (201503MOP-342469, DKP); European Union Seventh Framework Programme: Development of Strategies for Innovative Research to improve diagnosis, prevention and treatment in children with difficult to treat Epilepsy, "DESIRE" (602531, DKP); National Institute for Health Research Programme Grant for Applied Research: Changing Agendas on Sleep, Treatment and Learning in Epilepsy (CASTLE) RP-PG-0615-20007 (DKP); Medical Research Council (MRC) Centre grant (MR/N026063/1) (DKP); Waterloo Foundation Project Grant 164-3020 (DKP); Charles Sykes Epilepsy Research Trust (DKP); NIHR Specialist Biomedical Research Centre for Mental Health of South London and Maudsley NHS Foundation Trust (DKP). We thank the patients participating in this study, and we thank the Department of Clinical Research Support at Oslo University Hospital for advice on statistics and methodology.

Declaration of interests

Marte Syvertsen served on the advisory board of Eisai's epilepsy educational program and received speaker honoraria from Eisai. Kaja Selmer was an invited speaker at a seminary arranged by Kolfarma, and travel expenses were covered. The remaining authors have no conflicts of interest.

References

[1] Syvertsen M, Hellum MK, Hansen G, Edland A, Nakken KO, Selmer KK, et al. Prevalence of juvenile myoclonic epilepsy in people <30 years of age—a population-based study in Norway. Epilepsia 2017;58:105–12.
[2] Camfield CS, Striano P, Camfield PR. Epidemiology of juvenile myoclonic epilepsy. Epilepsy Behav 2013;28(Suppl. 1):S15–7.
[3] Kasteleijn-Nolst Trenite DG, Schmitz B, Janz D, Delgado-Escueta AV, Thomas P, Hirsch E, et al. Consensus on diagnosis and management of JME: from founder's observations to current trends. Epilepsy Behav 2013;28(Suppl. 1):S87–90.
[4] Pal DK, Durner M, Klotz I, Dicker E, Shinnar S, Resor S, et al. Complex inheritance and parent-of-origin effect in juvenile myoclonic epilepsy. Brain Dev 2006;28:92–8.
[5] Durner M, Keddache MA, Tomasini L, Shinnar S, Resor SR, Cohen J, et al. Genome scan of idiopathic generalised epilepsy: evidence for major susceptibility gene and modifying genes influencing the seizure type. Ann Neurol 2001; 49:328–35.
[6] Ottman R, Risch N. Genetic epidemiology and gene discovery in epilepsy. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, editors. Jasper's basic mechanisms of the epilepsies. 4th ed. Bethesda (MD): National Center for Biotechnology Information (US); 2012. p. 975–92.
[7] Janz D, Christian W. Impulsiv petit-mal. J Neurol 1957;176:346–86.
[8] Janz D. Juvenile myoclonic epilepsy. Epilepsy with impulsive petit mal. Cleve Clin J Med 1989;56(Suppl Pt 1):S23–33.
[9] Swartz BE, Halgren E, Simpkins F, Syndulko K. Primary memory in patients with frontal and primary generalized epilepsy. J Epilepsy 1994;7:232–41.
[10] Wolf P, Yacubian EM, Avanzini G, Sander T, Schmitz B, Wandschneider B, et al. Juvenile myoclonic epilepsy: a system disorder of the brain. Epilepsy Res 2015;114:2–12.
