Epidemiology of epilepsy in Buskerud County

emphasising clinical and psychosocial aspects of juvenile myoclonic epilepsy

Doctoral thesis by
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Summary

The present doctoral project investigated prevalence and aetiology of epilepsy in Buskerud County, Norway, with special emphasis on clinical and psychosocial aspects of juvenile myoclonic epilepsy. By means of a systematic review of medical records with a diagnostic code of epilepsy at Drammen Hospital (1999-2013), 1771 individuals with active epilepsy were identified (prevalence 0.65%), of which 56% had an unknown cause of epilepsy.

After contacting people with a registered diagnosis of genetic generalized epilepsy and specifically inquiring about the hallmark symptom of juvenile myoclonic epilepsy (myoclonic jerks), we estimated prevalence of juvenile myoclonic epilepsy to be 5.6/10,000. More than one third of those who fulfilled the diagnostic criteria of juvenile myoclonic epilepsy were previously undiagnosed because they had not mentioned their myoclonic jerks.

The pathophysiological process of juvenile myoclonic epilepsy is unknown, but it is believed to involve mechanisms within networks of the frontal lobe, areas of the brain which are important to decision-making and impulse control. When interviewing 92 patients with juvenile myoclonic epilepsy and 45 patients with other types of genetic generalized epilepsy, we found that those with juvenile myoclonic epilepsy had significantly higher rates of risk-related issues, like use of illicit recreational drugs, police charges, underage smoking, and self-withdrawal of antiepileptic drugs. They also had higher rates of being a victim of violence or abuse. In a logistic regression model, having a parent with psychosocial problems like addiction or violent behaviour was a significant predictor of being diagnosed with juvenile myoclonic epilepsy as opposed to another type of genetic generalized epilepsy. In females, being examined for attention deficit hyperactivity disorder was also a significant predictor of belonging to the juvenile myoclonic epilepsy group.

When analysing results from the Barratt Impulsiveness Scale, a standardized measure of behavioural impulsivity, we found that myoclonic jerks within the last year was a significant moderator of total impulsivity score, irrespective of epilepsy syndrome. Post hoc tests revealed that those who had myoclonic jerks within the last year had a significantly higher score, i.e. they were more impulsive, than those who did not have such seizures within the last year. Consequently, we question whether it is the presence of the hallmark symptom of juvenile myoclonic epilepsy, rather than the diagnosis per se, that is associated with impulsive behaviour.

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Preface

The following work was commenced on the initiative of the doctoral candidate, in co-operation with Jeanette Koht and Karl Otto Nakken. The research questions and study design were developed by the doctoral candidate, as was the practical implementation and organising of the study. The present project constitutes the foundation of Drammen Hospital Epilepsy Research Group, which has grown to five members during the project period, including three doctoral candidates. We are grateful to the Department of Neurology for allowing us to develop a research environment in close proximity to a large and representative group of patients with complex needs, and we look forward to future projects.

Drammen, January 2019
Marte Roa Syvertsen

Acknowledgements

The present study was carried out at the Department of Neurology, Drammen Hospital during 2013-2018. Research results are the products of intricate teamwork, and so, there are many indispensable people to thank along the way.

First of all, I would like to thank my supervisor, Jeanette Koht. It is doubtless that none of this would have happened without you. Believing in this project from the very beginning, you have been a guide, helper and a role model throughout a seemingly endless amount of applications, rejections, and disappointments. Likewise, you know how to celebrate when celebration is needed. I will always keep the five champagne corks of this thesis with me, and I thank you for introducing me to the French way of rejoicing accepted papers.

I thank my co-supervisor Kaja Selmer, who saw the potential in our work and enabled the very important collaboration with the BIOJUME research group. I would also like to thank you for invaluable advice on research methods and writing, and for always being available, with a smile to go. Your enthusiasm and positivity affects the people around you and makes us want to keep on working, in order to get one step closer to the answers we are looking for. Thank you Kaja, and thank you Jeanette. Our work has been inspiring, and I hope it will continue far beyond this doctoral thesis.

The next person to thank, who should perhaps have been the first, is Karl Otto Nakken. You are my epileptology role model, as you are for several others within this field. Your genuine care for the *people* you meet is inspiring, as is your extensive knowledge and experience. A nod from you meant a lot as an inexperienced doctor at The National Centre for Epilepsy, and it still does. Thank you for asking me, at the end of my stay at The National Centre, if I would like to look into juvenile myoclonic epilepsy. You said it would be interesting, and you were right.

An equally important role model is Eylert Brodtkorb. Thank you Eylert, for introducing me to the field of epileptology in such a fascinating way during my years at medical school. You are a worthy mentor of epilepsy research and epilepsy care in Norway, and I am proud to have been your student. Thank you for giving me the opportunity to work with juvenile myoclonic epilepsy in Trondheim at the initiation of my doctoral period. That formed an important base

and starting point for the interviews we conducted later. And thank you for making me take a photo with Dieter Janz.

I owe many thanks to Kristoffer Hellum and Gunnar Hansen for supervising my EEG-studies during the project period, and to Hege Rødby Larsen, Hilde Bjerknes Friberg, Lene Meinich, and Trude Heigrestad at the EEG-laboratory for being such great company in an otherwise quite lonely time.

I thank Astrid Edland, former head of the Department of Neurology, for making it possible to build a research environment from scratch. I thank Mai Bente Myrvold for the same reason, and Mette Bergum for continuing Astrid's work when she retired.

A big thank you must also be directed to Anna Smith, neuropsychologist at King's College London, and Deb Pal, head of the BIOJUME research group, King's College London. Thank you for welcoming me in such a generous way when I came to visit, first with all my ideas, and then with all my data. You have raised the quality of this project in a way that would not have been possible without you. I am proud to be a part of the BIOJUME team, and I hope to be able to contribute more in the months to come.

I am also very grateful for the excellent collaboration with Ida Fløgstad and Cecilie Johannessen Landmark on antiepileptic drug use in juvenile myoclonic epilepsy. Thank you Cecilie, for your major contribution to Paper III, and thank you Ida, for all the work you did and your superb master thesis.

I thank Ulla Enger, who played a key role during the recruitment and conduction of the clinical interviews. Without your company and aid, the study might only have reached half of its present size. I also thank Mari Wold Henriksen for nice company during the periods of writing, analysing and statistics, and for "skolebrød" when things looked gloomy.

I thank the Norwegian Epilepsy Association (NEF) for a very productive collaboration throughout the project, and I thank all the participants of the study in particular. It goes without saying that clinical research cannot be conducted without the contribution of participants. We hope to be able to bring a small step of progress in return.

Lastly, I thank my enduring and supportive family. A special thank you goes to my mother, Bente Roa Syvertsen, for introducing me to the world of books and reading, and for always being there when I am not. Thank you Kjersti Solum, for a thorough proof-read of this work,

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Drammen, January 2019
Marte Roa Syvertsen

Abbreviations

AED	Antiepileptic drug(s)
ADHD	Attention deficit hyperactivity disorder
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BIS	Barratt Impulsiveness Scale
CAE	Childhood absence epilepsy
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
EFHC1	EF-hand domain containing 1
EGTCS	Epilepsy with generalized tonic clonic seizures alone
FA	Fractional anisotropy
GABA	Gamma-aminobutyric acid
GABRA1	Gamma-aminobutyric acid type A receptor alpha1 subunit
GGE	Genetic generalized epilepsy
GTCS	Generalized tonic clonic seizure(s)
HADS	Hospital Anxiety and Depression Scale
IGE	Idiopathic generalized epilepsy
ICD-10	International Classification of Diseases, 10^{th} Revision
ILAE	The International League Against Epilepsy
JAE	Juvenile absence epilepsy
JME	Juvenile myoclonic epilepsy
MRI	Magnetic resonance imaging
VBM	Voxel-based morphometry
SMA	Supplementary motor area

List of publications

The thesis is based on the following original articles:

I. 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.

II. Syvertsen M, Hellum MK, Hansen G, Edland A, Nakken KO, Selmer KK, Koht J. Prevalence of juvenile myoclonic epilepsy in people < 30 years of age – a population based study in Norway. Epilepsia 2017;58:105-112.

III. Syvertsen M, Fløgstad I, Enger U, Landmark CJ, Koht J. Antiepileptic drug withdrawal in juvenile myoclonic epilepsy. Acta Neurologica Scandinavica 2019;139:192-198.

IV. Syvertsen M, Selmer K, Enger U, Nakken KO, Pal DK, Smith A, Koht J. Psychosocial complications in juvenile myoclonic epilepsy. Epilepsy & Behavior 2019;90:122-128.

V. Syvertsen M, Koht J, Selmer K, Enger U, Pal DK, Smith A. Behavioral impulsivity correlates with active myoclonic jerks in genetic generalized epilepsy. Manuscript submitted to Journal of Neurology, Neurosurgery, and Psychiatry, 16th Jan. 2019.

1 Introduction

1.1 Epilepsy

Epilepsy is one of the most common disorders affecting the central nervous system (1). In epidemiological research, it is normally defined as two or more unprovoked epileptic seizures occurring > 24 h apart (2, 3), and an epileptic seizure is defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (4).

Anything disturbing the electrical communication between the cell-bodies in the cerebral cortex could trigger an epileptic seizure. Thus, epilepsy has a wide spectrum of causes ranging from genetic mutations and molecular changes, to brain tumours, neurodevelopmental disorders, and scarring following stroke. The clinical manifestations and complications of epilepsy vary equally, comprising an extensive range of seizure types and comorbidities. Seizures may occur at any age, even prenatally, as damage to the central nervous system could take place at any stage of the life span. Thus, epilepsy affects new-born babies, adolescents, adults, and the elderly alike (5).

1.1.1 **The burden of epilepsy**

In a person with epilepsy, seizures may be triggered by identifiable factors like sleep deprivation, stress or even quite specific stimuli like music or visual patterns. The latter is called reflex epilepsy and can sometimes be controlled if avoidance of the triggering stimulus is possible (6). In most cases, however, the seizures occur independently of triggers and without warning. Some seizures manifest as altered behaviour, often with impaired awareness and inability to respond adequately. These symptoms are often not recognized as a seizure by the surroundings, and the episode may be embarrassing and compromising to the patient. In the case of a generalized tonic clonic seizure (GTCS), the symptoms are usually acknowledged as epileptic, but often give rise to considerable distress and fright in bystanders. Living with epilepsy means living without knowing when the next seizure will strike. In a clinical setting, our experience is that patients often describe losing control over their body as the worst part of the disorder. Symptoms of anxiety are overrepresented in the

epilepsy population, as are symptoms of depression, both of which influence the patients' quality of life to a greater extent than the seizures per se (7-10).

Additionally, the stigma of epilepsy is still very much present, even in societies with high standards of living and education (11, 12). People with epilepsy experience exclusion at work, in friendships, and in social activities. Sometimes this is caused by the patient's internal anxiety and an autonomous decision to stay away, but it may just as often be caused by the surroundings' anxiety of seizures, resulting in more or less deliberate exclusion (12).

All in all, epilepsy affects much broader aspects of life than seizures and medication alone. It influences choice of education and occupation, ability to work, and lastly acceptance and inclusion at work (13). It influences social and romantic relations, families and friends (14, 15). Consequently, a multi-disciplinary approach is of the utmost importance to the follow-up and care for people with epilepsy (16, 17).

1.1.2 **The epidemiology of epilepsy**

Considering the complexity of challenges related to the diagnosis of epilepsy and the heterogeneity of the epilepsy population, detailed knowledge about background, composition and magnitude of this population is highly important when planning and providing its health care. Investigating prevalence and incidence of epilepsy is not straight-forward, however. Firstly, prevalence and incidence of epilepsy varies with geography, age, and socio-economic status. The most apparent reason for this variation is that common causes of epilepsy, such as head injuries and perinatal complications, are influenced by factors like socio-economic status and age (18). Thus, there is a need for detailed epidemiological mapping of epilepsy from a wide variety of sources (19, 20). When local authorities plan for epilepsy care in their region, they should consult epidemiological data from a source as close to their target population as possible, preferably from the population itself.

Moreover, epidemiological research of epilepsy is hampered by bias. Studies based on registered diagnostic codes of epilepsy may over-estimate prevalence by as much as 20% (21). Hence, listed diagnostic codes of epilepsy in hospital records and national patient registries are often inaccurate. Population-based surveys and door-to-door investigations are vulnerable to low response rates and selection bias, and stigma may contribute to under-reporting. Thus, the identification and inclusion of patients in epidemiological studies of

epilepsy has varied considerably, as has the definition of epilepsy. Consequently, The International League Against Epilepsy (ILAE) issued international guidelines in 2011, aiming for a more homogenous approach to epidemiological epilepsy research (3).

When it comes to prevalence of epilepsy in the Nordic countries, this ranges from 0.34 to 0.76%, with considerable variation in methods and definitions (22-27). Studies of epilepsy incidence are rarer, as the gold standard would be a prospective approach. Such studies require more resources and are often difficult to conduct in practice. A prospective study from Iceland reported 33 new cases of epilepsy per 100,000 person years, and in Sweden the number of new epilepsy cases per 100,000 person years was 34 (28, 29).

1.1.3 **The causes of epilepsy**

The causes of epilepsy vary with age, geography and socioeconomic status, which is reflected by the variation in prevalence and incidence of epilepsy across different countries, regions, and age groups (18, 30). In the youngest, structural causes due to perinatal complications dominate (31). In the oldest age group, brain stroke is a leading cause of epilepsy, followed by neoplasia (32), whilst traumatic brain injury is more frequent in men (33). All in all, structural aetiologies are common, meaning that a focal seizure-causing brain lesion has been found (5). It is striking, however, that we fail to identify the cause of epilepsy in a very large proportion of patients. If accepting that the epilepsies formerly categorized as idiopathic generalized epilepsy (IGE), now usually referred to as genetic generalized epilepsy (GGE), in fact have no established cause either, the "unknown" group when it comes to aetiology comprises a surprisingly large amount of patients. In a population-based Icelandic study from 1999, 62% of the patients had epilepsy of unknown cause (26), whilst the figure was 65% in a Swedish study from 1992 (34). In Spain, the rate of unexplained epilepsy was 69% in 2001 (35), and in a study from the Aeolian Islands in Italy, the rate was as high as 87% in 2005 (36). One should think that the recent boom in genetic research and the development of sophisticated imaging tools would contribute to an increased number of "solved" epilepsy cases. In order to investigate whether this is the case, we are in need of updated epidemiological studies.

1.1.4 **The classification of epilepsy**

How to name and classify seizures and epilepsy has been under constant debate, reflecting the heterogeneity of the condition, but also its cultural impact. Until very recently, the

classifications in use were the ones issued by ILAE in 1981 and 1989. The 1989 classification of epilepsies and epileptic syndromes divided aetiology of epilepsy into three broad categories; idiopathic, symptomatic, and cryptogenic (37). Several suggestions for revised classifications have been proposed since then, all of which have been criticised and/or discarded. Finally, in 2010, ILAE issued an updated proposal for revised terminology for organisation of seizures and epilepsies. This proposal was largely adopted by the society of epilepsy researchers and clinicians (5). The latest proposal opted for clarification and simplification. In practice, according to the 1989 classification, "idiopathic" denoted a condition in which epilepsy was thought to be genetic, but where the genetic cause was not yet identified. Cryptogenic, on the other hand, denoted a suspected, but not yet identified, structural cause. The 2010 proposal suggested to replace "idiopathic" with "genetic", and to replace "symptomatic" with "structural-metabolic". Epilepsy of unknown cause should simply be classified as "unknown" (5).

1.1.5 **The classification of epileptic seizures**

The ILAE 1981 classification of epileptic seizures replaced the older terms "grand mal and "petit mal" with GTCS and absence seizures (38). Both in the 1981 and in the 2010 classification of epileptic seizures, the seizure types are broadly named generalized or focal. Focal seizures originate in a certain area of the brain. They are often caused by a local lesion in the same region, for instance a tumour or scar tissue. Seizure semiology will reflect the functions of the affected cerebral cortex. For instance, focal seizures starting in the motor cortex controlling the arm will cause twitching of that arm. Focal seizures starting in the visual cortex could give rise to simple visual hallucinations, like coloured circles (5, 38).

Generalized seizures, on the other hand, have no identifiable seizure focus in the cerebral cortex. They were initially thought to affect the cortex as a whole (38). However, the 2010 classification defines generalized seizures as originating within and spreading rapidly throughout bilateral neuronal networks (5).

Neither the 1989 classification nor the 2010 classification refer to generalized or focal as a classification of epilepsy *type*. Focal or generalized seizures can arise in idiopathic/genetic, symptomatic/structural-metabolic, or cryptogenic/unknown epilepsy alike. Nevertheless, presence of both generalized onset and focal onset seizures in the same patient is very rare.

Consequently, the majority of epilepsies could be named focal or generalized, irrespective of aetiology.

1.2 Generalized epilepsy

1.2.1 The seizure types of generalized epilepsy

The most typical generalized seizure type is a GTCS occurring without warning, reflecting rapid spread of epileptic discharges throughout bilateral neuronal networks (Figure 1) (5). A GTCS begins with sudden loss of consciousness and a tonic phase, in which all muscles contract. This is followed by a clonic phase, in which there is generalized twitching of the muscles causing rhythmical, bilateral jerking of the body and extremities. The seizure normally lasts for one to three minutes, and is followed by a prolonged post-ictal phase dominated by lethargy, headache and sometimes amnesia (39).

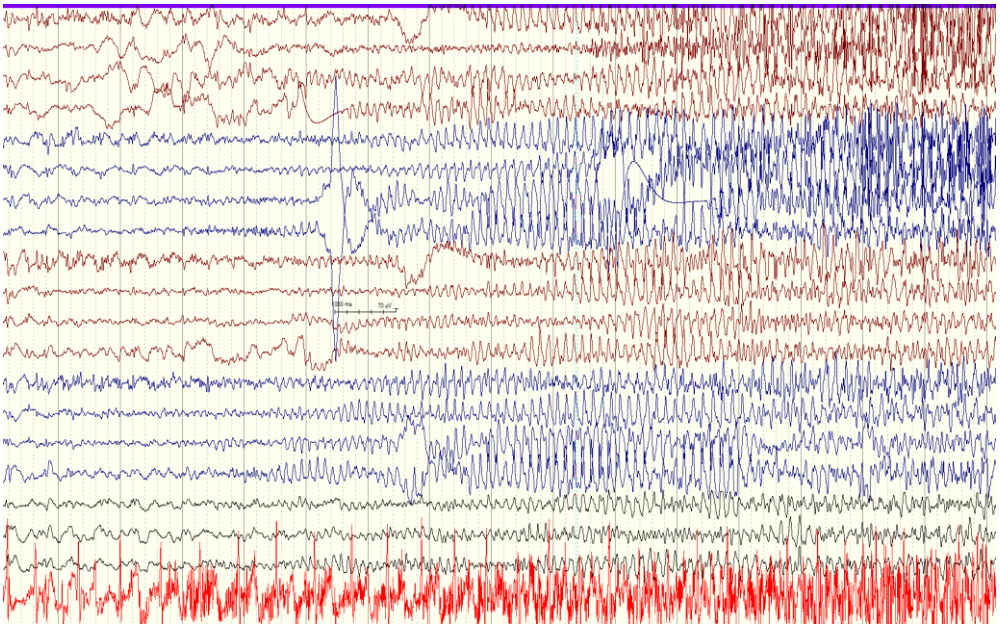

Figure 1. *EEG showing the onset of the tonic phase of a GTCS in a patient with JME (500μV/cm) (Marte Syvertsen/Kristoffer Hellum).*

Another common seizure type in generalized epilepsy is absences. Absence seizures cause an arrest in speech and/or activity, and generally last for a few seconds. They are subtle and sometimes very short, and therefore may go undetected. The ictal electroencephalogram (EEG) shows a very typical 3 hz spike- and wave pattern (Figure 2), which is thought to be generated by the thalamus (39).

