Chapter 5

Juvenile Myoclonic Epilepsy — A Maturation Syndrome Coming of Age

Russell D. Pella, Lakshmi Mukundan and
C. Akos Szabo

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/58372

1. Introduction

Juvenile Myoclonic Epilepsy (JME) was first described by Herpin [1] in the middle of the 19th century, reporting seizure symptoms he observed in his adolescent son. While Rabot also described myoclonia in 1899 [2], it was not until 1957 when Janz and Christian [3] provided a detailed explanation of the complete syndrome, which was subsequently called by Antonio Delgado-Escueta [4] as "JME of Janz". Since then, JME has become a well-defined epilepsy syndrome that is recognized as one of the most common forms of genetic generalized epilepsy (GGE). JME is primarily characterized by the hallmark manifestation of myoclonic seizures (mainly upon awakening), although patients also often present with a combination of absence and generalized tonic-clonic seizures (GTCS) as well. Other prevalent features of JME include various types of reflex seizures, particularly with photosensitivity. Electrophysiologically, there are prominent generalized ictal and interictal discharges on scalp electroencephalography (EEG). In contrast to other GGE syndromes, such as Childhood Absence Epilepsy (CAE), and contrary to earlier assumptions, JME has been shown to be associated with cognitive and behavioral problems, a lifetime risk of continued seizures, and medication resistance.

In this chapter, we will review the electroclinical definition of JME along with treatments for its associated seizure types, cognitive and behavioral complications, and underlying pathophysiology. In contrast to long-standing assumptions that JME is due to frontal lobe hyperexcitability that primarily involves corticothalamic pathways, recent literature suggests that JME likely reflects an underlying developmental disorder affecting multiple brain regions.

2. Clinical definition

In an historical context, the syndrome has been previously referred to as "impulsive petit-mal" epilepsy or Janz syndrome [5]. The International League Against Epilepsy (ILAE) later designated the term "Juvenile Myoclonic Epilepsy" in 1975. Under the revised Classification of Epilepsies and Epileptic Syndromes [6], the ILAE defined JME as follows:

Impulsive petit mal appears around puberty and is characterized by seizures with bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in the arms. Jerks may cause some patients to fall suddenly. No disturbance of consciousness is noticeable. Often, there are GTCS and, less often infrequent absences. The seizures usually occur shortly after awakening and are often precipitated by sleep deprivation.

While the duration of myoclonic seizures are routinely short to the effect that it is often not possible to determine if individuals lose awareness during episodes, repetitive or clustered myoclonic seizures may be associated with altered levels of consciousness. Although GTCS and/or absence seizures occur less frequently in JME, repetitive and clustered seizures can lead to secondarily generalized tonic-clonic episodes. Whereas it is nearly pathognomonic for seizures to occur upon awakening and are precipitated by sleep deprivation, an additional diurnal pattern may also be apparent as myoclonic seizures can occur late in the afternoon or in the evening as well. Electroclinically, interictal EEG patterns consist of generalized 4-6 Hz spike-or polyspike-and-wave discharges, and a relatively high prevalence of photosensitivity.

3. Epidemiology

JME accounts for approximately 4-11% of all epilepsies [7-12] with an incidence of 0.1 to 0.2 occurrences in 100,000 per year. In terms of gender effects, early studies reported that the incidence of JME was greater in male patients than females [13]; however, gender differences have not been consistent across studies, as some studies [9] have shown an equal distribution, and other researchers [10, 14-16] have reported a higher proportion (60%) of females. It is also a typically occurring GGE [12], with prevalence in GGE groups ranging from 5.5% [17] to representing the majority (45.5%) of patients [18]. Prevalence of JME as a proportion of GGE may also differ across the lifespan in some individuals as approximately 15% patients with childhood absence and juvenile absence syndromes develop JME as they age, especially those patients with photosensitive spike-and-wave findings on EEG [4, 19]. As there is a strong genetic component to JME, its prevalence is high among family members of JME patients as well, which has been shown to be the case for certain ethnic groups. Studies from Saudi Arabia, Turkey, and Iran have shown JME patients have a family association with rates that vary from 42.3 to 48.9% [18, 20, 21].