[11] Wandschneider B, Thompson PJ, Vollmar C, Koepp MJ. Frontal lobe function and structure in juvenile myoclonic epilepsy: a comprehensive review of neuropsychological and imaging data. Epilepsia 2012;53:2091–8.
[12] Knake S, Roth C, Belke M, Sonntag J, Kniess T, Krach S, et al. Microstructural white matter changes and their relation to neuropsychological deficits in patients with juvenile myoclonic epilepsy. Epilepsy Behav 2017;76:56–62.
[13] Walsh J, Thomas RH, Church C, Rees MI, Marson AG, Baker GA. Executive functions and psychiatric symptoms in drug-refractory juvenile myoclonic epilepsy. Epilepsy Behav 2014;35:72–7.
[14] de Araújo Filho GM, Pascalicchio TF, Sousa Pda S, Lin K, Ferraira Guilhoto LM, Yacubian EM. Psychiatric disorders in juvenile myoclonic epilepsy: a controlled study of 100 patients. Epilepsy Behav 2007;10:437–41.
[15] Trinka E, Kienpointner G, Unterberger I, Luef G, Bauer G, Doering LB, et al. Psychiatric comorbidity in juvenile myoclonic epilepsy. Epilepsia 2006;47:2086–91.
[16] Vollmar C, O'Muircheartaigh J, Symms MR, Barker GJ, Thompson P, Kumari V, et al. Altered microstructural connectivity in juvenile myoclonic epilepsy: the missing link. Neurology 2012;78:1555–9.
[17] O'Muircheartaigh J, Vollmar C, Barker GJ, Kumari V, Symms MR, Thompson P, et al. Abnormal thalamocortical structural and functional connectivity in juvenile myoclonic epilepsy. Brain 2012;135:3635–44.
[18] O'Muircheartaigh J, Vollmar C, Barker GJ, Kumari V, Symms MR, Thompson P, et al. Focal structural changes and cognitive dysfunction in juvenile myoclonic epilepsy. Neurology 2011;76:34–40.
[19] Bechara A, Van Der Linden M. Decision-making and impulse control after frontal lobe injuries. Curr Opin Neurol 2005;18:734–9.
[20] Carlen M. What constitutes the prefrontal cortex? Science 2017;358:478–82.
[21] Wandschneider B, Centeno M, Vollmar C, Stretton J, O'Muircheartaigh J, Thompson PJ, et al. Risk-taking behavior in juvenile myoclonic epilepsy. Epilepsia 2013;54: 2158–65.
[22] Zamarian L, Hofler J, Kuchukhidze G, Delazer M, Bonatti E, Kemmler G, et al. Decision making in juvenile myoclonic epilepsy. J Neurol 2013;260:839–46.
[23] Moschetta S, Valente KD. Impulsivity and seizure frequency, but not cognitive deficits, impact social adjustment in patients with juvenile myoclonic epilepsy. Epilepsia 2013;54:866–70.
[24] Victor SE, Johnson SL, Gotlib IH. Quality of life and impulsivity in bipolar disorder. Bipolar Disord 2011;13:303–9.
[25] Camfield CS, Camfield PR. Juvenile myoclonic epilepsy 25 years after seizure onset: a population-based study. Neurology 2009;73:1041–5.
[26] Schneider-Von Podewils F, Gasse C, Geithner J, Wang ZI, Bombach P, Berneiser J, et al. Clinical predictors of the long-term social outcome and quality of life in juvenile myoclonic epilepsy: 20–65 years of follow-up. Epilepsia 2014;55:322–30.
[27] Holtkamp M, Senf P, Kirschbaum A, Janz D. Psychosocial long-term outcome in juvenile myoclonic epilepsy. Epilepsia 2014;55:1732–8.