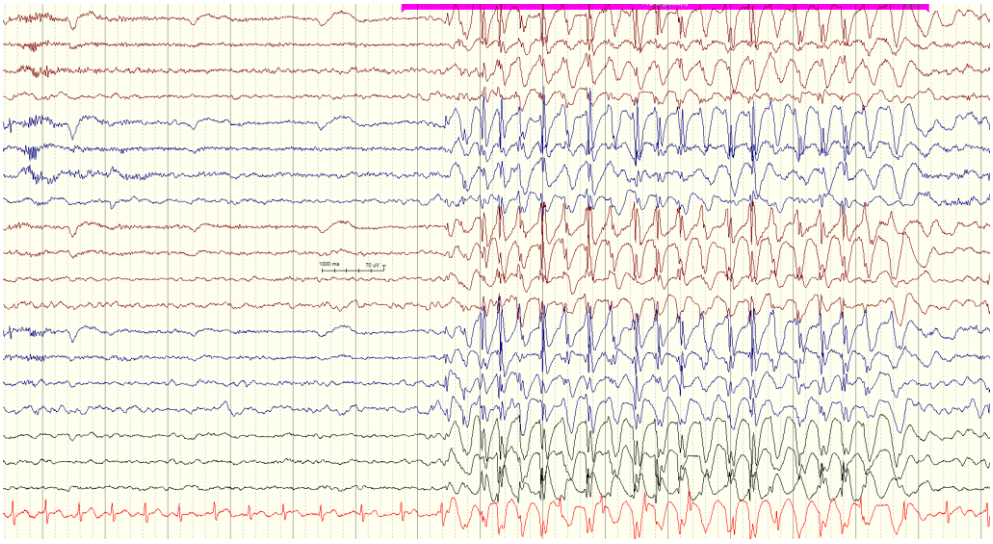

Figure 2. *EEG from a patient with CAE evolving to JME, showing an absence seizure with the typical 3 hz spike- and wave pattern (100μV/cm) (Marte Syvertsen/Gunnar Hansen).*

A myoclonic seizure is a generalized seizure which is too brief to affect awareness. In the EEG, it is accompanied by a generalized discharge of spike- and wave activity, often with irregular polyspikes (Figure 3). The symptom is a sudden muscular jerk, usually symmetrically in the proximal part of the upper extremities. It may affect the lower extremities as well, potentially causing falls and/or stumbling. Myoclonic seizures may also affect the muscles of the face, particularly the eyelids. Eyelid myoclonia is sometimes an accompanying symptom of absence seizures (39).

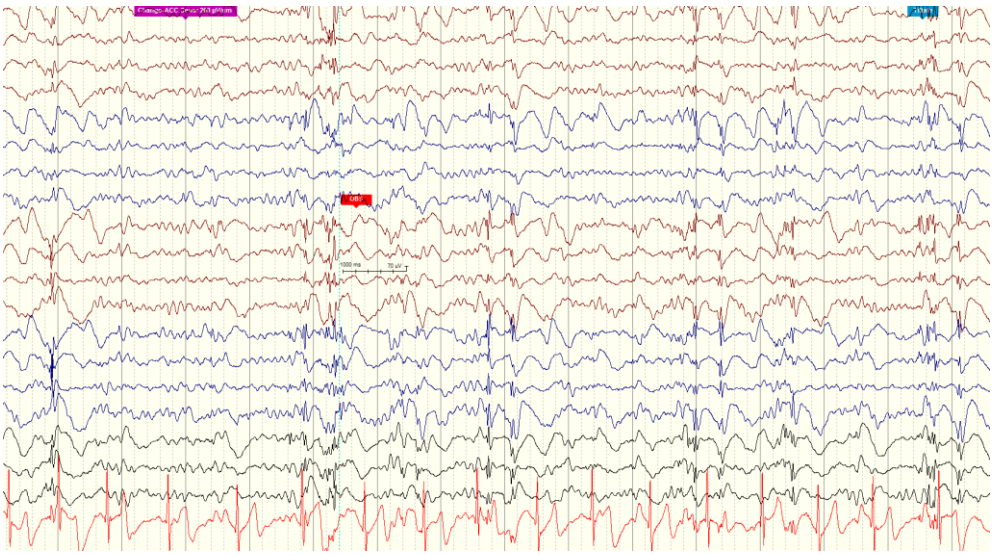

Figure 3. *EEG during a myoclonic seizure in a patient with JME. The myoclonic jerk is preceded by a short series of polyspikes, and the jerk coincides with the slow wave, where the red marker is placed (300μV/cm). (Marte Syvertsen/ Kristoffer Hellum).*

Other generalized seizure types include tonic seizures and atonic seizures, which are often associated with more severe types of epilepsy. A tonic seizure is equal to the initial part of a GTCS, although the seizure mechanism is thought to be different. In atonic seizures, there is a sudden, generalized loss of muscle tone making the body collapse, sometimes causing major injury (39).

1.2.2 **The epidemiology of generalized epilepsy**

The rate of epilepsy classified as generalized varies across different studies. Joenson reported 38% in a population based study at the Faroes in 1986 (25), and the Aeolian Island study from 2005 found exactly the same (38%) (36). A population based study from Iceland (1999), found that as much as 63% of all epilepsy was generalized (26), and in an Italian door-to-door study from 2001 it was 74% (40). In Sweden, the figure was 32%, including adults only (34).

1.2.3 **Electroclinical syndromes of generalized epilepsy**

The electroclinical epilepsy syndromes are often referred to as the highest level of precision in the clinical diagnostics of epilepsy. An electroclinical epilepsy syndrome encompasses patients with the same electroclinical picture. This means that key features like age of onset, seizure types, and prognosis are shared, and that EEG findings are generally the same. The list of electroclinical epilepsy syndromes is long, and it is usually organised according to age of seizure onset (5, 41). In generalized epilepsy, the most common electroclinical epilepsy syndromes are childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic clonic seizures alone (EGTCS). Other examples of generalized electroclinical epilepsy syndromes are Dravet syndrome, myoclonic epilepsy in infancy, epilepsy with myoclonic atonic seizures, and progressive myoclonus epilepsy (5).

1.2.4 **Genetic generalized epilepsy**

GGE is an umbrella term comprising electroclinical epilepsy syndromes characterized by generalized spike- and wave discharges in the EEG, giving rise to generalized epileptic seizures, namely GTCS, absences, and myoclonic jerks. Sleep-deprivation often triggers seizures in people with GGE, as does photic stimulation. A large proportion of GGE patients have a positive family history of epilepsy (39, 42). Hence, the GGEs were referred to as IGEs in the 1989 classification, the term “idiopathic” denoting a probable genetic origin. As mentioned above (1.1.4), “idiopathic” was replaced by “genetic” in the 2010 classification proposal (5). The outcome of GGE was thought to be favourable, with a generally good response to treatment and a lack of accompanying neurological deficits (37).

Not all generalized epilepsy fall into the GGE category. In the Faroe Island study, we noted that 38% of all epilepsy was generalized. In the same study, 35% of all epilepsy was classified

as IGE (25). In a study of newly diagnosed epilepsy in France (the CAROLE Study), 34% of all epilepsy was classified as generalized, and 27% of all epilepsy was IGE (43). Hence, GGE constitutes the majority of generalized epilepsy. Generalized epilepsy can also be symptomatic, however, and in some cases give rise to a more severe clinical picture, like the Lennox-Gastaut syndrome (43).

There has been some disagreement as to which electroclinical epilepsy syndromes should be included in the term GGE. However, it is beyond discussion that the core of GGE is constituted by CAE, JAE, JME, and EGTCS. Some authors will also include myoclonic epilepsy in infancy (39, 42, 43), epilepsy with myoclonic atonic seizures (39, 42), genetic epilepsy with febrile seizures plus (GEFS+) (42), and epilepsy with myoclonic absences (39, 42), though the latter syndromes are rare and would only make up a small part of the GGE spectrum (43, 44).

Of the four most typical GGE syndromes, CAE has the earliest debut, at four to ten years of age. It is characterized by absence seizures with the typical 3 hz spike- and wave EEG-pattern, which can often be seen in relation to hyperventilation. People with CAE may experience GTCS, and CAE may evolve into JAE or JME in adolescence. JAE and JME differ from each other in that absence seizures is the main feature of JAE, and myoclonic seizures is the main feature of JME. Moreover, people with JME tend to have seizures in the morning, whilst chronodependency of seizures is less evident in JAE. Both demonstrate generalized spike- and wave discharges in the EEG, but of a more irregular kind than the typical 3 hz pattern seen in CAE. People with EGTCS do not have absences and/or myoclonic jerks, but suffer from GTCS only, often in relation to awakening (39, 42). The seizure types of the GGE spectrum are illustrated by Figure 4. Absences is the main seizure type in CAE, but GTCS may occur, and some patients develop myoclonic jerks in youth. If myoclonic jerks become the dominating seizure type in youth, CAE has evolved into JME. As previously mentioned, myoclonic jerks dominate in JME, but GTCS are often present as well and about 1/3 has absences. In JAE absences dominate, but GTCS and myoclonic jerks may occur. Patients with EGTCS do not experience absences or myoclonic jerks. They have GTCS only, as the name indicates.

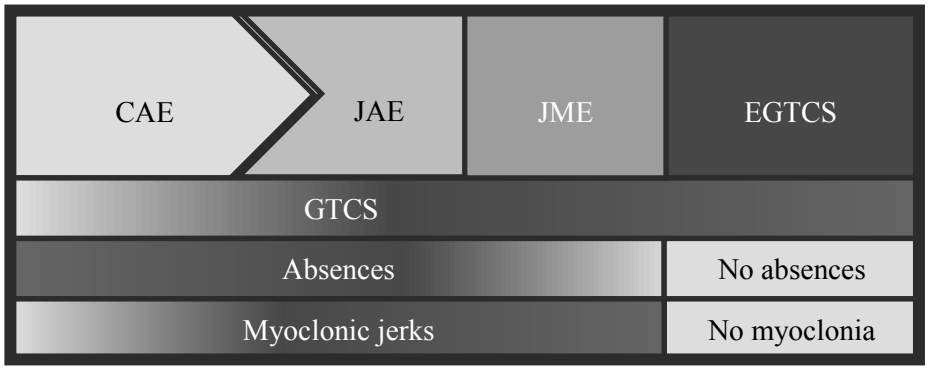

Figure 4. *Seizure types of the genetic generalized epilepsy (GGE) spectrum. Childhood absence epilepsy (CAE) may evolve to juvenile absence epilepsy (JAE) or juvenile myoclonic epilepsy (JME). EGTCS= Epilepsy with generalized tonic clonic seizures alone. GTCS=Generalized tonic clonic seizures. For the seizure types, light colour indicates few or no seizures, dark colour indicates frequent seizures (Marte Syvertsen).*

1.3 Juvenile myoclonic epilepsy

1.3.1 **Historical aspects**

The clinical picture of JME was first described by Théodore Herpin in "Des Accès Incomplets d'Épilepsie," published posthumously in 1867. Herpin mentioned patients who experienced brief, electric shock-like jerks, making them drop objects from their hands or even throw the object involuntarily (45, 46). It was not until 90 years later, however, that Dieter Janz (Figure 5) in collaboration with Walter Christian published the now famous series of 47 patients with a condition they named "impulsive petit mal," after the sudden jerks these patients experienced (47). The term "juvenile myoclonic epilepsy" was first used by Mogens Lund in Denmark in 1975, in an article focusing on psychosocial challenges (48). However, Janz and Christian's publications in German, and Lund's publications in Danish did not receive much attention internationally. The first two English-language articles regarding JME were published 27 years after the original work by Janz and Christian (49, 50). JME was included in ILAE's classification of the epilepsies in 1989 (37), 122 years after Herpin's initial descriptions.

Insight into the historical background and long road to recognition of JME as an electroclinical epilepsy syndrome is of importance when it comes to epidemiological research. Bearing in mind that JME was little known prior to the mid-eighties, patients with an earlier onset of epilepsy, i.e. older patients, will most likely not have been diagnosed with JME, but

been given an unspecific diagnosis of epilepsy instead, or IGE/GGE at best. Hence, the older the patients are, the less of them will have a confirmed diagnosis of JME.

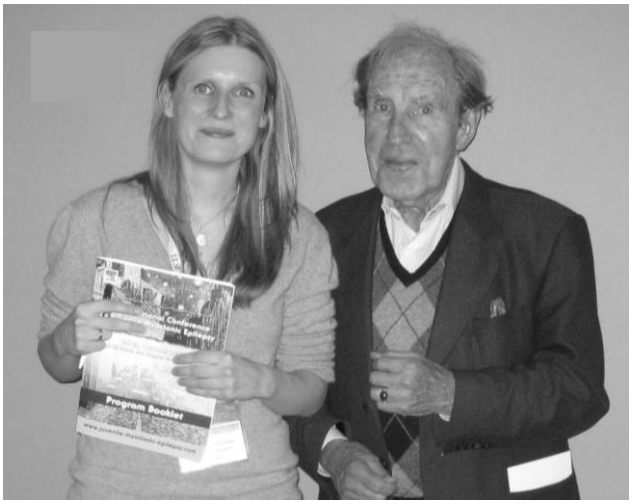

Figure 5. *A keen student who was lucky enough to meet Dieter Janz in person at the International Conference on Juvenile Myoclonic Epilepsy in The Hague, October 2012. He asked whether the photograph would be included in the doctoral thesis. (Photo: Eylert Brodtkorb).*

1.3.2 **The epidemiology of JME**

JME is often said to be the most common electroclinical epilepsy syndrome. In fact, experts state that all GTCS occurring in adolescence should be considered as JME until proven otherwise (51). The proportion of JME in large epilepsy cohorts ranges from 4% (the OREp group, Italy) (52) to 11% (Germany) (53). In the CAROLE study in France, 5% of all epilepsy was JME (43).

Data from population-based JME-specific studies are lacking, however. Five general epidemiological studies of epilepsy report prevalence of JME ranging from 1.0 to 2.6 per 10,000 (25, 26, 54-56). All of these studies are from the Nordic countries. Three of them were conducted in the eighties, when JME was little known. Moreover, none inquired specifically about myoclonic jerks, even though two included clinical interviews (55, 56). Most patients do not mention their myoclonic jerks unless they are asked specifically (57, 58). Hence, prevalence of JME is probably underestimated in these studies.

1.3.3 **Clinical manifestations and diagnosis**

The hallmark symptom of JME is myoclonic jerks, often occurring after awakening. The majority of patients also have GTCS, and some have absence seizures. JME may evolve from CAE. However, most patients with JME experience their first seizure in youth, usually at 12-16 years of age (59). Seizures are often triggered by sleep deprivation and stress. Furthermore, specific thoughts and concentration, in addition to performance of hand activities and

complex finger movements may trigger seizures in JME. In some cases the seizures are related to particular tasks, like reading, calculating or drawing, as in reflex epilepsy (60).

The EEG demonstrates 4-6 hz generalized polyspike- and spike-wave discharges, at times with bifrontal predominance (Figure 6). About one third are photosensitive, meaning that photic stimulation triggers epileptic discharges in the EEG. If routine EEGs are normal, a sleep deprived EEG may sometimes reveal generalized epileptic discharges (61).

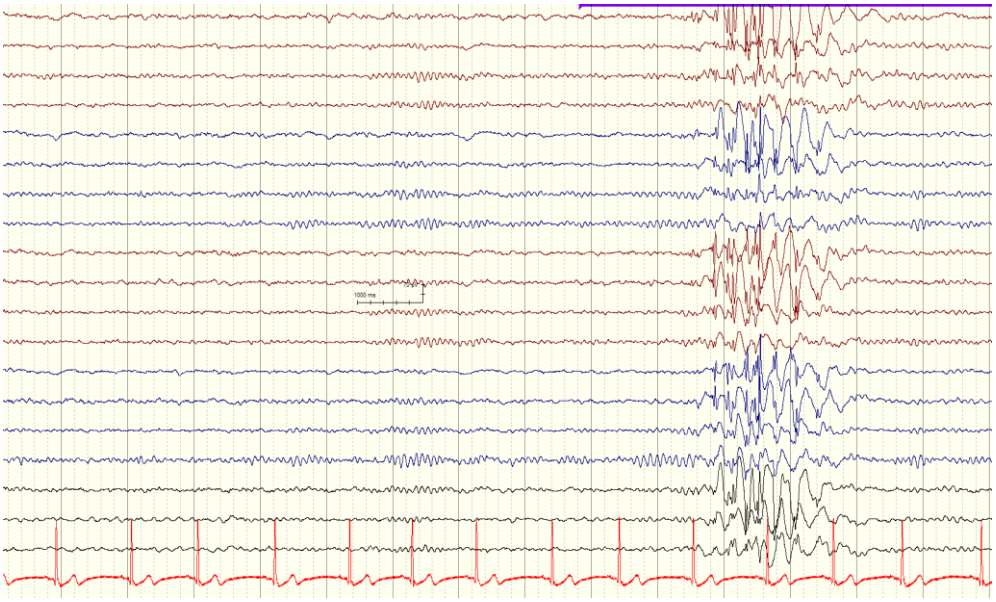

Figure 6. *EEG from a patient with JME, showing the typical interictal 4-6 hz polyspike- and wave activity. Background EEG activity is normal (100µV/cm) (Marte Syvertsen/ Kristoffer Hellum).*

1.3.4 **International consensus on diagnostic criteria of JME**

During an international JME workshop in Avignon in 2011, 45 experts (including Dieter Janz) reached a consensus on diagnostic criteria of JME (Table 1). The criteria were published following the 2nd International JME conference in The Hague in 2012 (62). The suggested diagnostic criteria are divided into class I and class II, with class I being the strictest. For both sets of criteria, all of the listed points must be fulfilled in order to make a diagnosis of JME. Both class I and class II criteria require presence of myoclonic jerks predominantly occurring on awakening, in addition to at least one EEG recording demonstrating generalized epileptic discharges. The class I criteria require at least one ictal EEG registration of a myoclonic jerk.

Diagnostic criteria for JME class I
1. Myoclonic jerks without loss of consciousness repeatedly occurring on awakening, i.e., within 2 h after awakening 2. EEG (routine, sleep, or sleep deprivation) that shows normal background and ictal generalized high amplitude polyspikes (and waves) with concomitant myoclonic jerks 3. Normal intelligence 4. Age at onset of between 10 and 25 years
Diagnostic criteria for JME class II
1. Myoclonic jerks *predominantly* occurring on awakening 2. Myoclonic jerks facilitated by sleep deprivation and stress and provoked by visual stimuli and praxis or GTCSs preceded by myoclonic jerks 3. EEG shows a normal background and at least once interictal generalized spike or poly-spike and waves with some asymmetry allowed with or without myoclonic jerks 4. No mental retardation or deterioration 5. Age at onset between 6 and 25 years

Table 1. *The international consensus on diagnostic criteria of JME (62).*

1.3.5 **Treatment and prognosis**

The initial reports of JME described a rather mild clinical picture, with a lack of accompanying neurological symptoms, cognitive abilities within the normal range, normal cerebral magnetic resonance imaging (MRI), and a favourable response to treatment in the majority of patients. In fact, it was named "benign juvenile myoclonic epilepsy" in the hallmark paper by Asconape and Penry in 1984 (49). In the widely used "Epilepsy: A comprehensive textbook" edited by Engel and Pedly (2008), it is stated that "the great majority of patients (with JME)… has an otherwise benign outcome with no other neurologic disturbances (than seizures)" (63).

Indeed, several studies report up to 80% seizure freedom in JME patients treated with valproate, an AED which for unknown reasons seems to be particularly effective in JME (50, 64, 65). However, this poses challenges to women of fertile age, as they are strongly discouraged from using valproate due to its teratogenic effects (66). Thus, levetiracetam or lamotrigine is often recommended in young females with JME. Lamotrigine can however, aggravate myoclonic jerks in some (67).

Even though response to treatment seemed good, both Janz and Delgado-Escueta reported high rates of seizure relapse upon withdrawal of AED. Based on their experience and publications the general advice evolved that AED treatment in JME should be lifelong.

However, their patient series were small (37 and 12, respectively) and AED withdrawal was conducted after only two years of seizure freedom (50, 68). Panayiotopoulos had the same experience, with seizure relapse in nine of 11 JME patients withdrawing AED after two years of seizure freedom (65).

Recent research has modified the prognostic view of JME, however. In 2008 Baykan and colleagues found that myoclonic seizures subsided in the fourth decade of life in a long-term follow-up study of 48 JME patients in Turkey (69). Other long-term follow-up studies reported that 10-26% of the included JME patients were seizure free and off AED > five years (70-72). A German study concluded that a history of GTCS preceded by myoclonic jerks, long duration of epilepsy with unsuccessful treatment, and AED polytherpay were significant predictors of persistent seizures in JME (72). However, this information is not helpful in predicting a safe withdrawal of AED, as that would concern a different group than the refractory one, i.e. the treatment responsive. Treatment dependence does not necessarily equal treatment refractoriness. In order to shed light on this issue, AED withdrawal studies in JME are needed. To date, such studies are virtually non-existing. This is probably due to the strong previous advice of lifelong treatment.

1.3.6 **Pathophysiology and genetics**

The pathophysiology of JME is unknown. Nevertheless, modest findings in genetic studies, in addition to age of onset and recent sophisticated imaging studies may give some clues: JME starts in the teens, a phase in which widespread cerebral changes take place as a part of the natural course of brain maturation. Main components of the cerebral maturation process in adolescence are *myelination* and *dendritic pruning*. The prefrontal cortex undergoes substantial change during this process, and is probably the last area of the brain to complete development. This does not happen until approximately 25 years of age (73).