Not only are prevalence rates sensitive to genetic influences, the proportion of patients in particular clinic settings may vary as well. For example, the prevalence in primary epilepsy clinics is high, while it tends to be much lower in tertiary referral centers, due in large part

http://dx.doi.org/10.5772/58372

because primary centers achieve successful treatment via antiepileptic medications. Moreover, JME is often under-diagnosed and misdiagnosed [22, 23], which can present a challenge to estimating its prevalence. As an illustration, a French study [24] showed that the prevalence of JME in one geographic area was 0% between 1986 and 1994, which rose to nearly 50% between 1996 and 2000, likely due to increased recognition of the syndrome. Moreover, variations in clinical onset can present a challenge to estimating the prevalence of JME. Although JME the peak age of onset is in adolescence (12-18 years), similar to most GGE syndromes [10, 25], the age of onset can vary from 8 to 36 years. There are also *de novo* diagnoses in early adulthood, and JME can, though rarely, begin or be reactivated in advanced ages. For instance, a case report presented two patients from Turkey in whom JME began after the age of 70 [26].

4. Clinical diagnosis

Myoclonic Seizures: As noted above, myoclonic movements are one of the main symptoms of JME and consist of generalized seizures which are brief, irregular jerks of the head, trunk, and limbs that can be either symmetric or asymmetric, and may involve isolated regions of the body or the whole body. They usually predominate in the upper limbs (mostly distal muscles), although they occasionally involve muscles in the abdomen, paraspinal distributions, and lower extremity [27]. It is not uncommon for myoclonic seizures to be so subtle or brief that they are perceived as benign "inner shocks". As subtle as the may be, patients tend to more readily notice asymmetric jerks involving the dominant upper extremity because such movements noticeably impair daily functioning. The jerks, if violent, may cause the patient to drop or throw objects, or fall to the floor-which may be mistaken for nonpathological clumsiness. Myoclonic seizures can manifest as discrete, single events or they may occur in clusters. They are usually not associated with loss of consciousness but it is not uncommon for patients to lose awareness during the jerks. Moreover, clusters of myoclonic events can evolve into a GTCS and cause post-ictal confusion. They can occur during transition to sleep or during awakening from sleep, usually in the early morning hours [28]. This early morning pattern of seizures is associated with an increase in cortical excitability during that time of day, which has been noted in other patients with GGE, but to a greater extent in JME patients [29]. Developmentally, these jerks often subside in the fourth decade of life, although GTCS or absence seizures tend to persist [30].

Generalized Tonic-Clonic Seizures: About 80% of the patients with JME have GTCS. These seizures are also more likely to occur if precipitated by sleep deprivation or alcohol intake. Usually, these events are immediately preceded by a series of myoclonic jerks and associated tongue biting prior to generalization. Because, as noted above, myoclonic events are often insidious, patients first seek treatment following an initial GTCS and are then subsequently diagnosed with JME. Typically, upon further evaluation, such patients acknowledge also that they have experienced myoclonic jerks, a description which adds additional clinical support for a JME diagnosis. Due to this association, some authors have proposed that clinicians should

strongly consider a JME diagnosis, until proven otherwise, when teens present with an initial unprovoked GTCS [31].

Absence Seizures: Absence seizures are characterized by a brief loss of awareness (i.e., a few seconds) without any motor manifestations. Such seizures are relatively uncommon in patients with JME. For example, Janz reported that 28% of his patients with JME had absence seizures [3, 13]. Commonly, children who initially experience absence seizures may develop myoclonus or GTCS within 1 to 9 years of their seizure onset, and then may subsequently be diagnosed with JME. The absence seizures of JME differ from those of other GGE, such as CAE or Juvenile Absence Epilepsy (JAE) as they are shorter in duration and associated with a lesser degree of altered consciousness [32].

Myoclonic Status Epilepticus: Myoclonic status epilepticus is rare in JME and can present in a variety of ways. Namely, patients can display prolonged myoclonic events, a combination of myoclonic seizures and GTCS, or GTCS that that can follow prolonged absence seizures. Risk factors for this clinical phenomenon include AED withdrawal, sleep deprivation, alcohol intake, and suboptimal therapy [33, 34].