[28] Syvertsen MR, Thuve S, Stordrange BS, Brodtkorb E. Clinical heterogeneity of juvenile myoclonic epilepsy: follow-up after an interval of more than 20 years. Seizure 2014;23:344–8.
[29] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7.
[30] Syvertsen M, Nakken KO, Edland A, Hansen G, Hellum MK, Koht J. Prevalence and etiology of epilepsy in a Norwegian county-a population based study. Epilepsia 2015;56:699–706.
[31] Thurman DJ, Beghi E, Begley CE, Berg AT, Buchhalter JR, Ding D, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 2011;52(Suppl. 7): 2–26.
[32] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–21.
[33] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389–99.
[34] Cross CP, Copping LT, Campbell A. Sex differences in impulsivity: a meta-analysis. Psychol Bull 2011;137:97–130.
[35] Tabachnick BG, Fidell LS. Multiple regression. In: Tabachnick BG, Fidell LS, editors. Using multivariate statistics. 6th ed. Boston: Pearson Education; 2013. p. 153–234.
[36] Hasselblad V, Hedges LV. Meta-analysis of screening and diagnostic tests. Psychol Bull 1995;117:167–78.
[37] Division of Health Informatics & Surveillance (DHIS), Center for Surveillance, Epidemioloy and Laboratory Services (CELS). Epi Info™. https://www.cdc.gov/epiinfo/index.html, Accessed date: 9 October 2018.
[38] Garcia-Marchena N, Ladron de Guevara-Miranda D, Pedraz M, Araos PF, Rubio G, Ruiz JJ, et al. Higher impulsivity as a distinctive trait of severe cocaine addiction among individuals treated for cocaine or alcohol use disorders. Front Psychiatry 2018;9:26.
[39] Patton J, Stanford M, Barratt E. Factor structure of the Barratt impulsiveness scale. J Clin Psychol 1995;51:768–74.
[40] Skretting A, Bye EK, Vedøy TF, Lund KE. Rusmidler i Norge 2016. [Drugs in Norway 2016]. Norwegian Institute of Public Health; 2016.
[41] Statistics Norway. Sanctions, by type of sanction, age and sex. https://www.ssb.no/en/sosiale-forhold-og-kriminalitet/statistikker/straff; 2017, Accessed date: 2 October 2018.
[42] Alfstad KA, Clench-Aas J, Van Roy B, Mowinckel P, Gjerstad L, Lossius MI. Psychiatric symptoms in Norwegian children with epilepsy aged 8–13 years: effects of age and gender? Epilepsia 2011;52:1231–8.
[43] Rubia K, Alegria A, Brinson H. Imaging the ADHD brain: disorder-specificity, medication effects and clinical translation. Expert Rev Neurother 2014;14:519–38.
[44] Rubia K. Cognitive neuroscience of attention deficit hyperactivity disorder (ADHD) and its clinical translation. Front Hum Neurosci 2018;12:100.
[45] Iqbal N, Caswell H, Muir R, Cadden A, Ferguson S, Mackenzie H, et al. Neuropsychological profiles of patients with juvenile myoclonic epilepsy and their siblings: an extended study. Epilepsia 2015;56:1301–8.
[46] Wandschneider B, Kopp UA, Kliegel M, Stephani U, Kurlemann G, Janz D, et al. Prospective memory in patients with juvenile myoclonic epilepsy and their healthy siblings. Neurology 2010;75:2161–7.
[47] Crespel A, Gelisse P, Reed RC, Ferlazzo E, Jerney J, Schmitz B, et al. Management of juvenile myoclonic epilepsy. Epilepsy Behav 2013;28(Suppl. 1):S81–6.
[48] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, et al. Dose-dependent teratogenicity of valproate in mono- and polytherapy: an observational study. Neurology 2015;85:866–72.
[49] Verrotti A, Prezioso G, Di Sabatino F, Franco V, Chiarelli F, Zaccara G. The adverse event profile of levetiracetam: a meta-analysis of children and adults. Seizure 2015;31:49–55.
[50] Halma E, de Louw AJ, Klinkenberg S, Aldenkamp AP, Ijff DM, Majoie M. Behavioral side-effects of levetiracetam in children with epilepsy: a systematic review. Seizure 2014;23:685–91.
[51] Chen B, Choi H, Hirsch LJ, Katz A, Legge A, Buchsbaum R, et al. Psychiatric and behavioral side effects of antiepileptic drugs in adults with epilepsy. Epilepsy Behav 2017; 76:24–31.
[52] Fiest KM, Birbeck GL, Jacoby A, Jette N. Stigma in epilepsy. Curr Neurol Neurosci Rep 2014;14:444.
[53] Kerling F, Mueller S, Pauli E, Stefan H. When do patients forget their seizures? An electroclinical study. Epilepsy Behav 2006;9:281–5.
[54] Osservatorio Regionale per l'Epilessia (OREp) Lombardy. ILAE classification of epilepsies: its applicability and practical value of different diagnostic categories. Epilepsia 1996;37:1051–9.
[55] Jallon P, Loiseau P, Loiseau J. Newly diagnosed unprovoked epileptic seizures: presentation at diagnosis in CAROLE study. Epilepsia 2001;42:464–75.
[56] Asconape J, Penry JK. Some clinical and EEG aspects of benign juvenile myoclonic epilepsy. Epilepsia 1984;25:108–14.