Due to positive family history of epilepsy in large proportions of people with JME, efforts to identify causative genes have been made. The findings are limited, however, and the general view to date is that the heredity of JME is multifactorial and complex (74, 75). Nevertheless, a few JME genes are listed in the Online Mendelian Inheritance in Man (OMIM) database, with GABRA1 (Gamma-aminobutyric acid type A receptor alpha1 subunit) and EFHC1 (EF-hand domain containing 1) among the interesting ones. GABRA1 is responsible for making a subunit of the $GABA_A$ receptor protein (76). Gamma-aminobutyric acid (GABA) is the main

inhibitory neurotransmitter of the brain. GABA neurotransmission remains under construction during adolescence, particularly in the prefrontal cortex, in contrast to excitatory glutamate neurotransmission, which is completed perinatally (73, 77).

The EFHC1 gene makes a protein which is thought to be directly involved in brain development. There are several hypotheses as to the exact mechanism of involvement, including proliferation, migration, apoptosis, axon overgrowth, dendritic arborisation, or connections formation (78).

In voxel-based morphometry (VMB) studies of JME, several authors report findings of increased grey matter volume within areas of the frontal lobe (79-83), which theoretically could reflect defects in pruning during adolescence, possibly caused by erratic apoptotic mechanisms. There is also evidence of white matter abnormalities in JME, i.e. reduced fractional anisotropy (FA) in different networks within the frontal lobes, and in fibres connecting the thalamus to areas of the frontal lobes (84-86). FA measures the degree of anisotropy of a diffusion process, with decreased values reflecting reduced microstructural integrity in the white matter tracts. FA is directly affected by the content of myelin in the white matter (87), and myelination is, as we remember, an important component of brain maturation in adolescence.

Also worth mentioning, is the excellent work of the London-based Koepp/Richardson-group, which demonstrated reduced connectivity from the thalamus to the supplementary motor area (SMA) in people with JME, leading to decreased thalamic inhibition of the SMA (84). By using a functional magnetic resonance imaging (fMRI) paradigm during a cognitive task, they also demonstrated increased functional connectivity between the motor system (SMA and primary motor cortex) and frontoparietal cognitive networks in JME, a possible explanatory framework as to how cognitive tasks may trigger myoclonic jerks (Figure 7). The findings were more prominent in those with more recent seizures, and less prominent with increasing doses of valproate (88).

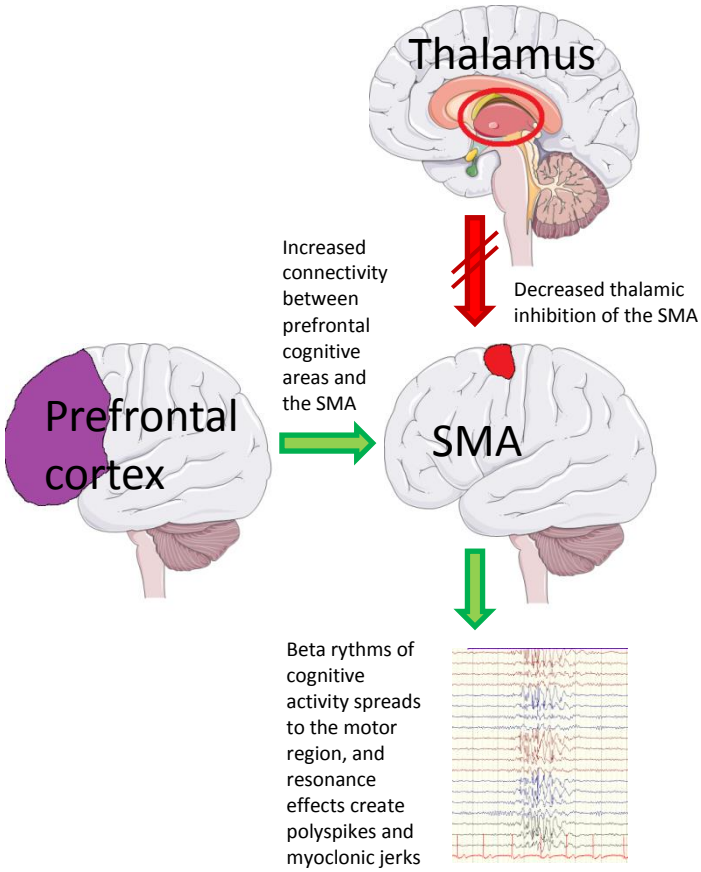

Figure 7*. Simplified interpretation of the findings of the Koepp/Richardson-group (84, 88); a possible mechanism of cognitively triggered myoclonic jerks in JME. There is increased connectivity between cognitive networks and the motor system during cognitive tasks, and the thalamus fails to inhibit impulses from the supplementary motor area (SMA) (Servier Medical Art/ Marte Syvertsen).*

All in all, evidence from imaging studies, clinical studies and genetic studies suggests that JME may be a neurodevelopmental disorder. The brain maturation process of dendritic pruning and myelinisation involving the frontal lobes in adolescence could be disturbed by DNA-related mechanisms, giving rise to hyperexitatory neuronal networks and seizures.

1.3.7 **Juvenile myoclonic epilepsy and the frontal lobe**

The evidence of involvement of cognitive networks, including prefrontal areas, in the seizure generating process of JME seems convincing. We know from focal epilepsy that the patients' symptoms may reflect the underlying function of the affected cerebral tissue. Consequently, it would be interesting to look into the functions of the cerebral tissue seemingly affected in JME.

The prefrontal cortex is thought to represent the brain area which is the most specific to humans, meaning that a perfect counterpart cannot be found in other species. Its networks are responsible for what is often summarized as executive functions. Executive functions comprise the ability to regulate behaviour in accordance with new and unexpected circumstances. Executive functions enable us to pursue a goal, suppress inopportune behaviour, and control our immediate impulses (89). Bearing the cerebral maturation process

in mind, it is not difficult to picture that a young child has greater difficulties in suppressing its immediate needs than an adult. Moreover, there are several examples that damage to the prefrontal cortex could cause severe changes of personality, difficulty in resisting impulses, or even sheer criminal and/or violent behaviour (90-93).

Early on, Dieter Janz stated that the people with JME he encountered often had an engaging, but emotionally unstable and immature personality (47, 94). In Denmark, Mogens Lund confirmed Janz' statements, by comparing the social outcomes of 33 patients with JME to 31 patients with other types of (GTCS) epilepsy. Lund found reduced occupational ability and disability pension to be more common in the JME-group, although not significantly. More patients with JME required social support, and they were more likely to report difficulties in contact with other people. Twelve patients with JME (36%) were diagnosed with "constitutional psychopathy," as opposed to none in the control-group (48). These findings were not followed up by other researchers however, and larger studies confirming Lund's statements are still lacking.

Consensus was that JME was a "benign" type of epilepsy, without any neurological deficit other than seizures (49, 63). Nevertheless, around the turn of the century widespread research of the neuropsychological profile of JME evolved. Findings pointed consistently towards a degree of executive dysfunction in this group of patients (95). Among the neuropsychological tests most commonly associated with deteriorated scores in JME were the Stroop test (96-100), the Trailmaking test (98, 100-102), and the Wisconsin Card Sorting test (96, 101). These tests measure the ability to inhibit immediate responses, and the ability to display flexibility when faced with changing or unexpected circumstances. Furthermore, two studies using the Iowa Gambling Task found that patients with JME were prone to make impulsive and unfavourable decisions (103, 104). A tendency towards impulsivity in people with JME has also been noted by others (105). Additionally, a high rate of personality disorders has been emphasized, mostly within the cluster B group (106, 107). Encompassing personality traits like emotional instability, impulsivity, and lack of discipline, the description matches Janz' initial remarks quite well.

In summary, the executive difficulties described in JME could be the clinical counterpart of the radiological evidence of structural and functional abnormalities within the frontal lobes of these patients. In fact, some studies combined the two and confirmed that neuropsychological test performance correlated with radiological findings (100, 102, 108). What consequences

such deficits may have to the patient is however under discussion. Results from several smaller follow-up studies concerning the psychosocial prognosis of JME are contradicting (70, 109, 110). The questions intended to map psychosocial prognosis were rather broad and general, however, focusing on issues like economic independence, employment, education, friendships, and psychiatric comorbidity. Failure in one or more of these fields could be caused by numerous reasons other than maladaptive or impulsive behaviour. Hence, there is a need for specific questions targeting the potential consequences of the behavioural issues that could be caused by frontal lobe deficits, i.e. a deteriorated ability to adapt behaviour, and failure to make favourable choices.

2 Aims of the study

The overall aim of the present research project was to map and classify the epilepsy population of a Norwegian county, with special emphasis on the most common type of epilepsy affecting youths: JME. A secondary aim was to investigate whether there was an excess of risk-taking behavioural patterns in an unselected and representative group of patients with JME.

The mentioned main research objectives were explored through the following specific, intermediate aims:

I. Assessing prevalence and aetiology of epilepsy in Buskerud County, implementing updated classification guidelines and terminology from the ILAE.

II. Assessing prevalence of JME in people < 30 years of age in Buskerud County, implementing the 2013 diagnostic criteria of JME.

III. Assessing the magnitude of AED withdrawal, including self-withdrawal, in a large and representative group of patients with JME.

IV. Investigating whether psychosocial issues associated with impulsivity are more prominent in people with JME than in those with other types of GGE.

V. Determining the strength of association of behavioural impulsivity in JME compared with GGE patients.

3 Materials and methods

3.1 Literature review and pilot project

In order to obtain a systematic overview of the relevant literature, two literature reviews were conducted (Table 2).

3.1.1 Literature review - epidemiology of epilepsy in the Nordic countries

In parallel with the identification of study participants through a systematic review of all prevalent cases of epilepsy in Buskerud County, we reviewed literature reporting prevalence and incidence of epilepsy in the Nordic countries. The search was restricted to the Nordic countries, as the epidemiology of epilepsy varies with geography and socioeconomic conditions (18). Thus, it would be relevant to relate our work to studies from regions with comparable economy, culture, and standard of living, i.e. the Nordic countries.

Original articles registered in PubMed up to January 1st 2015 were reviewed, using the search terms "epilepsy" and "epidemiology." We used the Boolean operator AND in combination with each of the Nordic countries separately. A search with the terms 'epilepsy AND (incidence OR prevalence)' in combination with each of the Nordic countries was performed as well. All in all, we identified 38 original articles in which prevalence and/or incidence of epilepsy was reported (111).

3.1.2 Literature review - juvenile myoclonic epilepsy

In the planning-phase of the current project, a review of available JME-related literature was performed (Table 2). The review was based on a PubMed search including the terms "juvenile myoclonic epilepsy," "myoclonic epilepsy," "myoclonic jerks," "idiopathic generalized epilepsy," and "epilepsy in adolescence." The search included articles published up to August 31st 2011, after which an automatic PubMed search with weekly updates was set up, using the term ("Myoclonic Epilepsy, Juvenile" [Mesh]) OR "juvenile myoclonic epilepsy."

3.1.3 **Pilot project**

In the initial phase of the present project, we participated in a long-term follow-up study of 42 patients with JME, conducted at St. Olav's Hospital in Trondheim, Norway (Table 2). The study comprised a thorough review of the medical records of the 42 patients with JME, in addition to a review of their answers in a previously conducted semi-structured interview concerning both medical and psychosocial prognosis. This project provided valuable insight into the history of the mentioned JME patients and served as an important hypothesis-generating foundation and guide when it came to selecting questions and points of interest to investigate in the present study. The main focus of the pilot study was seizure outcome and AED withdrawal, in addition to psychosocial difficulties.

Topic	**Publication**
Epidemiology of epilepsy in the Nordic countries – literature review	Syvertsen M, Koht J, Nakken KO. Prevalence and incidence of epilepsy in the Nordic countries. Tidsskr Nor Legeforen 2015; 135:1641-5
JME – literature review	Syvertsen MR, Markhus R, Selmer K, Nakken KO. Juvenil myoklonusepilepsi. Tidsskr Nor Legeforen 2012, 132;1610-3
Long – term prognosis of JME	Syvertsen M, Thuve S, Stordrange B, Brodtkorb E. Clinical heterogeneity of juvenile myoclonic epilepsy – Follow up after an interval of more than 20 years. Seizure 2014;23:344-8

Table 2. *Literature review and pilot project*

3.2 Study area and population

The present project was conducted at Drammen Hospital, located in Buskerud County, Norway. Buskerud County covers 14,908 km^2 and comprises 21 municipalities. The population on January 1st 2014 was 272,228 (5% of Norway's total population) (112). Drammen Hospital also serves the inhabitants of four municipalities outside Buskerud County; Svelvik, Sande, Asker, and Bærum, with a total population of 192,542 (January 1st 2014) (112). Prior to January 1st 2011, inhabitants of Asker and Bærum were served by Rikshospitalet in Oslo. The responsibility was transferred to Drammen Hospital following a hospital reform in 2011.

As of January 1st 2014 there was one department of neurology, one department of paediatrics, one department of neurohabilitation, and one EEG laboratory in Buskerud County, all located at Drammen Hospital. There was one private neurologist, and two private paediatricians in the county, none of which had access to EEG equipment on their premises. They would routinely refer patients to Drammen Hospital when in need of an EEG. In Norway, diagnosing and initiating treatment of epilepsy is delegated to specialists, i.e. paediatricians or neurologists. Moreover, EEG is part of the standard procedure in the diagnostic work-up of epilepsy, as recommended in the guidelines commonly used by paediatricians and neurologists across the country (113). Hence, it is very likely that close to all patients in Buskerud County with a diagnosis of epilepsy will have visited Drammen Hospital and are thus registered in our records.

However, there is a private neurologic outpatient clinic located 15km from the county border, and a tertiary referral centre for epilepsy (with a large EEG laboratory) 17km from the county border. Some patients from Buskerud could have received follow-up there. Nonetheless, a referral from a specialist is necessary to be admitted to the tertiary epilepsy centre. Consequently, such a patient would probably be registered and diagnosed at Drammen Hospital prior to referral to the tertiary centre.

3.3 Patient identification

We performed a systematic search of all consultations, hospital admissions and EEGs with an International Classification of Diseases, 10th Revision (ICD-10) code of epilepsy (G40.0-G40.9) for the time period 1999-2013. Included in the search were the department of neurology, the department of paediatrics, the department of neurohabilitation, and the EEG laboratory at Drammen Hospital. The prevalence day was January 1st 2014. Our search started on January 1st 1999, as medical records prior to 1999 were paper-based, and the ICD-10 coding system was not yet introduced. The search resulted in > 18.000 consultations in 2662 individuals (Figure 8). The medical record of each individual was then carefully reviewed, in order to verify the diagnosis and classify the epilepsy.

A similar search was performed at the outpatient clinic of the tertiary referral centre for epilepsy (The National Centre for Epilepsy – SSE), in order to identify patients from Buskerud receiving follow-up there. This search was not based on ICD-10 codes, but included the medical records of all patients who were residents in Buskerud County. The records of

The National Centre for Epilepsy were only searchable starting from 2010. However, patients receiving follow-up at the tertiary centre probably have a more complicated type of epilepsy and thus have most likely visited the centre at least once during the four-year-period of our search (2010-2013).

As a part of the review of medical records, all patients registered with GGE were identified. Of these, everyone aged 10-30 years (or their parents) were contacted in order to ask specifically about myoclonic jerks. Following this survey, all identified GGE patients aged 14-40 years were contacted and invited to a clinical interview. Additionally, people with GGE aged 14-40 years were recruited consecutively from the EEG-laboratory in the time period January 1st 2014 – January 1st 2018. This included patients from Asker, Bærum, Sande, and Svelvik municipalities as well. We also published information about the study and an invitation to participate in the magazine of The Norwegian Epilepsy Association.

3.4 Definitions used in this study

Epilepsy was defined as two unprovoked seizures occurring more than 24h apart, as recommended in the ILAE guidelines for epidemiologic studies of epilepsy (3). Active epilepsy was defined as ongoing AED treatment, and/or > 1 seizure within the last five years (3). The initial classification of epilepsy was based on the conclusions of the treating physician, as registered in the patient's medical record. Aetiologies were classified as genetic/presumed genetic, structural-metabolic, or unknown, based on the ILAE proposal for classification and terminology issued in 2010 (5).

The subclassification of GGE was based on information from interviews, in addition to information from medical files and EEG records. CAE, JAE, and EGTCS were defined according to ILAEs description of these electroclinical epilepsy syndromes (37). JME was defined according to the diagnostic criteria issued in 2013; class II (Table 1) (62). When separating JME from JAE, emphasis was placed on the dominating seizure type. Myoclonic jerks had to be the dominating seizure type in JME, and absences had to be the dominating seizure type in JAE.

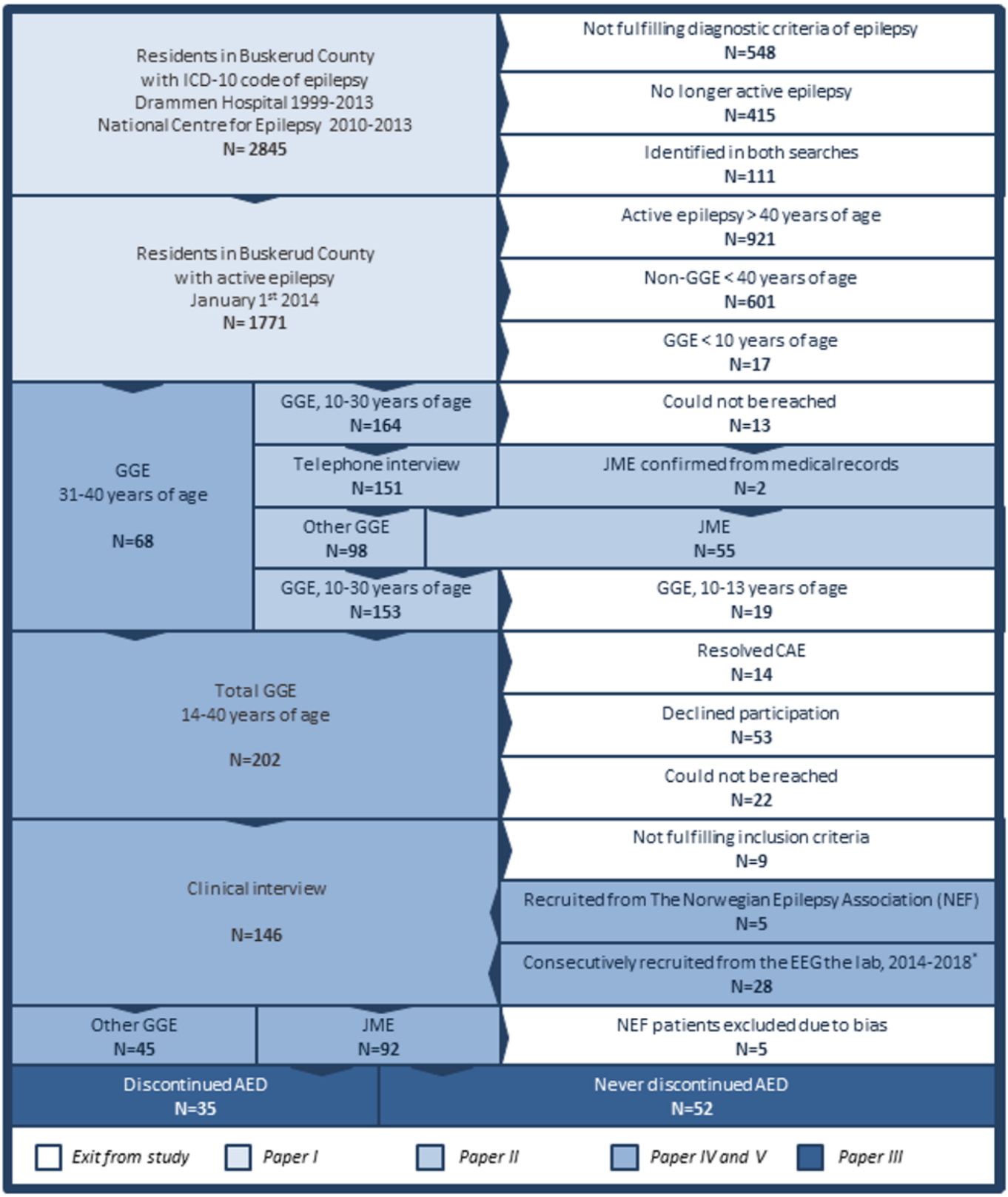

Figure 8. *Flow-chart of study participants. *Including patients from Asker, Bærum, Sande, and Svelvik municipalities. N=Number of patients (Marte Syvertsen).*

3.5 Inclusion and exclusion criteria

Inclusion and exclusion criteria are summarized in Table 3. All patients with active epilepsy as confirmed by the review of medical records living in Buskerud County and alive on the prevalence day (January 1st 2014) were registered in our database. People with febrile seizures only, neonatal seizures, a solitary unprovoked seizure, or acute symptomatic seizures were excluded, as suggested by the ILAE (3).