Precipitating Factors: As sleep deprivation is the usual precipitant of seizures in JME [35], adolescents or a young adults often experience myoclonic or GTC seizures precipitated by late night studying or socialization. Because of its strong association with precipitating seizures in JME patients, sleep deprivation is typically employed as an activation procedure to provoke characteristic EEG changes that are diagnostically relevant (4-6Hz generalized polyspike-and-wave discharges). Also associated with sleep patterns, sudden and provoked awakenings, pose additional increased risk for seizures in JME. Two-thirds of patients with JME have at least one provoking factor [28].

5. Reflex seizures associated with JME

Reflex seizures are temporally preceded by some type of external stimuli and may occur exclusively, or in conjunction with, spontaneous seizures. Common external triggers include alcohol use, flashing lights, heat, bathing, and eating. They can also be less frequently elicited by internal stimuli such as stress, fever, hyperventilation, thinking, fatigue, menstrual cycle, and sleep. The proclivity of certain stimuli for seizure provocation is often age-dependent. For instance, fever is a more common provoking stimulus in children than in adults.

Regardless of the suspected triggers, it is import to obtain a detailed history from patients and family members to determine if there is a reflex component to seizures. This should include querying about specific triggers, seizure semiology (partial or generalized), family history of reflex seizures, and whether unprovoked seizures occur as well. As patients rarely lose awareness with myoclonic seizures, they may have adequate awareness of their subjective triggers. Knowing the patterns of responses in patients along with prevalence of triggers is, therefore, key to initially investigating a reflex component prior to enlisting formal testing. Moreover, identification of triggering factors leads to finding ways to avoid precipitants and

http://dx.doi.org/10.5772/58372

develop nonpharmaceutical therapeutic interventions, which is important for the treatment of reflex seizures, in addition to an AED regimen [36].

Using a questionnaire, da Silva Sousa [35] found 23% of JME patients surveyed reported having reflex seizures with thinking and concentration, 20% with praxis, 11% with speaking in public, 15% with visual stimuli, 7% with reading, 5% with calculating and writing, 5% with music, and 3% with drawing. In a subsequent study by the same group, patients were continuously monitored for 4 to 6 hours by video-EEG while neuropsychological and physiological triggers were presented [37]. These triggers had a provocative effect in 38%, with praxis being most common trigger. There were also inhibitory effects of tasks in over 90%. 40% of the patients had no effects on ictal or interictal epileptic discharges. A more recent multicenter, video-EEG study, controlling for spontaneous fluctuation of ictal and interictal epileptic discharges, found the provocative effect of neuropsychological and physiological triggers was decreased from 22 to 18%, while the rate of inhibition was decreased from over 90% to 29% [38]. The inhibition was thought to be a non-specific effect of arousal and mental activation, while the provocative triggers were task-specific.

In clinical practice, if reflex epilepsy is suspected from convergence of other clinical data as noted above, clinical procedures can often helpful in identifying suspected triggers. Detailed neuropsychological testing can be conducted with patients who have seizures induced by thinking and completing complex mental activities [39]. Also, functional MRI can be used to study signal changes in the networks involved in generating reflex seizures during tasks.

Because the prevalence of photosensitivity in JME ranges from 25 to 40% [40], clinicians often opt to elicit reflex responses via intermittent photic stimulation (ILS) with concomitant routine EEG with video. Photic stimulation typically consists of flashing light at various frequencies in front of the patient, with seizures being most likely to be elicited by frequencies of 12-18Hz in individuals who are photosensitive. Various visual patterns may be used to provoke seizures as well, and include alternating, oscillating, black or white, or linear responses. Beyond formal testing procedures via ILS, photoparoxysmal and convulsive responses along with ictal and interictal epileptic discharges can be triggered by reading and praxis in patients with JME [13, 40, 41]. Patients who are photosensitive may have the following responses: photic driving, non-convulsive photoparoxysmal episodes, or photoconvulsive responses. Notably, photosensitivity in JME patients is increased in the early morning hours soon after awakening, which is consistent with the diurnal pattern of seizures in these patients [42]. There are no differences in age or gender of patients with reflex seizures in general; however, in patients with photosensitivity there is a clear predominance in adolescence and in the female sex [42].