Our second aim was to estimate prevalence of JME in Buskerud County. All patients with a diagnosis of GGE aged 10-30 years were contacted. Patients aged 10 years or less were not contacted, as the age of JME onset was defined to be 10-25 years (62). Consequently, patients younger than 10 years of age could not have JME. We excluded patients older than 30 years of age, as older patients may have been diagnosed with JME prior to our search of medical records (1999-2013). Seizure freedom is attained in the majority of patients with JME (63), and it is likely that some patients visit the hospital only at the time of diagnosis. Thus, if they were diagnosed prior to 1999, they could have been missed by our search. In the clinical part of the study, age at inclusion was raised to 40 years, in order to obtain a larger stud population and increased power.

Patients with GTCS only and normal EEGs were not included. It was not possible to tell whether these had focal epilepsy or GGE/EGTCS. Hence, they were classified as epilepsy of unknown aetiology .

Paper	Inclusion criteria	Exclusion criteria
I	Two unprovoked epileptic seizures >24h apart All age groups Alive on January 1st 2014 Resident in Buskerud County on January 1st 2014 Current AED treatment and/or >1 seizure within the last 5 years	Febrile seizures only Neonatal seizures only Solitary unprovoked seizure only Acute symptomatic seizures only Paroxysmal symptoms not consistent with epilepsy
II	Registered diagnosis of GGE in Paper I Age 10-30 years	Intellectual disability (IQ < 70) Dysmorphic features
III, IV, and V	Diagnosis of JME, CAE, JAE, or EGTCS Age 14-40 years	Intellectual disability (IQ < 70) Dysmorphic features CAE seizure free >1 year and off AED

Table 3. *Inclusion and exclusion criteria.*

3.6 EEG

All patients included in the clinical part of this project had at least one available EEG-recording, registered as part of their regular diagnostic work-up. Most patients had several EEG-recordings. All of the available EEG-recordings and –reports were re-evaluated at inclusion in the present project. EEGs were regular 20 minute recordings, with photic stimulation and hyperventilation. In some patients, sleep-deprived EEGs and long-term monitoring EEGs were available as well. Electrodes were placed according to the international 10-20 system.

3.7 Interviews

People with a registered diagnosis of GGE aged 10-30 (or their parents) were contacted and asked whether they (or their child) had ever experienced myoclonic jerks, and if so, whether this was the dominating seizure type.

In the next step of the study, all patients with a diagnosis of GGE aged 14-40 years were invited to a clinical interview at Drammen Hospital. Those who were not able to come to the hospital were offered a home visit. One hour was scheduled for each interview. The interviews were organized for research-purposes only, and were thus independent of ordinary clinical follow-up. Accompanying persons were asked to leave the room when sensitive questions were asked. For patients younger than 18 years of age, both the parents and the patient were informed about the nature of the questions before the parents were asked to leave the room.

The clinical interview consisted of a semi-structured questionnaire designed for the purpose of the present study (Supplement 1). The questionnaire contained sections about background, family, work, and education. Furthermore, it contained a section about medical history (seizure types and frequency, medical treatment, age at onset, etc.), and a section about psychosocial issues (use of illicit recreational drugs, contact with the police, etc.) The questionnaire also contained a section about withdrawal of AED, and whether or not this was done in collaboration with the treating physician. The interview was based on self-reporting, with supplementary information from available medical records.

In addition to the semi-structured interview, the patients responded to two standardized questionnaires; The Barratt Impulsivness Scale (BIS) (114, 115) version 11, and The Hospital Anxiety and Depression Scale (HADS) (116, 117) (Supplement 2 and 3).

3.8 Statistical methods

3.8.1 **Power calculations**

When analysing prevalence of epilepsy in Buskerud County, a de facto power estimation was performed. Based on the present study, a point prevalence of epilepsy of 0.65% was estimated from a population of 272,228 inhabitants. On the condition of no misclassification, a source sample population of >72,721 subjects would be needed to catch a prevalence of 0.65% with a precision interval from 0.60% to 0.70% and a probability of 95%.

When planning for analysis of JME prevalence, a power estimation based on six studies previously reporting prevalence of JME (mean 2.0/10,000) was performed (25, 26, 54-56, 118). Considering 98,152 inhabitants aged 0-30 years in the source population, an expected prevalence of JME of 2.0/10,000 and a precision of ±1/10,000, a study population of >43,092 subjects would be required to detect a prevalence of 2.0/10,000 with a precision interval from 1 to 3/10,000 and a probability of 95%.

In the clinical part of the study, we did not have the possibility to include more patients than the given number of people with GGE in our region who were willing to participate. Consequently, a post hoc power analysis was performed to determine the power we would have to detect significant differences between cases and controls. The power to detect a significant difference in police charges (α=0.05) between 92 cases of JME and 45 controls was 79%, with a rate of police charges at 26% in the JME group, 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 JME group, and 11% in the control group.

3.8.2 **Univariate analyses**

Univariate analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 23. Data was checked for normality, and independent t-tests were used when analysing continuous numerical variables. Chi-Square tests were used when analysing

categorical variables. Yate's Continuity Correction was used for 2x2 tables. The Fisher's Exact Probability test was used when the expected cell count was less than five in any cell. P-values ≤0.05 were considered statistically significant.

3.8.3 **Logistic regression**

A logistic regression model was built using the Statistical Package for the Social Sciences (SPSS), version 23, in order to analyse the variables predicting a diagnosis of JME as opposed to other types of GGE, adjusting for potential confounders.

Our samples size was bigger than that of previous comparable studies (70, 106, 107, 109, 110, 119) and representative of the population of interest. Hence, 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 (120). The dependent variable was diagnosis of JME or diagnosis of other type of GGE. Clinical and background variables with p-values < 0.20 when comparing the two groups entered the model as independent variables, in addition to psychosocial factors potentially associated with a diagnosis of JME. As impulsive behaviour is more prominent in men (121), interaction terms were entered one at a time for gender and each independent variable. P-values ≤0.05 were considered statistically significant.

3.8.4 **Analyses of variance**

An analysis of covariance (ANCOVA) was performed, in order to compare variability in BIS-scores between the groups JME/other types of GGE, controlling for other binary and linear potential moderators of BIS-score. Post hoc independent t-tests were conducted to determine the direction of the detected differences. A post hoc two-way between-groups analysis of variance (ANOVA) was performed investigating the interaction between ongoing myoclonic jerks and a diagnosis of JME on total BISs-core. P-values ≤0.05 were considered statistically significant.

3.8.1 **Collaboration**

Power analyses for the prevalence studies were performed in collaboration with the Department of Clinical Research Support at Oslo University Hospital. Power analyses for the

clinical part of the project were performed in collaboration with statisticians at King's College London. Logistic regression and ANCOVA/ANOVA analyses were performed in collaboration with Anna Smith and Deb Pal at King's College London.

4 Summary of results

4.1 Paper I

Syvertsen M, Nakken KO, Edland A, Hansen G, Hellum MK, Koht J. Prevalence and etiology of epilepsy in a Norwegian count – A population based study. Epilepsia 2015;56:699-706.

The aim of Paper I was to estimate the prevalence of epilepsy in our county using the updated classification and guidelines of the ILAE. Patients were identified by means of a systematic review of the medical records of all patients with a registered ICD-10 code of epilepsy at the departments of neurology, paediatrics, and neurohabilitation, and the EEG-laboratory, at Drammen Hospital for the time-period 1999-2013. Additionally, a search of patients with a home address in Buskerud County was performed at the National Centre for Epilepsy. In total, 2845 individuals with a registered diagnostic code of epilepsy were identified. Of them, 548 (19%) did not fulfill the diagnostic criteria of epilepsy. Of the remaining 2297, 415 (18%) no longer had active epilepsy. In a total population of 272,228 in Buskerud County, 1771 subjects had active epilepsy. Point prevalence of active epilepsy on January 1st 2014 was 0.65%. The aetiology was genetic or presumed genetic in 20%, structural-metabolic in 43%, and unknown in 32%. In 4% aetiology could not be determined due to lack of information. We concluded that epilepsy is common, but a considerable percentage of those who were registered with an ICD-10 code of epilepsy did not fulfill the criteria of the diagnosis. Hence, care must be taken when basing epilepsy prevalence estimates on unverified diagnoses from registries. Moreover, in spite of recent advances in genetics and imaging technology, a large proportion of patients still have an unknown cause of epilepsy.

4.2 Paper II

Syvertsen M, Hellum MK, Hansen G, Edland A, Nakken KO, Selmer KK, Koht JK. Prevalence of juvenile myoclonic epilepsy in people < 30 years of age – A population-based study in Norway. Epilepsia 2017;58:105-112.

In the second paper, the aim was to estimate prevalence of JME. We hypothesised that JME is more common than previously stated, due to under-reporting of myoclonic jerks. Based on the reviews of medical records published in Paper I, all patients aged 10-30 years with a diagnosis of GGE were identified. They were then contacted and asked specifically about myoclonic jerks, the hallmark symptom of JME. The participation rate was 93%. A total of 55 subjects fulfilled the diagnostic criteria of JME, of which 21 (38%) were previously undiagnosed. Of the 42 patients with a diagnosis of JME according to medical records, seven (17%) did not fulfil the criteria of this diagnosis. The point prevalence of JME in people < 30 years of age in Buskerud County was 5.6/10,000, or 9% of all active epilepsy in this age group. In conclusion, we noted a considerably higher prevalence of JME than previously reported, demonstrating that the diagnostics of JME in regular clinical practice may be imprecise, and emphasising the importance of specifically inquiring about myoclonic jerks.

4.3 Paper III

Syvertsen M, Fløgstad I, Enger U, Landmark CJ, Koht J. Antiepileptic drug withdrawal in juvenile myoclonic epilepsy. Acta Neurologica Scandinavica 2019;139:192-198.

In Paper III we aimed at assessing the magnitude of AED withdrawal in JME, a type of epilepsy in which lifelong AED treatment has generally been recommended. Patients with GGE aged 14-40 years were invited to participate in a semi-structured clinical interview. The interview included questions about background, medical history, psychosocial factors, and use of AED. Epilepsy was classified as JME, JAE, CAE, EGTCS, or non-GGE based on information from the interview, supplied by information from medical charts and EEG-records. The participation rate was 69%. Eighty-seven patients had JME, and 45 had other types of GGE (8 CAE, 22 JAE, and 15 EGTCS). Nine patients did not fulfill the inclusion criteria. Of the participants with JME, 35 (40%) had at some point discontinued AED treatment, and 74% of these had done so without consulting a doctor. When comparing self-withdrawal of AED in JME to self-withdrawal of AED in other types of GGE, the rate of self-withdrawal was significantly higher in JME. For those with JME, having a parent with psychosocial difficulties like addiction or violent behaviour was significantly more common in people who chose to self-withdraw medication. Of those who discontinued AED, 12 (34%) were free from GTCS and off AED >1 year. Age at first motor seizure was significantly lower in patients with an unfavourable outcome of AED withdrawal. We concluded that the rate of self-withdrawal in JME is high, and that special attention must be payed to families with psychosocial difficulties. Nevertheless, some patients may discontinue AED without experiencing GTCS relapse. As treatment resistance does not equal risk of recurrence upon AED withdrawal, dedicated withdrawal studies are needed in order to identify JME patients who may withdraw medication safely.

4.4 Paper IV

Syvertsen M, Selmer K, Enger U, Nakken KO, Pal DK, Smith A, Koht J. Psychosocial complications in juvenile myoclonic epilepsy. Epilepsy & Behavior 2019;90:122-128.

Paper IV investigates whether psychosocial issues associated with impulsivity are more prominent in JME than in other types of GGE. Information collected in the semi-structured interview described in Paper III was used. Variables associated with risk-taking and impulsive behaviour were analysed in a multiple regression model, including potential confounders like age, gender, and AED use. The outcome variable was whether the patient was diagnosed with JME or another type of GGE. In univariate analyses, being charged by the police, use of illicit recreational drugs, being a victim of violence or abuse, and smoking prior to the age of 18 was significantly more common in the JME-group. Use of levetiracetam was also more common in the JME-group. When these variables were included in a stepwise regression model (in addition to gender, age, being diagnosed with attention deficit hyperactivity disorder/ADHD, and having a parent with psychosocial difficulties like addiction or violent behaviour) the following came out as significant predictors of belonging to the JME-group: Being examined for ADHD in females (OR 15.5), having a parent with psychosocial difficulties (OR 3.5), and use of levetiracetam (OR 5.1). Being charged by the police (OR 4.2) and use of illicit recreational drugs (OR 3.4) remained at the last step of the regression model, but with borderline significance. We conclude that potentially severe psychosocial difficulties and risk-taking behaviour may be associated with JME, and that this diagnosis may comprise greater challenges than previously thought.

4.5 Paper V

Syvertsen M, Koht J, Selmer K, Enger U, Pal DK, Smith A. Behavioral impulsivity correlates with active myoclonic jerks in genetic generalized epilepsy. Manuscript submitted to Journal of Neurology, Neurosurgery, and Psychiatry, 16th Jan. 2019.

The aim of Paper V was to investigate the strength of association between behavioural impulsivity in JME compared with other types of GGE, hypothesising that behavioural impulsivity would be more prominent in JME. Following the semi-structured interview described in Paper III, the BIS questionnaire was administered to all participants. BIS is a well-established tool for investigating behavioural impulsivity, with higher scores indicating more impulsive behaviour. An ANCOVA model was used in order to analyse variability in total BIS-score between patients with JME and those with other types of GGE, controlling for other possible moderators of BIS-score. Type of epilepsy (JME versus other types of GGE) was not a significant moderator of BIS-score. However, ongoing myoclonic jerks (i.e. myoclonic jerks within the last year) correlated with total BIS-score, irrespective of epilepsy diagnosis ($F=5.56$, $p=0.02$). Post hoc t-tests revealed that mean BIS-score was higher in those with ongoing myoclonic jerks than in those without such seizures during the last year (mean 66.5±9.5/61.5±10.0, $p=0.004$). The study demonstrates that impulsivity may be a behavioural trait across the syndromes of GGE, and that it is associated with the presence of myoclonic jerks.

5 General discussion

5.1 Prevalence of epilepsy

In our systematic review of medical records with an ICD-10 code of epilepsy at Drammen Hospital, we discovered 1771 individuals with active epilepsy, or 0.65% of Buskerud's total population.

To the best of our knowledge, this is the largest non-registry based epidemiological study of epilepsy from any of the Nordic countries. In our systematic review of studies investigating prevalence and/or incidence of epilepsy in the Nordic countries, we identified three studies with a methodology comparable to the present project (111). The number of cases in these studies ranged from 333 to 635 (22, 25, 26).

A methodological issue of particular importance was whether or not comparable studies were register-based. The findings of our study illustrate why. Of the 2662 cases with a registered diagnostic code of epilepsy at Drammen Hospital, the review of medical records revealed that 20% did not have epilepsy. The most common explanation was that a diagnosis of epilepsy had been *suspected*, but had later been rejected as a consequence of diagnostic work-up. Hence, ICD-10 codes do not always reflect the final conclusion of the treating physician and must be considered more like an administrative tool. A study validating epilepsy diagnoses of the Danish National Hospital Register reached the same conclusion. One hundred and eighty-eight medical records were reviewed, of which 19% did not fulfil the ILAE diagnostic criteria of epilepsy (21). Looking at Nordic registry-based studies, we note that the reported prevalence of epilepsy is higher than that of non-registry-based studies, ranging from 0.57 to 0.90%, compared to 0.32 - 0.77% in non-registry-based studies (111).

Another parameter that should be considered is age. As the incidence of epilepsy varies substantially with age (28, 32, 122), we found it important to include all age groups in the present study. Moreover, only active epilepsy was included, as recommended by ILAE (3). We found that 415 patients no longer had active epilepsy, meaning that they were not using AED and had been seizure free for more than five years. If these had been included, we would have reported *lifetime* prevalence of epilepsy, rather than prevalence of active epilepsy, and prevalence would thus have risen from 0.65% to 0.80%.

Consequently, our results were not directly comparable to studies including restricted age groups, reporting lifetime prevalence and/or using a registry-based approach. When excluding these, only three studies remained, all of which identified cases of epilepsy by means of hospital-based reviews of medical records, like the present project. The study reporting the lowest prevalence (0.34%) was Icelandic. It was conducted more than 50 years ago, and the low prevalence could perhaps be explained by under-diagnosing due to stigma and economic consequences in rural areas, where the main sources of income often included operation of heavy machinery, i.e. fishing and farming (22). A study from the Faroe Island in 1986 found a considerably higher prevalence of epilepsy, at 0.76%. The author of this study noted that some cases of non-epilepsy could have been registered as epilepsy, because medical records were generally written by people without experience in the field of epileptology (25). In the present study, medical records were written by neuro-paediatricians or neurologists, often with a particular interest in follow-up and treatment of epilepsy. The third study, also from Iceland (1999), reported prevalence of epilepsy to be 0.48%, which is slightly lower than the present study. However, a stricter definition of active epilepsy was used. Only patients with >1 seizure within the last year were included, as opposed to >1 seizure within the last five years in the present study. Moreover, patients not using AED for at least one year prior to the prevalence day were excluded (26). Thus, more patients were included in the definition of active epilepsy in the present study, which may explain the higher prevalence.

In summary, several factors of methodology must be carefully considered when interpreting studies of epilepsy prevalence. As illustrated, the definition of epilepsy, the age of the study, the age of included participants, and the approach to case identification all influence results directly, as do geographical area and socioeconomic status of the participants.

5.2 Aetiology and classification of epilepsy

We found it striking that as many as 645 (36%) of the patients in the present project had an unknown cause of epilepsy. Additionally, 320 patients had GGE, and 27 had possible epileptic encephalopathy. In fact, none of the GGE patients, and none of those with a possible epileptic encephalopathy had a known cause of epilepsy either, even though it is suspected to be genetic. Consequently, 992 (56%) of the patients with active epilepsy in Buskerud County do not know why they suffer from seizures.

In the Icelandic study from 1999, the rate of epilepsy of unknown aetiology (including GGE) was 62% (26), and in a Swedish study of adults (>17 years of age) from 1992, 65% had an unknown cause of epilepsy (including GGE) (34). The present study demonstrates that in spite of ground-breaking advances in genetics, and the development of increasingly sophisticated imaging technology, the proportion of patients with "unsolved" epilepsy remains nearly as high as it was in the nineties.

However, the question of aetiology is probably evaluated at the time of diagnosis and perhaps not always re-evaluated at a later stage. Thus, it could be that a larger proportion of the older patients have an unknown cause of epilepsy, as diagnostic tools were less developed when they were diagnosed. If looking at the youngest patients separately, one should hope that the rate of epilepsy with an unknown cause would be lower. A recent Norwegian study mapped the causes of epilepsy in children up to 13 years of age. Surprisingly, the rate of epilepsy of unknown cause was even higher in this age group, at 67% if including GGE (123). When investigating the youngest age groups in the present material, we found that 53% of those under 10 years of age had epilepsy of unknown aetiology (124). These findings are worrying, keeping in mind that epileptic seizures merely reflect that something has gone wrong in the communication between the cells in the cerebral cortex. As long as we are not able to identify exactly *what* has gone wrong, we will not have much to offer other than symptomatic treatment by means of AED. The booming of genetic research offers optimism, however. New genes explaining the occurrence of seizures and their accompanying symptoms emerge continually, offering insight into the pathophysiology of epileptic seizures, and research targets for disease-specific therapy (125). Hopefully, ongoing genetic discoveries will translate into a diminished proportion of epilepsy of unknown aetiology in the future. For the time being, there seems to be a significant gap between the progress made in laboratories and the patients who would benefit from such progress. Perhaps a more systematic approach to the diagnostics of epilepsy could contribute to shrinking this gap.

When it comes to classification, the proposal issued in 2010 was followed by unavoidable debate. Finally, in 2017, a concluding ILAE classification of epilepsies and epileptic seizures was published (126, 127). Whereas the 1989 and 2010 classification divide the types of epilepsy into three broad groups based on confirmed or presumed aetiology (idiopathic/genetic, symptomatic/structural-metabolic, and cryptogenic/ unknown), the 2017 classification includes three levels of diagnostic precision (Figure 9). The first level establishes whether seizure types are focal or generalized. The second level involves

confirming whether the epilepsy type, not just the seizures, should be considered focal and/or generalized. Finally, the third level of precision determines type of epilepsy syndrome. Overarching all of these levels is aetiology, which is now underlined as an area of particular importance. Hence, the conclusions of the present study are in line with the updated priorities of ILAE. Aetiology must be considered at each step of the diagnostic procedure and should be more precisely categorised within one of six groups; structural, genetic, infectious, metabolic, immune, and unknown (127). The 2017 classification incorporates and reflects what clinicians normally do in practice, that is to determine whether the epilepsy is focal or generalized from the very beginning. Naming the epilepsy as idiopathic/genetic, symptomatic/structural-metabolic, or cryptogenic/unknown most likely came in second line in a clinical setting, and is now replaced by the six more specific categories of aetiology.

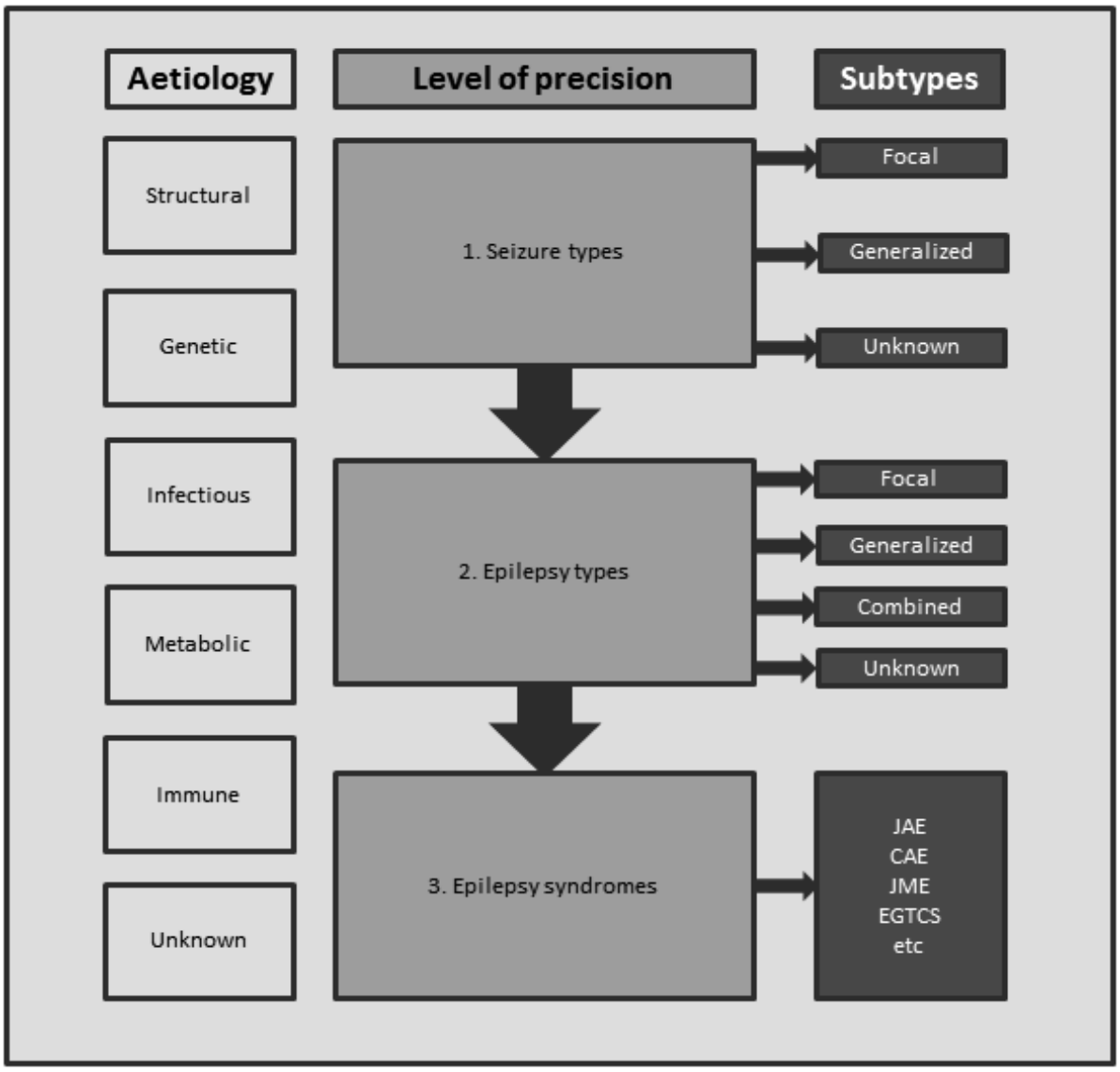

Figure 9. *The 2017 International League Against Epilepsy classification of the epilepsies (125). JAE=juvenile absence epilepsy , CAE=childhood absence epilepsy, JME=juvenile myoclonic epilepsy, EGTCS=epilepsy with generalized tonic-clonic seizures only (Marte Syvertsen).*

5.3 Prevalence and classification of JME

It is often claimed that JME is one of the most common electroclinical epilepsy syndromes, and that it is the most common type of epilepsy affecting youth (44, 128). However, the actual prevalence of JME is poorly documented. Throughout our systematic review of epilepsy epidemiology in the Nordic countries (111), in addition to evaluation of central review articles of epilepsy epidemiology in Europe (30), and the world (18), we were only able to identify six articles estimating prevalence of JME. Two of these studies included clinical interviews (55, 56). The remaining were based on reviews of medical records (25, 26, 54) (118). All of them focused on prevalence of epilepsy in general, but included prevalence estimates of epilepsy subsyndromes identified in the given population. Prevalence of JME ranged from 1.0-3.0/10,000 (25, 26, 54-56, 118).

In the present study, focusing on JME in particular, we found a considerably higher prevalence, at 5.6/10,000. We specifically asked all identified individuals with GGE aged 10-30 whether they had ever experienced myoclonic jerks, following an explanation of the nature of this symptom. When doing so, we revealed that several individuals diagnosed with unspecific GGE, or even CAE/JAE, in fact had JME. Of the total number of JME cases, 38% were previously undiagnosed. Myoclonic jerks are sometimes subtle, and as other authors have repeatedly stated, these seizures are often overlooked by both patients and clinicians (57, 58, 129-131). Thus, JME is likely to be underdiagnosed, and prevalence will be underestimated unless myoclonic jerks are specifically inquired about.

Surprisingly, we also found that 17% of those with a diagnosis of JME according to medical records, in fact did not match the diagnostic criteria of this electroclinical epilepsy syndrome. The finding illustrates that diagnosing epilepsy at ILAE's 3rd level of precision (Figure 9) (127) may be challenging in a clinical setting. It may be problematic to differentiate the subsyndromes of GGE, particularly JME and JAE. Both of these epilepsy syndromes may include absences, myoclonic jerks, and GTCS (Figure 4), and EEG findings may be identical. The diagnostic criteria of JME do not give any hints as to how one should differentiate JME from JAE. However, it is stated that the myoclonic jerks of JME must occur predominantly on awakening (Table 1) (62). Others have indicated that the myoclonic jerks of JAE are less chronodependent than those of JME (42). Correctly differentiating the subsyndromes of GGE was of the utmost importance in the present project (Paper III, IV, and V). Problems arose when we were left with a substantial group of patients with myoclonic jerks as their main

seizure type, but without morning predominance. Within this group, several patients had never had absences. Hence, they did not have CAE/JAE. As they had frequent myoclonic jerks, neither could they have EGTCS. What type of GGE did they have, if not JME? We chose to include these patients in the JME group, emphasising myoclonic jerks as the main seizure type. However, strictly speaking, they did not fulfil all of the diagnostic criteria listed in the international consensus (Table 1) (62). As this posed a challenge to the present research group, one can only imagine how difficult classification may be in a busy clinical setting. It is thus easy to understand why so many patients are left with an unspecific diagnosis of GGE (45% of all the GGE patients in Paper I) (118). Perhaps it is time to discuss and evaluate the implementation of the 2013 JME diagnostic criteria.

5.4 Risk-taking behaviour in JME

5.4.1 **Psychosocial challenges**

The present study revealed considerably higher rates of psychosocial difficulties like drug abuse and police charges, than previously reported in people with JME. Moreover, we found that those who had a biological parent with psychosocial difficulties like addiction or violent behaviour were more likely to be diagnosed with JME.

Quite persuasive evidence suggests that the pathophysiological process of JME involves networks within the frontal lobes (95, 132), areas of the brain which are important to decision-making, impulse control and regulation of behaviour (89, 133). A timely question to ask is whether abnormal function within these networks affects the daily lives of patients, apart from lowering the seizure-threshold. The first to specifically address outcomes of a possible frontal lobe deficit in JME were Camfield and Camfield, who included 23 patients with JME 25 years after seizure onset in a population based study in Nova Scotia. In this study population, they found that 11 pregnancies (80% of total pregnancies in 23 patients with JME) were unplanned and outside of a stable relationship. Moreover, 31% of the included patients were unemployed, 48% reported behavioural problems at school, and 22% received methyl-phenidate for attentional deficits. Three (13%) were arrested for criminal offense. None admitted to use recreational drugs (70).

Five years after the Nova Scotia study, in 2014, three more studies investigating psychosocial issues of JME were published. Interestingly, the patients initially diagnosed by Janz were

followed up >20 years after seizure onset, and their psychosocial outcomes were compared to those of people with absence epilepsy. Forty-one patients were included in each group, and variables like education, employment, economical situation, family, friendships, and psychiatric comorbidity were inquired about. The study concluded that there was no difference in psychosocial outcome between the two groups, contradicting the notion of JME-specific psychosocial challenges (109). Another German study including 33 patients with JME >20 years after seizure onset focused on aspects similar to those of the Camfield study. They found the rate of unplanned pregnancies to be 36%. Twenty-six percent of the patients were unemployed. This was higher than the unemployment rate among people with active epilepsy in Germany (13%). One patient (3%) admitted to use recreational drugs (110).

In our pilot long-term follow-up study of 42 Norwegian patients with JME, we noted that seven (17%) admitted to use recreational drugs or excessive use of alcohol. Moreover, four (10%) were convicted of criminal offense (119).

The present study is different from the studies quoted above in several ways; First of all, the participation rate was high, at 69%. In comparison, the participation rate in the two German studies was 37% (110) and 50% (109). Assuming that people with difficulties like criminal behaviour and drug related problems are hard to recruit to clinical studies, a low participation rate would represent a bias towards less such problems in the investigated group of patients.

Secondly, the sample size of the present project (N=92) was considerably larger than in any of the previous project evaluating psychosocial outcome in JME, in which the number of participants ranged from 23 to 42 (70, 109, 110, 119). This allowed us to control for potential confounders, like AED use. Considering the adverse effect profile of levetiracetam (i.e. irritability and aggression) (134, 135), and the fact that levetiracetam was more commonly used in the JME-group, it was particularly important to control for this confounder.

Another important issue to consider is that the present study explicitly addressed problems that could be related to risk-taking behaviour. Deteriorated impulse-control and unfavourable decision-making are traits related to abnormalities involving the prefrontal cortex and could lead to a risk-taking behavioural profile (103, 104). We found it less likely that general psychosocial issues, like mental health problems, marital status, social network, or income level would be significantly different in the JME-group. Such difficulties could be consequences of risk-taking behaviour, but could just as well be caused by the stigma and

challenges related to seizures in general. Indeed, the German study comparing JME to absence epilepsy found no difference between the two groups when it came to family status, financial situation, social integration, and psychiatric comorbidity (109).

Lastly, recall bias must be considered. The previous studies investigating psychosocial outcome of JME were long-term follow-up studies, with mean age of participants ranging from 36 to 61 years (70, 109, 110, 119, 136). Use of recreational drugs is more common in youth (137). It is possible that some of the older patients could have forgotten that they tried such substances in the past. Mean age of JME patients in the present study was 26 years.

In summary; a larger sample size, diminished selection bias and recall bias, in addition to questions specifically targeted towards the potential consequences of impulsive behaviour, probably contributed to the evident traits of psychosocial challenges revealed in the present study. Moreover, these traits were overrepresented in the JME-group compared to other types of GGE, delineating a JME-specific behavioural pattern.

We also found that females who were previously examined for ADHD were fifteen times more likely to be diagnosed with JME as opposed to other types of GGE. The behavioural traits now emerging in the description of JME (i.e. executive dysfunction and impulsivity) are well described in ADHD (138). Hence, it may not be surprising that ADHD was suspected in several of the JME patients. That this was most evident in females could be explained by the fact that ADHD is more common in men (138). An increased prevalence of ADHD in people with epilepsy is well known (139), but the link between JME and ADHD remains to be explored. Bearing in mind that JME constitutes up to 10% of all epilepsy (128), as confirmed by the present project (9%), it is possible that the high percentage of ADHD in the epilepsy population is largely due to JME.

Interestingly, we noted that patients reporting that one of their parents had psychosocial challenges, like addiction or violent behaviour, were more likely to have JME. To the best of our knowledge, this has not been demonstrated by previous studies. However, two studies showed that siblings of people with JME also had inferior scores on tests of executive function compared to healthy controls, even if they did not have a history of epileptic seizures (99, 140). One could speculate that a possible frontal lobe dysfunction demonstrates heritable traits as well, perhaps with a milder phenotype not involving seizures. Moreover, we must bear in mind that relatives may have experienced myoclonic jerks without having consulted a

doctor, as people often do not consider myoclonic jerks bothersome, or fail to realize that they represent epileptic seizures (58). At present time this remains speculative, and differentiating between shared environment and shared heredity is difficult. The psychosocial profile of JME families merits further and more thorough investigation in future studies.

5.4.2 **Self-withdrawal of antiepileptic drugs**

Considering the rigorous advice that people with JME should not discontinue AED medication, (68) (50, 65), we wanted to investigate whether this advice was followed, and the consequences in case it was not. Lifelong treatment involves a considerable exposure to drugs with undesirable short- and long-term effects. Recent long-term follow-up studies, including our pilot study from Trondheim, suggest that some people with JME may discontinue medication and remain seizure-free (69-72, 119).

We found that as many as 40% of the JME patients had discontinued AED at some point, and 3/4 had done so without consulting a doctor. Assuming that doctors had informed about the elevated risk of GTCS relapse upon AED withdrawal, choosing to discontinue AED without consulting a doctor must be considered a type of risk-taking behaviour, in line with the hypothesis of a specific behavioural profile in JME. This is supported by the fact that self-withdrawal of AED was significantly more common in the JME-group than in the group with other types of GGE.

When exploring the possible reasons of self-withdrawal of AED, we found a significantly higher rate of having a parent with psychosocial problems like addiction or violent behaviour in the self-withdrawal group. Other factors (like age, epilepsy severity, type of AED, or adverse effects) did not differ significantly between those who self-withdrew AED and those who did not. Whether this confirms a specific family trait of taking risks is uncertain. Nevertheless, we think that the decision of AED discontinuation had mostly been made by the patients themselves, and not the parents, as the mean age of seizure onset in the present study was 15 years, and mean age at the time of the interview was 26 years. Families with JME may need increased attention and improved follow-up, particularly if impulsive traits are suspected.

Even if 40% of the patients discontinued AED and the majority did so against medical advice, 12 of those who stopped AED medication (34%) were free from GTCS > 1 year and did not

restart AED therapy. In line with the long-term follow-up studies, we found that lifelong AED treatment may not be a necessity for all people with JME. Several studies attempting to identify predictors of AED refractoriness in JME are summarized in a recent meta-analysis (141). However, when trying to predict the safety of AED withdrawal, these data are not helpful. A patient could very well respond to AED treatment, but still experience seizure relapse upon withdrawal. Hence, refractoriness does not equal drug-dependence, and withdrawal studies are the only means to identify predictors of safe AED withdrawal. However, people with JME are often excluded from AED withdrawal studies, due to the presumed high risk of seizure relapse (142, 143). When looking at factors that could differ between those who remained free from GTCS without AED, and those who experienced GTCS relapse and/or restarted AED, we found that age at seizure onset was significantly higher in those who remained free from GTCS without AED. Another study suggests that photoparoxysmal response (i.e. generalized spike-wave discharges in the EEG when exposed to flickering lights) could be a predictor of seizure relapse upon AED withdrawal in JME (72). The rate of photoparoxysmal response in the present study was considerably lower in those who remained free from GTCS without AED (33% vs 65%), however not significantly. Larger and ideally, prospective, studies are needed to identify predictors of seizure relapse upon AED withdrawal in JME.

5.5 Myoclonic jerks and classification of GGE

When investigating behavioural impulsivity by means of the BIS, the hypothesis was that people with JME would be more impulsive than those with other types of GGE. However, this was not the case. Group differences in BIS score (JME versus other types of GGE) were analysed in an ANCOVA model, controlling for gender, intentional noncompliance, ongoing GTCS (GTCS within the last year), ongoing myoclonic jerks (myoclonic jerks within the last year), being examined for ADHD, history of valproate use, history of levetiracetam use, and age. It was not surprising that being examined for ADHD was a strong moderator of BIS score, as impulsivity is part of the definition of ADHD (138). We found it interesting, however, that ongoing myoclonic jerks was also a significant moderator of BIS score, whereas type of epilepsy (JME versus other type of GGE) was not. In post hoc ANOVA models there was no significant interaction between ongoing myoclonic jerks and a diagnosis of JME, demonstrating that ongoing myoclonic jerks per se, rather than ongoing myoclonic jerks within the JME-group, influence impulsivity as measured by BIS. Post hoc t-tests

exploring the direction of the association revealed that those who had experienced myoclonic jerks within the last year had significantly higher BIS scores than those who had not experienced such seizures within the last year.

When it comes to confounders, we found it particularly important to control for non-compliance. Intentional non-compliance was defined as withdrawing AED medication against medical advice. One could think that impulsive individuals are more likely to do this, and that this could explain the link between ongoing myoclonic jerks and impulsivity. Intentional non-compliance was not a significant moderator of BIS score, however. We were unable to control for non-intentional non-compliance, i.e. forgetting to take AED as prescribed. Due to non-intentional forgetfulness, impulsive individuals could struggle adhering to medical advice, leading to breakthrough seizures. However, non-compliance, whether intentional or not, could also lead to breakthrough GTCS. Ongoing GTCS did not have an impact on impulsivity scores in the ANCOVA model, strengthening the theory of a specific link between myoclonic jerks and impulsive behaviour.

The link between ongoing seizure activity and impulsivity is supported by two other studies investigating impulsivity in JME by means of a card game task, the Iowa Gambling Task. Both studies found that people who still experienced occasional seizures (GTCS, absences, or myoclonic jerks) made riskier card choices than those who were seizure free (103, 104). However, we are not aware of any other study investigating impulsivity across different GGE subsyndromes and establishing a link between a specific seizure type (myoclonic jerks) and impulsivity, irrespective of epilepsy syndrome.

Consequently, the present study adds to the continuing debate on classification and categorisation of epilepsy. Firstly, we have demonstrated how difficult it may be to differentiate between the subsyndromes of GGE in a clinical setting, and that the differentiation between JME and JAE may be particularly challenging (144). Secondly, we have demonstrated that such a differentiation matters, as people with JME may be at risk of making unsafe choices (145) and a potentially hazardous lifestyle (146). Last but not least, we have demonstrated that it could be the hallmark *symptom* of JME (the myoclonic jerks), rather than the epilepsy syndrome per se, that is associated with a tendency to make impulsive choices. Perhaps we need to rethink the way we classify GGE in the future, using the identification of clinical subtypes across the syndromes of GGE as an aid when searching for genetic causes in this large group of epilepsy. It is beyond doubt that GGE runs in families,

but there can be several syndromes of GGE manifesting within the same family, and large-scale genetic studies of GGE and GGE subsyndromes have produced disappointingly scarce findings to date (75). Perhaps it could be helpful to focus on other aspects than just type of GGE. Could it be that we have been missing the forest for the trees?

5.6 Methodological considerations

5.6.1 **Prevalence of epilepsy**

The first aim of the present project was to identify all individuals with active epilepsy in Buskerud County, including all age groups. The method of subject identification was a systematic search of medical records at Drammen Hospital for the period 1999-2013, and at the National Centre for Epilepsy for the period 2010-2013. We assume that all people with epilepsy in Buskerud County will visit Drammen Hospital at the time of diagnosis, as a consultation with a specialist and an EEG-recording is the recommended routine when diagnosing epilepsy in Norway (113, 147). Regular follow-up by a specialist is recommended as well. However, during the clinical interviews of the present project we experienced that a considerable proportion of patients had not seen a specialist for several years. Likewise, 1/3 of the patients included in the pilot study had not seen a neurologist for more than ten years (119). Hence, it is likely that newly diagnosed patients do not always continue follow-up at the hospital, especially if their seizures are easily controlled by AED. As a consequence, we might have missed patients diagnosed prior to 1999, i.e. adults and older patients, in particular if they had a mild type of epilepsy. Moreover, we suspect that epilepsy starting in advanced age, for instance as a complication following brain stroke or Alzheimer's disease, is not always examined and diagnosed at the hospital. It could be that AED treatment in some cases was initiated via telephone consultation, in order to avoid moving and stress for patients with substantial comorbidities. Such consultations would not be captured by our search. Moreover, seizures are often focal in the oldest age groups. Unless the epileptic activity spreads to a bilateral tonic clonic seizure, symptoms may be subtle and remain undiagnosed. Our suspicion that we might have missed cases in the oldest age groups is confirmed by an unexpected drop in prevalence for those > 80 years of age (Figure 10). A study of epilepsy in the elderly from the Netherlands found prevalence to be 1.2% in those aged 85-94 (148). In the present study, prevalence of epilepsy was 0.77% in those older than 80 years. On the other hand, many of the disorders potentially causing epilepsy in the elderly (i.e. brain stroke,

tumors, degenerative neurological diseases, etc.) are associated with increased mortality. Hence the drop in prevalence in the oldest age group may not solely be caused by missing cases, but could also in part be explained by increased mortality.