In terms of the biological mechanisms of reflex seizures in JME patients, particular cerebral regions have been implicated. Myoclonic seizures in JME are expressed in the primary motor and supplementary motor cortices [43], which are extensively connected to the primary sensory and association cortices. It is not clear whether visual stimuli generates a response from the sensory cortices that propagates to functionally connected cortical and subcortical structures, or if a there is parallel synchronization of larger networks induced by the stimuli [44, 45]. In the case of photosensitivity, visual stimulation likely synchronizes frontoparietal cortices prior to the onset of the epileptiform discharge [44-46], a phenomenon suspected on

the basis of large cortical blood flow increases even before the appearance of hyperventilation-induced generalized spike-and-wave discharges in absence epilepsy [47, 48]. Given the variety of aforementioned triggers, it is expected that reflex seizures are provoked by stimulation of different sensory cortices, such as the primary somatosensory cortex, primary auditory cortex, or related association areas. For instance, somatosensory or cognitively evoked seizures are evoked in physiologically activated cortical areas that overlap with hyperexcitable cortices giving rise to ictal or interictal epileptic discharges [49].

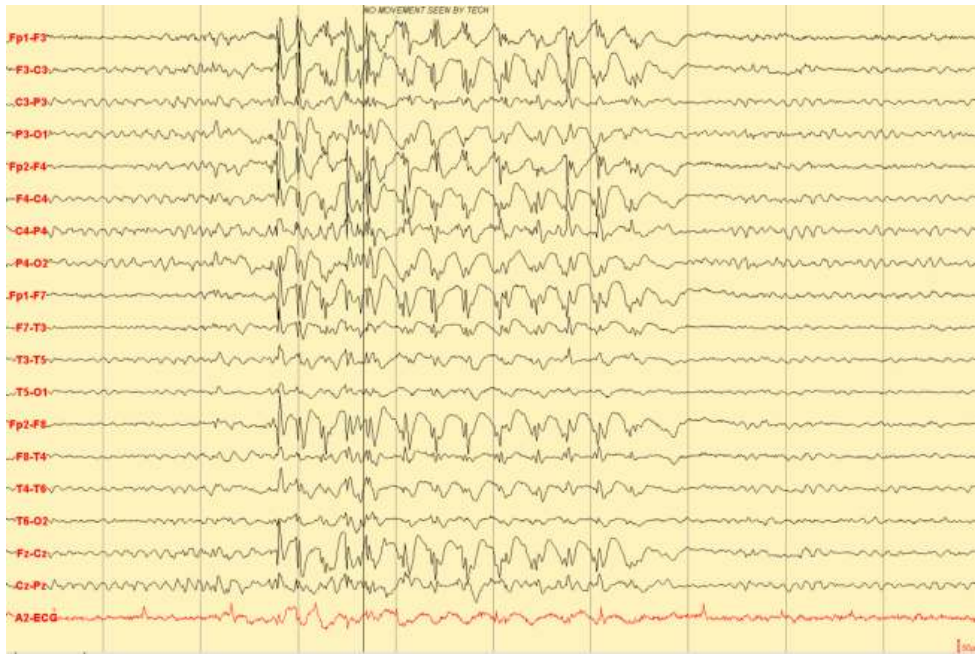
6. Electrographic findings

Given the rate of reflex seizures in JME, it is clinically indicated to conduct a sleep-deprived EEG with activation procedures, such as photic stimulation and hyperventilation. Although a positive EEG highly supports a clinical diagnosis of JME, a negative EEG does not definitively rule out the diagnosis. When examining EEG results, there are typical EEG patterns that occur in JME that should be considered.

Interictal Pattern: The interictal background activity is usually considered normal in patients with JME [4, 7, 50, 51]. However, Genton et al. [52] found that routine EEGs were normal in 27% of cases and misleading or nonspecific in 20% of cases; although, 54% showed generalized interictal epileptic discharges (IEDs). Other studies have reported percentages of abnormalities, consisting of generalized polyspike-and-wave or spike-and-wave complexes in 75 to 85% of probands [9, 53, 54]. The typical interictal EEG finding in JME is a 3.5-6 Hz spike-and polyspike-and-wave pattern with a frontocentral predominance that lasts up to 15 to 20 seconds [50, 55]. While a pattern of more prolonged IEDs with a 2-3 Hz frequency is not specific to patients with absence seizures, there may be an increased risk of clinical absence seizures if a 3Hz spike-and-wave interictal pattern is noted. IEDs are primarily detected during drowsiness and or sleep onset, or upon awakening [56, 57] (see Figures 1-3), during ILS (photoparoxysmal response) (see Figure 4), and hyperventilation. They may be associated with myoclonic seizures or GTCS (photoconvulsive response). Family members of JME are often affected or carry the abnormal EEG traits, as 80% percent of symptomatic siblings and 6% of asymptomatic siblings have diffuse 4-6 Hz spike-and-wave complexes [58]. Photoparoxysmal EEG response is another heritable trait of JME, and can be found in 20 to 60% of near relatives of probands [59].

Ictal Pattern: The ictal EEG during myoclonic jerks (see Figure 5) typically reveals a sudden onset of brief (less than 0.5 sec) bursts of 10-16 Hz polyspike-and-wave discharges often followed by 1-3 Hz slow waves [60]. The number of spike-and-wave complexes ranges from 5 to 20 per discharge and correlates with the intensity, rather than the duration of each seizure [3]. Absence seizures in patients with JME are usually associated with 3 Hz spike-and-wave activity, which is sometimes preceded by 4-6 Hz polyspike-and-wave discharges that decrease in frequency to 3 Hz as the patient loses consciousness. These spike-and-wave discharges are usually shorter in duration than those observed in childhood and juvenile absence epilepsies [61].

http://dx.doi.org/10.5772/58372



Legend: The discharge is originally 5 Hz, slowing down to 3 Hz. No clinical signs were noted.