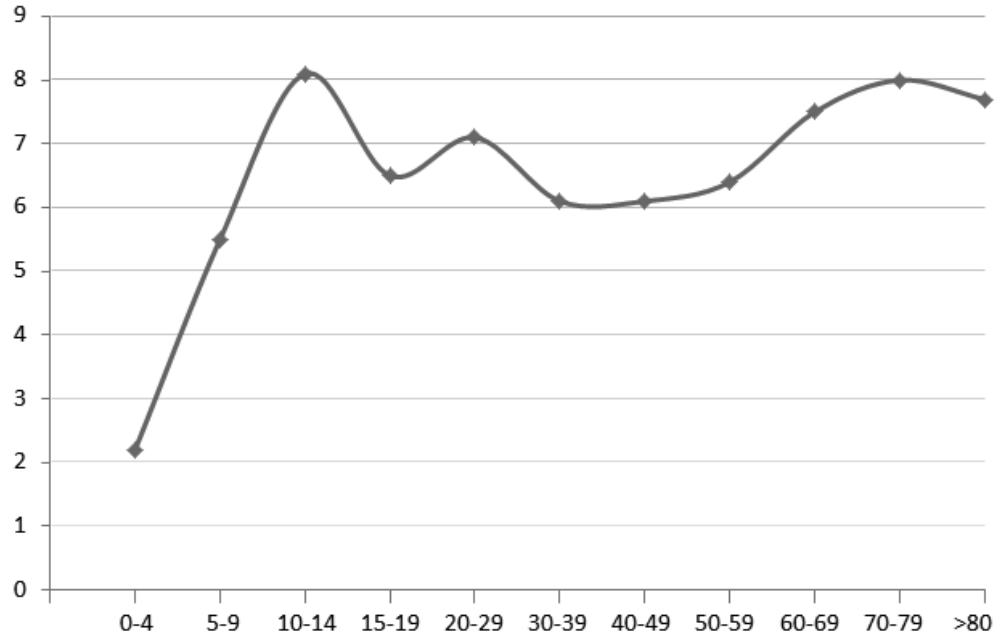

***Figure 10**. Age-specific prevalence of epilepsy in Buskerud County, showing an unexpected drop in prevalence for those > 80 years of age. The x-axis shows the different age groups in years, and the y-axis shows prevalence per 1000 inhabitants (Marte Syvertsen).*

Even though the sensitivity of the present study might be reduced due to missed mild cases diagnosed prior to 1999 and some newly diagnosed patients in the oldest age groups, the specificity of the included cases is likely to be high. The diagnosis of every single case was confirmed by a thorough review of medical records, excluding 19% who did not fulfill the ILAE definition of epilepsy (Figure 8). Thus, the estimated prevalence of active epilepsy in Buskerud County (0.65%) must be considered a *minimum prevalence*. However, identification of cases and classification of epilepsy was performed by one single reviewer, based on the conclusions of the treating physicians. It must be considered a limitation that a second reviewer did not go through the cases as well.

5.6.2 **Prevalence of juvenile myoclonic epilepsy**

When investigating prevalence of JME, the issue of cases diagnosed prior to 1999 was even more pressing, as the majority of patients with JME attain seizure freedom upon initiation of AED treatment (149). Patients could have visited the hospital prior to 1999 and potentially not be identified by our search of medical records. In order to increase the likelihood of

identifying every single case of JME in a given age group, we wanted to include only those who would have been diagnosed within the time period of our search (1999-2013). However, we assumed that children with newly diagnosed epilepsy would receive follow-up at the paediatric outpatient clinic for a few years, even if seizure freedom was attained. Hence, we allowed for epilepsy onset up to five years prior to 1999 (Figure 11). Diagnosis of JME was defined according to the class II diagnostic criteria (Table 1). However, we defined age of epilepsy onset to minimum ten years of age, according to the class I criteria, as that would allow for a slightly larger study population. In conclusion, we included all patients who were < 30 years of age at the prevalence day, meaning that they would have been no more than 15 years of age at the initiation of our search (1999). If we had used the age criterion of class II (epilepsy onset at minimum 6 years of age), we could only have included subjects up to 26 years of age, or those who were no more than 11 years old in 1999.

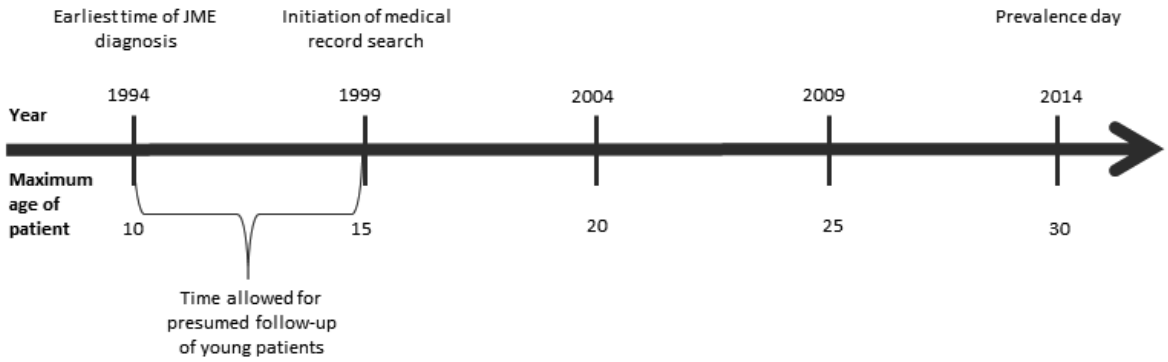

Figure 11. *Timeline of medical record search and age of patients included in the study of JME prevalence. The earliest onset of JME was defined as 10 years of age, according to the class I diagnostic criteria (Table 1) (Marte Syvertsen).*

A strength of the JME prevalence study is that we were able to contact nearly all the subjects with GGE in the given age group (93%) and inquire specifically about myoclonic jerks. Norway is well suited for the study design applied here, as there are very few private clinics, the health care system is well established and accessible to all, and the unique national identity number of all inhabitants simplifies patient identification.

Even though the diagnosis of every single case was thoroughly evaluated, making specificity high, we cannot make the same claim for sensitivity. We might have missed cases, for instance any diagnosed in a different county who had later moved to Buskerud. Thus, the

prevalence estimate of JME must be considered a *minimum prevalence*, just like the prevalence estimate of active epilepsy.

Another limitation to consider is recall bias. When asking patients if they had ever experienced myoclonic jerks, it is possible that some could have forgotten that they had such seizures in the past. People tend not to notice their myoclonic jerks (58), and these seizures could have disappeared upon initiation of AED treatment several years prior to the present survey. Thus, it is possible that some of those classified as non-JME in fact belonged to the JME-group, which strengthens the statement that the reported prevalence is a minimum prevalence.

5.6.3 **Clinical interviews**

In the clinical part of the study, we were less strict about the age criterion (i.e. maximum 40 years as opposed to maximum 30 years) as this would allow for a larger study population and increased power. However, we did not include patients older than 40 years, in order to avoid bias towards treatment-resistant epilepsy. Older patients who still visit the hospital regularly could have a more complicated type of epilepsy. People with CAE who were off AED and seizure free for more than one year were excluded, as we wanted to include only patients affected by epilepsy in youth. The aim was for the control group to be as similar to the JME-group as possible (i.e. comparable EEG-findings, epilepsy duration, epilepsy severity, medication, etc.) Hence, the control group consisted of patients with other types of GGE. If concluding that those with JME had a different kind of behavioural profile, we would have increased certainty in claiming this to be a JME-specific trait, and not just related to the stigma and challenges people with epilepsy may be exposed to (12).

A limitation of the clinical part of the study was that except from BIS and HADS, variables were collected by means of a semi-structured questionnaire as opposed to validated tools and standardized instruments. A semi-structured approach was chosen in order to allow the participants to expand upon their experiences. Additionally, it allowed a rather broad approach, exploring different aspects of the psychosocial issues that could be related to executive dysfunction. Hence, the present study must be considered hypothesis generating and in need of confirmation and elaboration by future projects that could target the problems brought to light here by means of validated questionnaires.

When it comes to the sample size, we recruited the maximum number of identified and consenting people with GGE in our region. Even though we reached a considerably larger sample size than any of the previous studies investigating psychosocial difficulties in JME (70, 109, 110, 119), police charges and use of illicit recreational drugs did not reach statistical significance as predictors of belonging to the JME-group. Collaboration across regions and/or countries is needed to increase the sample size and thus improve the quality of clinical JME studies. This is necessary in order to bring clarity to some of the questions raised in the present project.

As for the prognosis of AED withdrawal in JME, the results must be interpreted with great care, as the observation time for GTCS was just one year. It is highly possible that some patients would experience relapse of GTCS at a later stage, especially if their rate of GTCS was low in the first place. However, due to the hospital-based identification of patients, all people >40 years of age were excluded in order to avoid bias towards treatment-resistant epilepsy. Hence, a different study design would be needed to determine long-term seizure outcome.

A strength of the study is that offering home visits to those who were unable to come to the hospital may have diminished selection bias. This was particularly important, as people with severe psychosocial difficulties are most likely hard to recruit to clinical studies. Consequently, a low participation rate could lead to bias towards less psychosocial difficulties.

As a result of systematic patient identification and the offering of home visits, we do, to the best of our knowledge, present the most extensive study of the psychosocial issues of JME to date, adding weight to Janz's initial remarks about a JME-specific behavioural profile.

6 Conclusions

We conclude that epilepsy is a common type of neurologic disorder, directly affecting more than 1700 people of all ages in Buskerud County. Of all the types of epilepsy in those <30 years of age, JME constitutes 9%, and is considerably more common in the general population than previously reported. Even though JME was said to be a benign type of epilepsy by leading experts in the field (49, 63), we present evidence of a risk-taking behaviour profile in this group of patients. When compared to other types of GGE, people with JME have higher rates of police charges and use of illicit recreational drugs, and they have higher rates of AED self-withdrawal, which is thought to represent a particularly increased risk of seizure recurrence in JME. Nevertheless, 1/3 of those who discontinued medication remained free from GTCS and did not restart AED. Hence, it is possible that the strong advice against AED withdrawal in JME should be reconsidered, and that an effort must be made to identify the patients who could safely attempt withdrawal.

Finally, when measuring behavioural impulsivity by means of the BIS, we found that myoclonic jerks within the last year was a significant moderator of BIS score, irrespective of GGE type. Hence, it seems to be the presence of the hallmark *symptom* of JME, the myoclonic jerks, rather than the diagnosis of JME per se that is associated with impulsivity. This interesting finding merits further investigation in future studies, focusing on behavioural challenges across the different subsyndromes of GGE. The discussion on classification and terminology of epilepsy will probably continue, and the last word has most likely not been said on how to organise and diagnose GGE.

7 Ethical aspects

The study was approved by the Regional Committee for Medical Research Ethics (REK), South East Norway (ethical agreement no. 2013/1027) and by the data protection officer of Drammen Hospital. Written informed consent was obtained from all participants in the clinical part of the study. It was underlined that participation was voluntary, and that decline or acceptance would not influence regular clinical follow-up at the hospital.

Patients unable to give informed consent (i.e. patients with intellectual disability) were not interviewed in this study. Ten patients aged 14-16 years were included, as the youngest participants. They were given age-appropriate written information, as recommended by REK. Written informed consent was signed by their parents. Written information for parents of minor study participants was handed out to all parents.

In some participants, potential for improved treatment was discovered. The treating physician was contacted, and alteration of treatment was carried out in co-operation with him/her. If a participant expressed a wish to continue follow-up with a doctor in the research team, this was offered, in agreement with the treating physician. Some participants did not attend regular specialist follow-up, even when suffering from ongoing seizures. In these cases, follow-up was offered by a doctor in the research team. In some of the study participants, AED treatment was changed and seizure-freedom was attained as a direct consequence of inclusion in the present study.

Ample time was scheduled for the clinical interview, considering the sensitive nature of some of the questions. These questions were always asked in private, after establishing a relation through conversation, and through the initial parts of the semi-structured interview. Parents were asked to leave the room during this part, after having been informed about the nature of the questions.

The contact information of the research team was given to all study participants and parents. They could freely reach out to the research team following the clinical interview, in case of questions or additional information, or in case they wished to withdraw their consent. None of the participants chose to do so.

8 Collaboration

8.1 Oslo University Hospital

When investigating prevalence of epilepsy in Buskerud County, we collaborated with The National Centre for Epilepsy, Oslo University Hospital, where we searched medical records in order to identify patients from Buskerud. Karl Otto Nakken at The National Centre for Epilepsy played a key role in initiating and planning of the present project, and it was he who introduced JME as a topic of interest.

Regarding our participation in the Biology of JME (BIOJUME) research project (see 8.3 BIOJUME), we have collaborated with The Department of Medical Genetics at Oslo University Hospital, where DNA was extracted from the collected blood samples. Kaja Selmer at Oslo University Hospital was responsible for this part of the project, and she played a key role in establishing our collaboration with BIOJUME.

8.2 St. Olav's Hospital

We were invited to participate in a long-term follow-up study of 42 patients with JME at St. Olav's Hospital in Trondheim, supervised by prof. Eylert Brodtkorb. This study served as an important preparation and was hypothesis-generating for the present research project.

8.3 BIOJUME

At the initiation of our project, we were invited to participate in the international multicentre study BIOJUME, led by prof. Deb Pal at King's College London. BIOJUME aims to improve understanding of the pathophysiological process of JME by means of genetic studies. The goal is to include DNA-samples from 1000 people with JME, and analyse these in a genome-wide association study (GWAS). The onset of the clinical part of our project coincided with the kick-off meeting of BIOJUME, which opened a collaboration of mutual benefit. Through BIOJUME we have been able to consult leading experts within the field of epilepsy in general and JME in particular, including members of the consortium defining the diagnostic criteria of JME (62), and members of the Koepp/Richardson-group, who coined the mechanism behind cognitively triggered myoclonic jerks in JME (84, 88). Head of BIOJUME, prof. Deb Pal, and

neuropsychologist Anna Smith (King's College) participated in generating the hypotheses for the clinical part of our project, and they were central in analysing and interpreting data from the interviews. This partnership has improved the quality of our work and paved the way for future projects. In return, we will contribute a substantial part of the DNA-samples collected in BIOJUME, and we have contributed to introducing impulsivity as a focus of interest.

8.4 Oslo Metropolitan University

Throughout the clinical part of our project, we have collaborated with master student Ida Fløgstad at the Programme for Pharmacy, Oslo Metropolitan University, and her supervisor prof. Cecilie Landmark Johannessen. Fløgstad investigated use of AED, therapeutic drug monitoring, and AED adherence in JME participants of the present study, completing a master thesis on the topic. Their expertise was of great help when analysing AED withdrawal in JME (Paper III).

8.5 The Norwegian Epilepsy Association

We have an ongoing collaboration with the Norwegian Epilepsy Association (NEF), initiated at the onset the present project. Information about the clinical part of the study and an invitation to participate was published in their magazine for members, "Epilepsinytt." When designing the semi-structured interview we had meetings with Claudia Ursulescu at Norsk Epilepsiforbund Ungdom (NEFU) and NEF leader Henrik Peersen. We participated at NEFU's summer camp twice in order to share information about the project and receive input on topics of interest to NEFU members. Based on the feedback from NEFU, we initiated a master thesis on the topic of psychosocial difficulties in young people with epilepsy, by Thea Moth and Samitha Vasantharajan at The Faculty of Medicine, University of Oslo.

9 Future perspectives

Through a retrospective review of medical records in addition to consecutive recruitment from the EEG laboratory, and offering home visits to those who were unable to come to the hospital, the present project was able to include a large and representative group of people with JME. Furthermore, by comparing to other types of GGE, we were able to highlight issues that may be JME-specific, and not just related to living with epilepsy in youth. By means of this approach, we contribute to challenging some of the established "truths" about JME: 1. That it is a benign type of epilepsy with a psychosocial prognosis that does not differ much from that of other people with epilepsy (63, 109). 2. That all people with JME should stay on AED treatment throughout life (42, 63). 3. That they actually follow this advice and continue treatment throughout life.

When it comes to the first point, it is tempting to draw a line between behavioural issues possibly caused by impulsivity, the structural changes demonstrated within the frontal lobes of people with JME (87), and executive dysfunction as demonstrated for instance by the Stroop task (95). This assumption cannot be made based on the present material, however, as neuroimaging and neuropsychological testing was not performed. It would be interesting, if a future project could unite these three entities; i.e. sophisticated imaging techniques (tractography and VBM), neuropsychological testing, and a careful history of behavioural difficulties, preferably including standardized tools like BIS or Behaviour Rating Inventory of Executive Function (BRIEF), highlighting behaviours associated with taking risks in particular. Moreover, a prospective approach would be ideal, mapping the presence of myoclonic jerks at time of diagnosis, preferably prior to the initiation of treatment. It would then be possible to pursue the hypothesis of persistent myoclonic jerks as a predictor of impulsive behaviour, and the consequences thereof. If this link is established, a different approach to treatment and follow up of GGE would be called for. At present, treatment is often aimed at controlling GTCS, whilst occasional myoclonic jerks are tolerated, as they are usually not perceived as bothersome, if noticed at all.

That being said, we also discovered that a large proportion of people with JME did not follow the advice of continuing AED treatment. We assume that they had been informed about the risks thought to be associated with AED withdrawal. Still, a considerable amount of those who withdrew medication obtained a positive result; i.e. they did not experience GTCS

relapse and did not restart medication. They choose this risk above the daily impact of AED medication, which might be understandable. That they were strongly advised against withdrawal, but still perceived the outcome as positive, might have an impact on trust and relations to care-givers in the health care system. On the other hand, if persistent myoclonic jerks really are related to behavioural issues, we might need to completely change treatment goals and information given to this group of patients. We must be able to identify those who could safely taper AED medication, preferably without recurrence of GTCS or myoclonic jerks. Presently, we give strong advice on treatment, which a large group choose not to follow. Consequently, they probably see less reason to seek specialist help again and are lost to follow-up.

In summary, it may seem like JME, which is considered to be one of the most classical types of epilepsy and a now well-established neurological diagnosis, also touches upon the fields of psychiatry and psychology. Simplifying matters, we could say that neurologists have been overly concerned with the parietal, occipital, and temporal lobes, whilst the frontal lobe has been the domain of psychologists and psychiatrists. Interestingly, the region thought to be central in the generation of myoclonic jerks, the SMA (88), is located right at the border of the parietal and the frontal lobe (Figure 7). Perhaps unravelling the pathophysiological process of JME will contribute to bridging of the unnatural gap between neurology and psychiatry/psychology.

If joining forces across specialities, regions, and/or country borders, we might be able to bring together all existing knowledge, analysing larger cohorts and generating more robust results, and eventually understand exactly what happens within the neuronal networks of people who experience myoclonic jerks.