Figure 1. Generalized Interictal Epileptic Discharge in Drowsiness

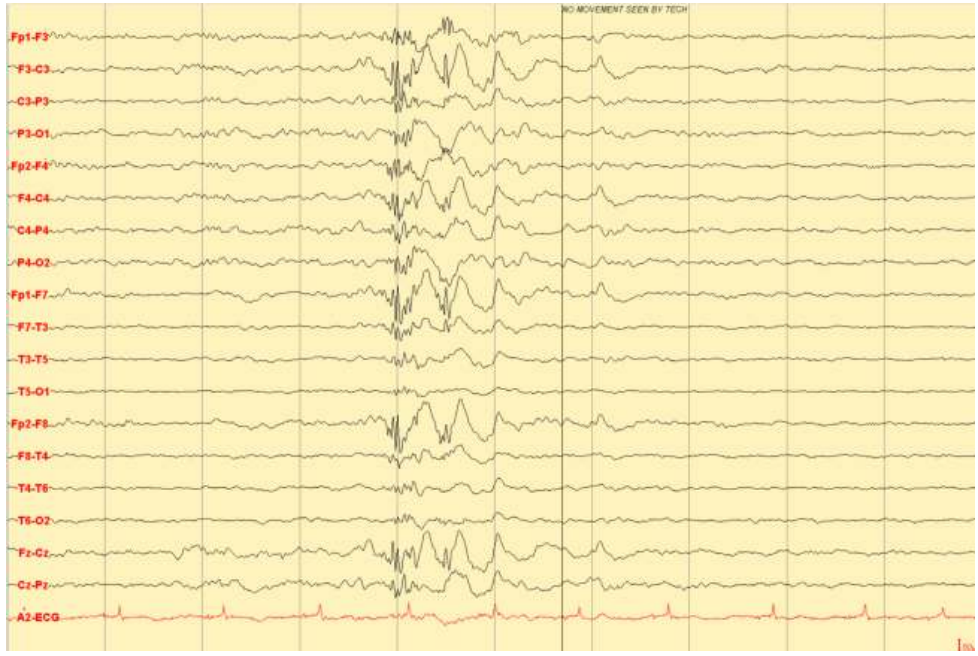


Figure 2. Generalized Polyspikes Activated in Stage II Sleep

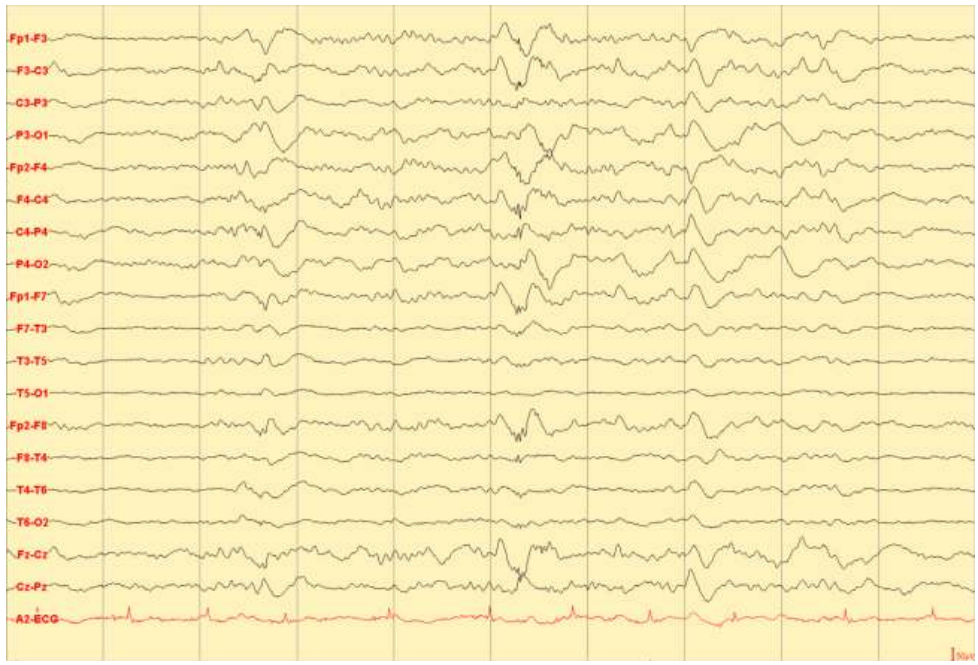


Figure 3. Fragmented Spikes in Slow-Wave Sleep

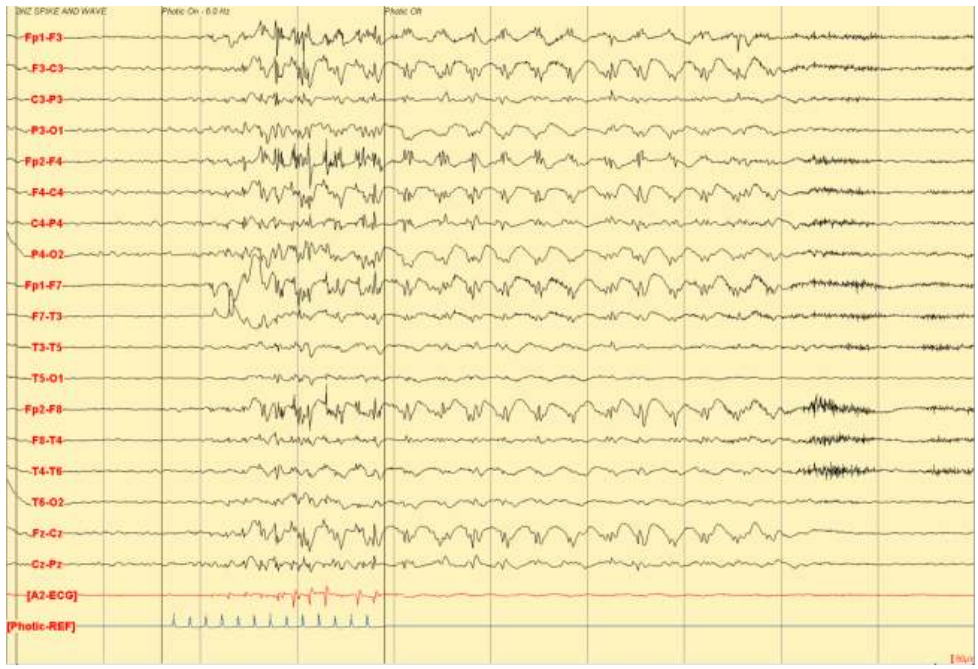
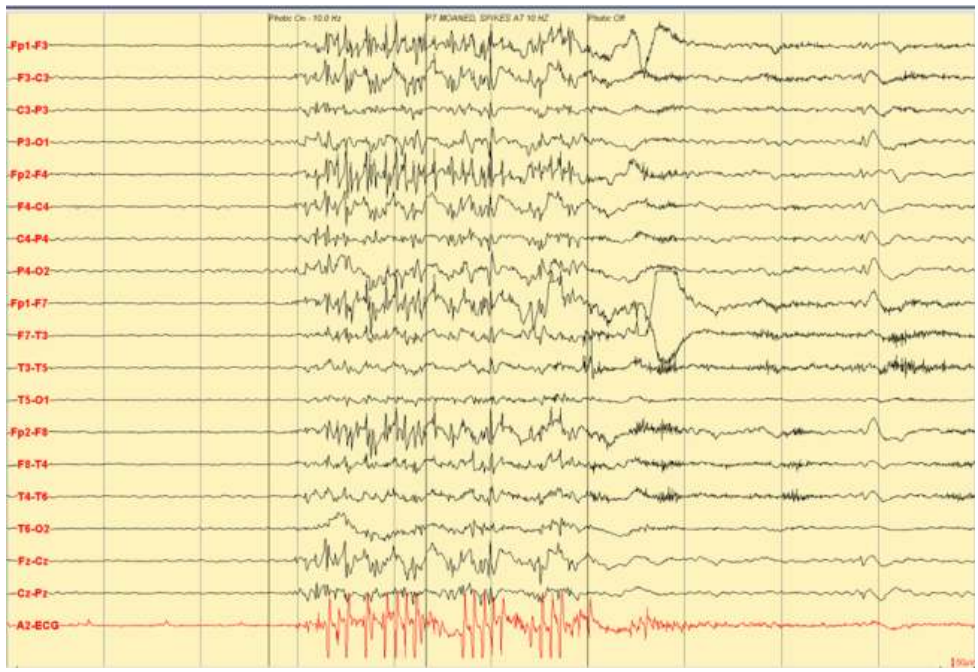


Figure 4. Photoparoxysmal Response

http://dx.doi.org/10.5772/58372



Legend: Note movement artifact on ECG channel.

Figure 5. Myoclonic Seizure

7. Focal features of EEG

Accurate identification of EEG patterns is crucial to avoid misdiagnosis of JME (e.g., misidentified as a partial seizure). As an illustration, some researchers have reported that clinical and EEG asymmetries can lead to a delay in the diagnosis of JME by an average of 2 years [62]. Thus, it is important to understand that although JME is classified as a GGE, myoclonic seizures and GTCS may be associated with a combination of focal clinical and/or EEG findings. However, focal abnormalities are rarely found on routine neurological exams or MRI studies. Further, the challenges of making a diagnoses by electroclinical data is best exemplified by evidence of versive seizures or circling seizures that are associated with generalized discharges on EEG [63, 64].

Data from JME patients in the UK found that 36.7% of EEGs had focal slow waves, spikes, and sharp waves as well as focal onset of a generalized discharge. In more than half of the JME patients, at least one EEG showed focal abnormalities [65]. 18 patients with JME were studied in Poland which demonstrated that 8 patients had focal abnormalities on EEG that previously led to misdiagnosis [66]. Further, a large study of JME patients in India [67] found asymmetrical clinical presentations in 17% of patients and focal EEG abnormalities were seen over 45% of patients. Of these patients, focal findings seen on EEG included amplitude asymmetry or a lateralized onset of generalized discharges in 45% and independent focal EEG abnormalities

in 33% of patients. A video-EEG study from the Cleveland Clinic Foundation [68] reported that of the patients with only JME, 54% exhibited either focal semiologic or electroencephalographic features or a combination thereof. Focal myoclonic seizures (i.e., unilateral myoclonic jerks, version, and asymmetric limb posturing) were recorded in six patients whose ictal EEG showed a generalized seizure pattern. Two patients had lateralized upper extremity extensor posturing ("sign of four") with evolution of a GTCS. They also reported that one patient had primary GTCS presenting after successful resection of a parietal tumor, and two patients had temporal lobe epilepsy in addition to JME. Taken together, the findings of focal or multifocal clinical or EEG abnormalities suggest the possibility of a symptomatic etiology, and may reflect an underlying genetically mediated neurodevelopmental disorder.