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Supplements

SPØRRESKJEMA
JUVENIL MYOKLONUSEPILEPSI (JME)
/GENETISK GENERALISERT EPILEPSI (GGE)

Bakgrunn

1. Kjønn ❑ Kvinne ❑ Mann

2. Alder: _____ år

3. Har noen andre i familien epilepsi?
- ❑Mor/far
- ❑Søsken
- ❑Egne barn
- ❑Besteforelder

4. Har pasienten egne barn?
❑Ja ❑Nei

5. Har pasienten hatt behov for barnevernstjenester?
❑Fosterhjem ❑Annet ❑Vet ikke

6. Har pasientens eventuelle barn hatt behov for barnevernstjenester?
❑Fosterhjem ❑Annet ❑Vet ikke

7. Har pasienten hatt behov for spesialundervisning i skolen?
❑Ja ❑Nei ❑Vet ikke

8. Synes pasienten selv at det har vært mye fravær fra skole?
❑Ja ❑Nei ❑Vet ikke

9. Hvilken utdanning er den høyeste fullførte?
- ❑Mindre enn 7 år grunnskole
- ❑Grunnskole 7-10 år
- ❑Videregående skole/yrkesskole 10-13 år
- ❑Høyskole/Universitet mindre enn 4 år
- ❑Høyskole/Universitet 4 år eller mer

10. Arbeid/utdanning
- ❑Lønnet arbeid
- ❑Selvstendig næringsdrivende
- ❑Hjemmeværende uten stønad
- ❑Skoleelev/utdanning
- ❑Mottar stønad fra NAV

11. Har epilepsien hatt innflytelse på utdannings- eller yrkesvalg?
❑Ja ❑Nei ❑Vet ikke

Epilepsi

12. Hvilke anfallstyper har pasienten?

- ❑Myoklonier
- ❑Absencer
- ❑GTK

13. Alder ved anfallsdebut

Myoklonier:_____
Absencer:_____
GTK/grand mal:_____

14. Alder ved oppstart av medikasjon

_____

15. Anfallshyppighet myoklonier

- ❑Daglig
- ❑Ukentlig
- ❑Månedlig
- ❑Sjeldnere enn månedlig
- ❑Anfallsfri i mer enn ett år
- ❑Har aldri hatt myoklonier

16. Anfallshyppighet absencer

- ❑Daglig
- ❑Ukentlig
- ❑Månedlig
- ❑Sjeldnere enn månedlig
- ❑Anfallsfri i mer enn ett år
- ❑Har aldri hatt absencer

17. Anfallshyppighet GTK

- ❑Daglig
- ❑Ukentlig
- ❑Månedlig
- ❑Sjeldnere enn månedlig
- ❑Anfallsfri i mer enn ett år
- ❑Har aldri hatt GTK

18. I hvilket år var det siste anfallet?

Myoklonier:_____
Absencer:_____
GTK:_____

19. Når på døgnet kan myoklonier oppstå?

- ❑Om morgenen
- ❑Midt på dagen
- ❑Om natten
- ❑Etter søvn generelt (f.eks. etter en middagslur)
- ❑Ettermiddag/kveld

20. Når på døgnet kan absencer oppstå?

❑Om morgenen
❑Midt på dagen
❑Om natten
❑Etter søvn generelt (f.eks. etter en middagslur)
❑Ettermiddag/kveld

21. Når på døgnet kan GTK oppstå?

❑Om morgenen
❑Midt på dagen
❑Om natten
❑Etter søvn generelt (f.eks. etter en middagslur)
❑Ettermiddag/kveld

22. Føler pasienten seg uvel/dårlig/spesielt trøtt om morgenen?

❑Ja ❑Nei ❑Vet ikke

Antiepileptisk medikasjon

23. Antall antiepileptika i bruk per nå

❑Ingen
❑Ett
❑To
❑Flere enn to

24. Respons på behandling

❑Anfallsfri p.g.a. endringer i livsstil, uten antiepileptika
❑Anfallsfri på ett antiepileptikum
❑Anfallsfri på to antiepileptika eller flere
❑Behandlingsrefraktær
❑Pseudrefraktær (adekvat antiepileptikum i adekvate doser ikke utprøvd)

25. Hvilken antiepileptisk medikasjon er i bruk nå? *(Preparatnavn + dose)*

26. Hvilken antiepileptisk medikasjon er forsøkt tidligere? *(Preparatnavn + dose)*

27. Er det andre faste legemidler i bruk? *(Preparatnavn + dose)*

28. Har pasienten forsøkt seponering av antiepileptisk medikasjon?

❑Ja ❑Nei

Hvis ja, hva ble resultatet?

❑Forble anfallsfri og medikamentfri
❑Residiv, men valgte å fortsette uten medikamenter
❑Residiv, reoppstart av medikasjon og anfallsfrihet
❑Residiv, reoppstart av medikasjon, behalingsrefraktær

Hvem tok initiativet til seponering?

❑Autoseponering
❑Pasienten tok det opp med legen
❑Legen tok det opp med pasienten

Hvor lang anfallsfrihet var det før seponering?

❑0-2 år
❑2-5år
❑5-10 år
❑Mer enn 10 år

Psykososiale aspekter

29. Har det vært behov for tjenester innen psykisk helsevern?

❑Ja ❑Nei ❑Vet ikke

30. Er det utredet eller behandlet for ADHD?

❑Utredet
❑ADHD diagnose stillet
❑Nei
❑Vet ikke

31. Har pasienten vært diagnostisert med psykose?

❑Ja ❑Nei ❑Vet ikke

32. Har pasienten følt seg ekskludert p.g.a. epilepsi?

❑Ja ❑Nei ❑Vet ikke

33. Har pasienten selv utelatt å være med på sosiale aktiviteter p.g.a. epilepsien?

❑Ja ❑Nei ❑Vet ikke

34. Har pasienten opplevd mobbing?

❑Ja ❑Nei ❑Vet ikke

35. Har pasienten bevisst holdt diagnosen skjult?

❑Ja ❑Nei ❑Vet ikke

36. Har pasienten hatt selvmordstanker?

❑Ja ❑Nei ❑Vet ikke

37. Har pasienten utført noen form for selvskading?

❑Ja ❑Nei ❑Vet ikke

38. Har det vært alvorlige psykososiale utfordringer hos en eller begge foreldre?

❑Ja ❑Nei ❑Vet ikke

39. Har pasienten vært utsatt for vold eller overgrep?

❑Ja ❑Nei ❑Vet ikke

40. Har pasienten vært gravid uten at det var planlagt?

❑Ja ❑Nei ❑Vet ikke

41. Har pasienten brukt ulovlige rusmidler mer enn to ganger?

❑Ja ❑Nei ❑Vet ikke

42. Har pasienten røkt sigaretter før fylte 18 år?

❑Ja ❑Nei ❑Vet ikke

43. Har pasienten vært anklaget for noe av politiet?

❑Ja ❑Nei ❑Vet ikke

BIS-11

Spørsmålene nedenfor handler om hvordan du vanligvis reagerer og handler. Svar ut fra hvor godt du synes utsagnene beskriver deg. Svaralternativene er ”Sjelden/aldri”, ”Av og til”, ”Ofte” og ”Nesten alltid/alltid”.

		SJELDEN/ALDRI	AV OG TIL	OFTE	NESTEN ALLTID/ALLTID
BIS-11 1	Jeg planlegger oppgaver nøye.	☐	☐	☐	☐
BIS-11 2	Jeg gjør ting uten å tenke.	☐	☐	☐	☐
BIS-11 3	Jeg gjør meg fort opp en mening.	☐	☐	☐	☐
BIS-11 4	Jeg er en ubekymret og sorgløs person.	☐	☐	☐	☐
BIS-11 5	Jeg er ikke oppmerksom.	☐	☐	☐	☐
BIS-11 6	Jeg har tanker som raser av gårde.	☐	☐	☐	☐
BIS-11 7	Jeg planlegger reiser god tid i forveien.	☐	☐	☐	☐
BIS-11 8	Jeg er selvkontrollert.	☐	☐	☐	☐
BIS-11 9	Jeg konsentrer meg lett.	☐	☐	☐	☐
BIS-11 10	Jeg sparer regelmessig.	☐	☐	☐	☐
BIS-11 11	Jeg ”vrir meg” på teateret eller under forelesninger.	☐	☐	☐	☐
BIS-11 12	Jeg er en grundig tenker.	☐	☐	☐	☐
BIS-11 12	Jeg planlegger for å ha en sikker jobb.	☐	☐	☐	☐
BIS-11 14	Jeg sier ting uten å tenke.	☐	☐	☐	☐
BIS-11 15	Jeg liker å tenke over komplekse problemer.	☐	☐	☐	☐
BIS-11 16	Jeg skifter jobber.	☐	☐	☐	☐
BIS-11 17	Jeg handler på impuls.	☐	☐	☐	☐
BIS-11 18	Jeg kjeder meg fort når jeg løser tankeproblemer	☐	☐	☐	☐
BIS-11 19	Jeg handler ut fra øyeblikket.	☐	☐	☐	☐
BIS-11 20	Jeg er en stødig tenker.	☐	☐	☐	☐
BIS-11 21	Jeg endrer bosted.	☐	☐	☐	☐
BIS-11 22	Jeg kjøper ting på impuls.	☐	☐	☐	☐

		SJELDEN/ALDRI	AV OG TIL	OFTE	NESTEN ALLTID/ALLTID
BIS-11 23	Jeg kan bare tenke på et problem av gangen.	☐	☐	☐	☐
BIS-11 24	Jeg bytter hobbyer.	☐	☐	☐	☐
BIS-11 25	Jeg bruker eller låner mer enn jeg tjener.	☐	☐	☐	☐
BIS-11 26	Jeg har ofte forstyrrende tanker når jeg tenker.	☐	☐	☐	☐
BIS-11 27	Jeg er mer interessert i nåtiden enn fremtiden.	☐	☐	☐	☐
BIS-11 28	Jeg er rastløs i teateret eller under forelesninger.	☐	☐	☐	☐
BIS-11 29	Jeg liker gåtefulle oppgaver/problemer.	☐	☐	☐	☐
BIS-11 30	Jeg er fremtidsorientert.	☐	☐	☐	☐

HAD

Hospital Anxiety & Depression Scale (januar 1999)

Navn: _____ Fødselsdato: _____

Dato for utfylling: _____ Pasient nr.: _____

Behandler: _____

Rettledning

Legen er klar over at følelser spiller en stor rolle ved de fleste sykdommer. Hvis legen vet mer om følelser, vil han/hun bli bedre i stand til å hjelpe deg.

Her kommer noen spørsmål om hvorledes du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser den siste uken. Ikke tenk for lenge på svaret – de spontane svarene er best.

1. Jeg føler meg nervøs og urolig

- ❑ 3 Mesteparten av tiden
- ❑ 2 Mye av tiden
- ❑ 1 Fra tid til annen
- ❑ 0 Ikke i det hele tatt

2. Jeg gleder meg fortsatt over tingene slik jeg pleide før

- ❑ 0 Avgjort like mye
- ❑ 1 Ikke fullt så mye
- ❑ 2 Bare lite grann
- ❑ 3 Ikke i det hele tatt

3. Jeg har en urofølelse som om noe forferdelig vil skje

- ❑ 3 Ja, og noe svært ille
- ❑ 2 Ja, ikke så veldig ille
- ❑ 1 Litt, bekymrer meg lite
- ❑ 0 Ikke i det hele tatt

4. Jeg kan le og se det morsomme i situasjoner

- ❑ 0 Like mye nå som før
- ❑ 1 Ikke like mye nå som før
- ❑ 2 Avgjort ikke som før
- ❑ 3 Ikke i det hele tatt

5. Jeg har hodet fullt av bekymringer

- ❑ 3 Veldig ofte
- ❑ 2 Ganske ofte
- ❑ 1 Av og til
- ❑ 0 En gang i blant

6. Jeg er i godt humør

- ❑ 3 Aldri
- ❑ 2 Noen ganger
- ❑ 1 Ganske ofte
- ❑ 0 For det meste

7. Jeg kan sitte i fred og ro og kjenne meg avslappet

- ❑ 0 Ja, helt klart
- ❑ 1 Vanligvis
- ❑ 2 Ikke så ofte
- ❑ 3 Ikke i det hele tatt

8. Jeg føler meg som om alt går langsommere

- ❑ 3 Nesten hele tiden
- ❑ 2 Svært ofte
- ❑ 1 Fra tid til annen
- ❑ 0 Ikke i det hele tatt

9. Jeg føler meg urolig som om jeg har sommerfugler i magen

- ❑ 0 Ikke i det hele tatt
- ❑ 1 Fra tid til annen
- ❑ 2 Ganske ofte
- ❑ 3 Svært ofte

10. Jeg bryr meg ikke lenger om hvordan jeg ser ut

- ❑ 3 Ja, jeg har sluttet å bry meg
- ❑ 2 Ikke som jeg burde
- ❑ 1 Kan hende ikke nok
- ❑ 0 Bryr meg som før

11. Jeg er rastløs som om jeg stadig må være aktiv

- ❑ 3 Uten tvil svært mye
- ❑ 2 Ganske mye
- ❑ 1 Ikke så veldig mye
- ❑ 0 Ikke i det hele tatt

12. Jeg ser med glede frem til hendelser og ting

- ❑ 0 Like mye som før
- ❑ 1 Heller mindre enn før
- ❑ 2 Avgjort mindre enn før
- ❑ 3 Nesten ikke i det hele tatt

13. Jeg kan plutselig få en følelse av panikk

- ❑ 3 Uten tvil svært ofte
- ❑ 2 Ganske ofte
- ❑ 1 Ikke så veldig ofte
- ❑ 0 Ikke i det hele tatt

14. Jeg kan glede meg over gode bøker, radio og TV

- ❑ 0 Ofte
- ❑ 1 Fra tid til annen
- ❑ 2 Ikke så ofte
- ❑ 3 Svært sjelden

Takk for utfyllingen!

Sum A:

1+3+5+7+9+11+13= _____

Sum D:

2+4+6+8+10+12+14= _____

Sum A + D: _____

Skåringsveiledning til HAD

(Hospital Anxiety and Depression Scale)

Selvutfylling på sju angst- og depresjonsspørsmål.

Sum A eller Sum D:
En skår på 11 eller mer regnes for å være et tilfelle av angst eller depresjon som vil trenge nærmere utredning (med SPIFA for eksempel) og eventuelt behandling. En skår på 8-10 anses som et mulig tilfelle, og lavere skår uttrykker en viss symptombelastning, som kan ha betydning samlet sett, men som i seg selv ikke krever spesifikk behandling av angst eller depresjon.

Sum A + Sum D:
Det er også mulig å legge sammen angst- og depresjonsskåren til en totalskår fordi en del pasienter har en blanding av angst og depresjon. Et tilfelle vil da ha en totalskår på 19 eller mer. Et mulig tilfelle vil ha en skår på 15-18. Skår på over 15 vil trenge oppfølging og eventuelt behandling.

Dersom inntil to spørsmål på HAD er ubesvart, vil det være mulig å beregne totalskår. Sumskåren deles med antallet besvarte spørsmål og svaret ganges med 14. Dette gir estimert totalskår.

Referanser:

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.

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Paper III

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ORIGINAL ARTICLE

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Antiepileptic drug withdrawal in juvenile myoclonic epilepsy

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Objectives: Withdrawal of antiepileptic drugs (AEDs) has been discouraged in juvenile myoclonic epilepsy (JME). However, impulsivity as a consequence of executive dysfunction in JME may influence treatment adherence. The aim of the present study was to assess how common withdrawal of AEDs is in a large and representative JME group.

Materials and methods: Patients with genetic generalized epilepsy (GGE) were identified through a retrospective search of medical records at Drammen Hospital, Norway, and invited to a clinical interview. Information related to AED withdrawal was analyzed in those classified as JME.

Results: A total of 132 patients with GGE were interviewed (87 JME). Thirty-five patients with JME (40%) discontinued AEDs, of which 74% did so without consulting a doctor. The rate of self-withdrawal was significantly higher in JME than in other types of GGE. Having a parent with psychosocial difficulties was significantly overrepresented in the JME self-withdrawal group. Twelve of those who discontinued AEDs (34%) were free from generalized tonic-clonic seizures (GTCS) and without antiepileptic drugs >1 year. All but one of them withdrew AEDs without consulting a doctor. Age at first motor seizure was significantly higher in those with a favorable outcome of AED withdrawal.

Conclusions: Self-withdrawal of AEDs is common in JME, especially in those with troublesome conditions at home. However, about 1/3 may remain free from GTCS without AEDs. The findings indicate a need for a stronger follow-up with appropriate information about the prognosis of the disorder.

KEYWORDS
adherence, antiepileptic drugs, juvenile myoclonic epilepsy, withdrawal

1 | INTRODUCTION

Juvenile myoclonic epilepsy (JME) is the most common type of epilepsy affecting adolescents, and it is hallmarked by myoclonic jerks, predominantly after awakening, aggravated by sleep deprivation and stress.[1] The majority of patients have occasional generalized tonic-clonic seizures (GTCS), and about one-third have absence seizures.[2] The antiepileptic drugs (AEDs) most commonly used in the treatment of JME are valproate, lamotrigine, levetiracetam, topiramate, and zonisamide.[3]

Juvenile myoclonic epilepsy was initially considered a manageable type of epilepsy, with intellectual abilities within the normal range, normal neurologic examination, normal magnetic resonance imaging of the brain, and a favorable response to treatment in the majority of patients.[4,5] However, the rate of relapse upon withdrawal of AEDs was high, and the general advice was that these patients ought to continue medication throughout life.[5-7] Smaller, but more

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recent, retrospective studies support this, with seizure relapse in eight of ten and 17/17 JME patients attempting AED withdrawal.[8,9] Consequently, people with JME have been excluded from prospective AED withdrawal trials.[10,11]

Lifelong treatment of a disorder starting in youth means exposure to a considerable burden of medication, including short-term adverse effects, which generally subside when treatment is ended, and long-term adverse effects. Long-term adverse effects may persist for months or years after withdrawal of the causative agent. Moreover, AEDs is a challenging group of drugs to be managed in mono- or polytherapy due to pronounced pharmacokinetic variability and numerous pharmacokinetic interactions.[12,13] It is not certain, however, that all people with JME need treatment with AEDs throughout life. Some are able to control seizures by avoiding trigger factors like sleep deprivation and stress.[14] Several long-term follow-up studies of JME state that some patients may discontinue AED treatment and remain seizure-free.[15-21] Discrepancies between medical advice and the patient's experience or ability to follow such advice may lead to distrust, and it is likely that people with JME experience challenges with adherence to treatment as a potential consequence of executive dysfunction and impulsive decision making.[22-24] These issues are probably overlooked in clinical practice, as patients distrusting their doctor will most likely not return to the hospital for follow-up. The aim of the present study was to assess the magnitude of AED withdrawal in a large and representative group of patients with JME.

2 | METHODS

2.1 | Study area

Recruitment of patients was based on a search of medical records at Drammen Hospital in the time period 1999-2013. All medical records containing an International Classification of Diseases, 10th Revision (ICD-10) code of epilepsy (G40) were reviewed.[25] Drammen Hospital serves the inhabitants of Buskerud county and four neighboring municipalities, that is, a population of 477 000 people, or 9.1% of Norway's total population.[26] Buskerud county has one department of neurology, one department of pediatrics, and one electroencephalogram (EEG) laboratory, all located at Drammen Hospital. There is one private neurologist, and two private pediatricians in the county, who will refer patients to Drammen Hospital when in need of an EEG recording. EEG recordings and consultations with a specialist are standard procedure when diagnosing epilepsy in Norway.[25] Thus, we hypothesized that the vast majority of patients with epilepsy in our region visited Drammen Hospital at least once and would be registered in our records.

2.2 | Participants

As the diagnosis of JME can be highly unreliable based on medical records only,[1] all patients with genetic generalized epilepsy (GGE) aged 14-40 years were invited to a clinical interview at Drammen Hospital. Patients older than 40 years were not contacted, as including older age-groups could have biased our results toward more treatment-resistant epilepsy. We assumed that several of those diagnosed prior to 1999 who responded well to treatment did not return to the hospital and would not be identified in our search of medical records from 1999 to 2013. Patients with childhood absence epilepsy (CAE) who did not use AEDs and were seizure-free for more than 1 year were not contacted. If a patient was younger than 18 years, the parents were contacted. After finalizing the search of medical records, patients with GGE aged 14-40 years were consecutively recruited from the EEG laboratory at Drammen Hospital. Those who declined a hospital visit were offered a home visit.

2.3 | Clinical interview

The clinical interviews were conducted between November 2016 and February 2018 at Drammen Hospital or in the participant's home. A semistructured questionnaire designed for the purpose of this study was used. The questionnaire contained sections on background and medical history, AED treatment, and AED withdrawal. Additionally, the Hospital Anxiety and Depression Scale (HADS) and the Barratt Impulsiveness Scale (BIS) were administered.[27,28] HADS is scored on a 0-42 point scale, with higher scores indicating more anxiety and depression. Total BIS score may range from 30 to 120, with higher scores indicating more impulsive behavior. The interviews were organized for research purpose only, independent of regular clinical follow-up.

2.4 | Classification and definitions

As suggested by the International League against Epilepsy (ILAE), GGE included the following electroclinical epilepsy syndromes: JME, CAE, juvenile absence epilepsy (JAE), and epilepsy with generalized tonic-clonic seizures only.[29] The definition of JME was based on the consensus on diagnosing and management of JME issued in 2013.[2] Myoclonic jerks had to be the dominating seizure type.[1] Patients were classified as JME or non-JME based on information from the clinical interview, medical records, and EEG recordings. Generalized spike or polyspike and wave activity had to be present on at least one EEG recording, and EEG background activity had to be normal.[2] Polytherapy was defined as two or more AEDs used concomitantly. Self-withdrawal was defined as intentional discontinuation of antiepileptic medication without consulting a doctor.

2.5 | Statistical methods

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 23. Variables potentially influencing AED self-withdrawal were analyzed one by one, as were variables potentially influencing the outcome of withdrawal. Student's *t* tests were used for comparison of continuous variables, and chi-square tests were used for comparison of categorical variables, with Yate's continuity correction

for 2x2 tables. When expected cell count was less than five in any cell, Fisher's exact probability test was used. *P*-values ≤0.05 were considered significant.

2.6 | 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, and from parents if the participant was younger than 18 years.

3 | RESULTS

3.1 | Participants

We contacted 205 patients with GGE, of which 141 (69%) agreed to participate in the study. Eighty-seven patients (62%) were classified as JME. Forty-five (32%) were classified as other types of GGE. Nine patients were excluded as they could not be classified as GGE according to the inclusion criteria. Demographic and clinical characteristics of the patients with JME and other types of GGE are summarized in Table 1. Antiepileptic drugs used in the patients with JME are presented in Figure 1. Eighteen patients with JME had been off AED medication for >1 year. Two of them (11%) had a GTCS within the last year. In comparison, 18 of the 74 patients using AEDs (24%) had a GTCS within the last year. Fifteen patients not using AEDs (83%) had myoclonic jerks within the last year, compared to 48 (65%) of those using AEDs. The differences were not statistically significant.

TABLE 1 Demographic and clinical characteristics of 132 patients with GGE

	JME *N* = 87	Other GGE *N* = 45[a]
Female/Male	50/37 (57%/43%)	26/19 (58%/42%)
Mean age at inclusion (y)	25.7 (SD = 6.7)	23.5 (SD = 6.7)
Mean age at first seizure	14.8 (SD = 2.8)[b]	12.1 (SD = 5.2)
Mean epilepsy duration (y)	10.9 (SD = 6.4)	11.4 (SD = 8.1)
History of absence seizures	28 (32%)	30 (67%)
History of myoclonic jerks	87 (100%)	12 (27%)
History of GTCS	80 (92%)	39 (87%)
Off antiepileptic drugs >1 y	18 (21%)	7 (16%)
Never started antiepileptic drug treatment	4 (5%)	1 (2%)
Monotherapy	56 (64%)	34 (76%)
Polytherapy	13 (15%)	4 (9%)
No GTCS within the last year	69 (79%)	37 (82%)
No seizures within the last year[c]	28 (32%)	26 (58%)

SD, standard deviation.
[a]8 childhood absence epilepsy, 22 juvenile absence epilepsy, 15 epilepsy with GTCS only.
[b]Mean age at first motor seizure. Nine patients (10%) had CAE evolving to JME.
[c]Including GTCS, absences, and myoclonic jerks.

3.2 | Rate of antiepileptic drug withdrawal

Thirty-five patients with JME (40%) had a history of withdrawing AED treatment, of which 26 (74%) did so without consulting a doctor. In the group with other types of GGE, 24 patients (53%) withdrew AED, of which ten (41%) did so without consulting a doctor. The rate of self-withdrawal was significantly higher in the JME group (*P* = 0.024). Factors potentially influencing self-withdrawal in JME are presented in Table 2. A parent with psychosocial difficulties like addiction or violent behavior (as reported by the patient) was significantly more common in the group with a history of AED self-withdrawal (*P* = 0.006). Sixteen of those who self-withdrew AEDs (62%) did so within 2 years of their last GTCS.

3.3 | Outcome of antiepileptic drug withdrawal

The outcomes of AED withdrawal in 35 patients with JME are presented in Figure 2. Twelve patients (34%) experienced no relapse of GTCS and did not restart AED therapy. All but one of them self-withdrew their AEDs. Factors potentially influencing outcome of AED withdrawal are presented in Table 3. Age at first motor seizure was significantly higher in the group with the most favorable outcome.

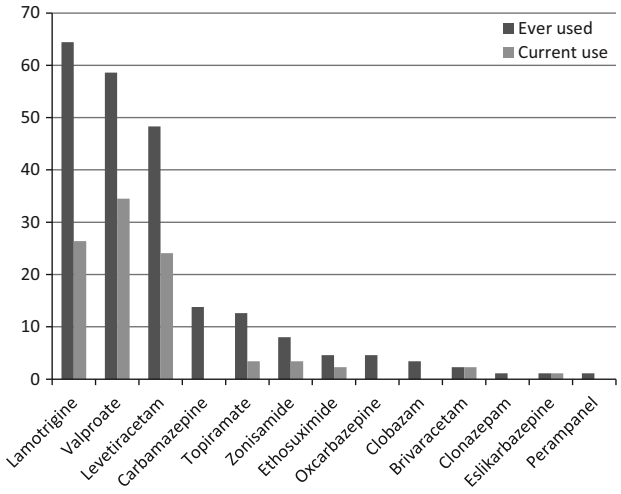

FIGURE 1 History of antiepileptic drug use in 87 patients with JME. Numbers are in percent

4 | DISCUSSION

To the best of our knowledge, we present the largest study assessing AED withdrawal in JME, reflecting the regular clinical setting of

TABLE 2 Clinical and psychosocial factors in 87 patients with JME in relation to self-withdrawal of AED treatment

	Self-withdrawal of AEDs *N* = 26	No self-withdrawal of AEDs *N* = 61
Female/male	16/10 (62%/38%)	34/27 (56%/44%)
Age at inclusion (y)	26.9 (SD = 6.5)	25.2 (SD = 6.8)
Epilepsy duration (y)	11.8 (SD = 5.9)	10.6 (SD = 6.6)
Polytherapy	1 (4%)	12 (20%)
Antiepileptic drugs, previous or present		
Lamotrigine	19 (73%)	37 (61%)
Levetiracetam	8 (31%)	32 (53%)
Topiramate	5 (19%)	6 (10%)
Valproate	18 (69%)	34 (56%)
Zonisamide	2 (8%)	5 (8%)
Adverse effects of antiepileptic drugs[b]	11 (42%)	27 (44%)
Identifiable seizure trigger factors	25 (96%)	55 (90%)
Currently employed or studying	21 (81%)	47 (77%)
High school degree	18 (69%)	35 (57%)
Ever in need of psychiatric health care	15 (58%)	32 (53%)
Parent with psychosocial difficulties[b,c]	**15 (58%)**	**15 (25%)**
Current quality of life[e]	6.9 (SD = 2.6)	7.3 (SD = 7.3)
Total BIS score	66.8 (SD = 9.5)	64.4 (SD = 10.3)
Total HADS score	10.8 (SD = 6.0)	11.9 (SD = 6.9)
Depression subscore	4.0 (SD = 3.5)	3.8 (SD = 3.0)
Anxiety subscore	6.9 (SD = 4.0)	8.1 (SD = 4.5)

Statistically significant findings are marked in bold.
SD, standard deviation.
[b]Rash on lamotrigine, and/or mood change on levetiracetam, and/or weight gain on valproate.
[c]Addiction or violent behavior, as reported by the patient.
[d]Statistically significant ($P \leq 0.05$).
[e]Measured by a visual analogue scale (1-10).

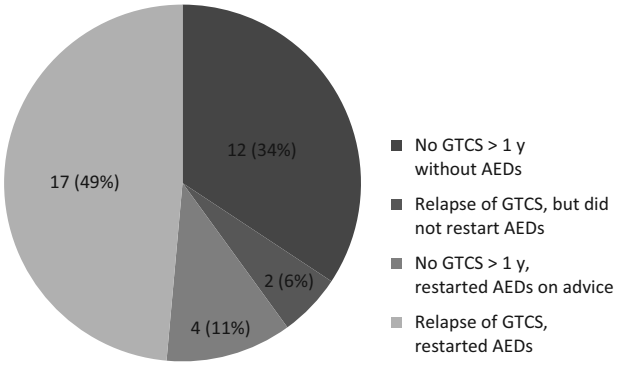

FIGURE 2 Antiepileptic drug withdrawal in 35 patients with JME

a regional department of neurology. In spite of the general advice against treatment withdrawal in JME, 40% of the included patients had discontinued AED treatment. Self-withdrawal was common, and more so in JME than in other types of GGE. Nevertheless, 1/3 of those who discontinued AED therapy remained free from GTCS and did not restart AEDs.

4.1 | Self-withdrawal of antiepileptic drugs

Considering previous studies strongly discouraging AED withdrawal in JME,[5-7] it may not be surprising that most of the JME patients opting for treatment withdrawal did so without consulting a doctor. The treating neurologist may not have provided information about the possibility of AED withdrawal, or even advised against it. Several authors state that there could be a JME-specific, risk-taking behavioral pattern related to executive dysfunction, as a consequence of deficits in thalamo-frontal-cortical neuronal circuits.[22-24] Self-withdrawal of AED may be considered a type of risk-taking behavior, as the chance of GTCS recurrence would be highly present. Thus, our findings are in support of the hypothesis of a JME-specific behavioral pattern. Furthermore, it has been demonstrated that the neuropsychological deficits delineated in JME are present in otherwise healthy siblings as well.[30] Bearing in mind that frontal lobe dysfunction and risk-taking behavior may lead to psychosocial difficulties like drug abuse and criminal behavior, it is possible that such problems may be found to a greater extent in families affected by JME.[28,31] We find it remarkable that the single factor standing out as overrepresented in the self-withdrawal JME group was having a parent with psychosocial difficulties like addiction or violent behavior. It is likely that parents with poor psychosocial outcome would have difficulties adhering to medical advice. However, mean age at seizure onset in the present study was 15 years. Consequently, the decision of self-withdrawal was most likely made by the patients themselves. All in all, if it is the case that JME families are prone to issues related to frontal lobe deficit, the follow-up and care for these patients and their families require special attention, particularly when it comes to treatment adherence, as the present study demonstrates.

Adverse effects, on the other hand, did not seem to be more common in the self-withdrawal group, which is surprising. Adverse effects are normally closely linked to non-adherence and sometimes influence quality of life to a greater extent than seizures per se.[32-34] However, adverse effects were not systematically assessed by means of standardized tools in the present study. Troublesome weight gain caused by valproate, irritability and aggression caused by levetiracetam, and rash caused by lamotrigine were inquired about specifically. Other common and sometimes disabling adverse effects of AEDs were not included, such as dizziness, headaches, and nausea.

Another interesting aspect was that more than 60% of self-withdrawal happened within 2 years of the last GTCS. This could reflect distrust in the information about a possible need for lifelong treatment, and it could reflect willingness to take a risk. Nevertheless, nearly 60% of those who self-withdrew AEDs had no relapse of

TABLE 3 Clinical and psychosocial factors in the 35 JME patients who withdrew AED treatment in relation to outcome

	No AEDs and no GTCS>1 y *N* = 12	Recurrence of GTCS and/or restart of AEDs *N* = 23
Female/male	8/4 (67%/33%)	13/10 (57%/43%)
Age at inclusion (y)	28.1 (SD = 6.8)	24.3 (SD = 6.7)
Epilepsy duration (y)	11.9 (SD = 6.1)	11.1 (SD = 6.5)
Age at first motor seizure (y)[b]	**16.2 (SD = 2.6)**	**13.2 (SD = 2.4)**
<2 y since last GTCS at time of withdrawal	7 (58%)	13 (57%)
2-5 y since last GTCS at time of withdrawal	3 (25%)	8 (35%)
>5 y since last GTCS at time of withdrawal	2 (17%)	2 (9%)
Photoparoxysmal response in EEG	4 (33%)	15 (65%)
Polyspikes in EEG	8 (67%)	11 (48%)
JME evolved from CAE	2 (17%)	3 (13%)
Three seizure types[c]	2 (17%)	6 (26%)
Self-withdrawal	11 (92%)	15 (65%)
Currently employed or studying	9 (75%)	21 (91%)
High school degree	8 (67%)	16 (70%)
Ever in need of psychiatric health care	8 (67%)	11 (48%)
Total BIS score	66.1 (SD = 11.3)	64.7 (SD = 8.1)
Total HADS score	11.4 (SD = 6.2)	10.2 (SD = 6.5)
Depression subscore	3.2 (SD = 2.5)	4.1 (SD = 3.7)
Anxiety subscore	8.3 (SD = 4.7)	6.1 (SD = 3.6)

Statistically significant findings are marked in bold.
SD, standard deviation.
[b]Statistically significant ($P \leq 0.05$)
[c]Absences, GTCS, and myoclonic jerks

GTCS and did not restart AED therapy. In fact, the rate of GTCS was lower in those who did not use AEDs than in those who were on medication, although not significantly. Myoclonic jerks on the other hand seemed to be more common in those who did not use AEDs. It is possible that patients who discontinued AED therapy had a milder type of JME with rare GTCS and that those who experienced more GTCS or a more active type of epilepsy were more motivated to continue AEDs. It seems that as long as GTCS do not recur, patients accept myoclonic jerks in order to avoid taking AEDs.

4.2 | Outcome of antiepileptic drug withdrawal

More than half of the JME patients withdrawing medication in the present study experienced GTCS relapse. Efforts have been made to identify predictors of treatment resistance in JME, and we found that age at first motor seizure was significantly lower in the group experiencing relapse and/or restarting AED therapy. This is in line with the conclusions of a recent meta-analysis, stating that low age at seizure onset is a predictor of refractory JME. They also found that absence seizures, three seizure types, JME evolving from CAE, and psychiatric comorbidities were predictors of refractoriness.[35] In the present study, neither three seizure types, nor need of psychiatric health care, nor JME evolving from CAE was overrepresented among those who experienced relapse of GTCS and/or restarted AEDs. The meta-analysis did not find photoparoxysmal response (PPR) to be a predictor of treatment-resistant JME.[35] In the present study, photoparoxysmal response was more common in the group experiencing recurrence of GTCS and/or restarting AED therapy, but not significantly. Interestingly, a German study found a significant association between seizure recurrence and PPR in JME patients withdrawing medication, while there was no association between treatment resistance and PPR. The study was small, however ($N = 31$).[16] Nevertheless, PPR as a possible predictor of seizure recurrence following AED withdrawal in JME may be an interesting and useful lead to follow in future studies. A patient with PPR may attain seizure control easily, but possibly has an increased risk of recurrence if treatment is withdrawn. Consequently, larger studies of the outcomes of AED withdrawal in JME, and not just seizure

outcome in general, are needed in order to help predicting the risks at AED withdrawal in the individual JME patient.

4.3 | Methodological considerations

A strength of the study is the recruitment of patients through a systematic search of medical records containing close to all patients with epilepsy in our region. Furthermore, a considerable participation rate was reached by offering home visits to those who were unable to come to the hospital. Thus, selection bias was reduced. The retrospective review of medical records made us able to identify those who no longer attended regular follow-up at the hospital, an essential point when it comes to exploring treatment adherence. That the interviews were independent of regular clinical follow-up is a strength as well. This probably contributed to more reliable answers when it came to adherence to treatment and medical advice.

A limitation of the present study was that observation time of seizure outcome was short. It is possible that several of the patients who had no GTCS within the last year could have a GTCS relapse at a later stage, especially if frequency of GTCS was low in the first place. However, in the hospital-based design of the study, people older than 40 years were excluded in order to avoid bias toward treatment-resistant epilepsy. Consequently, a different study design and recruitment method would be needed (ie, a follow-up study) in order to provide information about 5- and 10-year seizure outcome.

Another methodological consideration is the restricted sample size, making sophisticated statistical methods like logistic regression less suitable. Regression models would have been valuable in the assessment of potential predictors of self-withdrawal and the outcomes of such withdrawal. Nevertheless, we identified factors of interest, which could be further explored in future studies of larger sample sizes.

The lack of a systematic assessment of adverse effects is also a limitation. We sought to minimize the number of questionnaires in order to increase participation and reliability of results, considering that attention and ability to concentrate may be reduced in JME.[22] Thus, only a few adverse effects considered relevant for the drugs most commonly used in the treatment of JME were inquired about. Furthermore, investigating other aspects of non-adherence in JME would be important, as the present study evaluated self-withdrawal only. Executive dysfunction could lead to challenges related to organizing and maintaining a stable intake of AEDs. Consequently, a study of non-intentional non-adherence in JME would be of interest, for instance, by means of therapeutic drug monitoring (TDM).[36]

5 | CONCLUSION

Withdrawal of AEDs is common in JME, and self-withdrawal in particular. Self-withdrawal may be related to troublesome conditions at home, and special attention must be payed to the follow-up of people with JME and their families, particularly when it comes to treatment adherence. Some may continue without AEDs and remain free from GTCS, however. A higher age at first motor seizure may indicate a more favorable outcome.

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CONFLICT OF INTEREST

Marte Syvertsen served on the advisory board of Eisai's epilepsy educational program and received speaker honoraria from Eisai. The remaining authors have no conflict of interests.

AUTHORS' CONTIBUTION

Marte Syvertsen designed the study, had a major role in the acquisition and analyses of the data, and drafted the manuscript. Ida Fløgstad had a major role in the acquisition of data, assisted in analysis of the data, and revised the manuscript. Ulla Enger had a major role in the acquisition of data. Cecilie Johannessen Landmark had a major role in analyses and interpretation of the data and in revising the manuscript. Jeanette Koht designed and supervised the study, and revised the manuscript.

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Psychosocial complications in juvenile myoclonic epilepsy

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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

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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

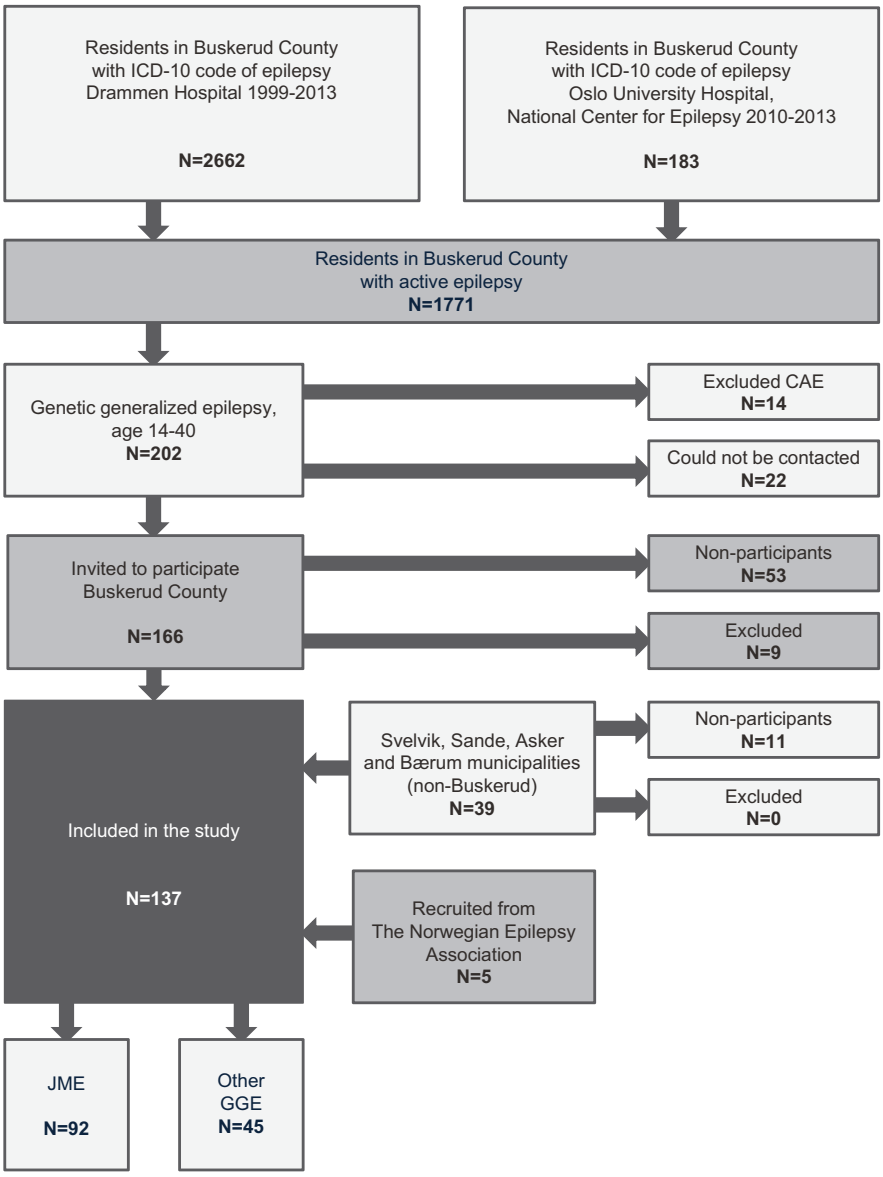

Fig. 1. Identification and inclusion of study participants. GGE = Genetic generalized epilepsy. JME = Juvenile myoclonic epilepsy. CAE = Childhood absence epilepsy.

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.

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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.

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