It has also been suggested that asymmetric EEG findings in such patients increase the probability of decreased response to standard antiepileptic therapies. A group of Canadian researchers [69] presented data showing 90% of their JME patients had generalized epileptiform discharges on EEG and 57% of patients had asymmetric EEG abnormalities, including focal epileptic discharges or slowing. Of their patients, over 39% were medically refractory to at least one AED, and a poor treatment response was observed to a greater degree in patients with EEG asymmetries. Nevertheless, the clinical significance of focal clinical or EEG abnormalities has not received much attention in the literature.

8. Differential diagnosis

Doose Syndrome: Myoclonic-astatic epilepsy was first described by Dr. Hermann Doose in 1970 [70]. The ILAE classified it formally as symptomatic generalized epilepsy, and it was renamed as epilepsy with myoclonic-atonic seizures. It is much less prevalent than JME (1 to 2% of all epilepsies) and has a younger onset age (7 months to 6 years, peak of 2 to 4 years) with a greater prevalence among males. Unlike JME, there is an association with cognitive impairment, which is severe in some cases of Doose Syndrome. This syndrome is characterized by symmetric myoclonic jerks followed by sudden atonia. During a myoclonic atonic seizure, the EEG consists of irregular generalized 2-3Hz or more spike-and polyspike-and-wave discharges. The atonic seizures coincide with subsequent slow waves. The interictal EEG background similarly consists of frequent 2-3 Hz generalized spike-and polyspike-and-wave discharges, contrasted 4-6 Hz discharges in JME. Up to 50% of patients may achieve seizure freedom and continue to have normal development, but the remainder may have severe impairments in cognitive functioning, behavioral problems, and ataxia [71].

Childhood Absence Epilepsy (CAE): CAE is a type of GGE that has an age of onset of 4 to 10 years with a peak between 5 to 7 years [72]. The characteristic seizure type is an absence seizure during which there is brief loss of consciousness for a few seconds with associated behavioral arrest, eyelid myoclonia, and rare hand and facial automatisms [73]. They may occur multiple times a day. While absence seizures may also occur in JME, their frequency and duration is far less than in CAE. The interictal EEG of CAE is characterized generalized spike-and polyspike-and-wave discharges of 3Hz frequency [6]. Prognosis for CAE is considered excellent, with

http://dx.doi.org/10.5772/58372

possibility of remission upon discontinuation of antiepileptic medications. In patients with CAE, the development of GTCS or myoclonic seizures may indicate a poorer prognosis, and increases the probability that such patients will develop JME.

Juvenile Absence Epilepsy (JAE): Similar to JME, JAE is a GGE that mainly presents during adolescence, usually at the age of 10 to 17 years. Although the central semiology is signified by absence seizures, there is often less impairment of consciousness than in CAE, and the seizures do not tend to occur in clusters. On the other hand, GTCS seizures are more common (reported in 80% of patients) with JAE, similar to JME. While some authors have contended that myoclonic jerks do not occur in JAE [32], the ILAE has included them in the definition of JAE [6]. As such, 15 to 25% of JAE patients have myoclonic jerks-they are infrequent, mild, and of random temporal distribution [74]. In comparison to JME, myoclonic movements usually occur in the afternoon rather than in the morning after awakening.

Myoclonic Absence: This rare epilepsy syndrome begins in preadolescence and is characterized by prolonged absence seizures lasting 10-60 seconds in duration with rhythmical bilateral myoclonias affecting the extremities, often synchronously with 3 Hz polyspike-and-wave discharges [75]. This syndrome is associated with cognitive dysfunction and is medically refractory in a majority of the patients.

Generalized Tonic-Clonic Seizures Upon Awakening: The onset of this epilepsy syndrome is also in adolescence [6]. As in JME, the GTCS tend to occur upon awakening. There is still debate on whether this syndrome should be classified with JME, due to electroclinical similarities and possible genetic associations [76]. However, patients with GTCS Upon Awakening do not exhibit myoclonic or absence seizures.

Progressive Myoclonic Epilepsy (PME): Progressive myoclonic epilepsies are a group of genetic disorders which are characterized by myoclonus, seizures, and advancing cognitive and neurological decline [77]. Examples of PMEs include Lafora disease, neuronal ceroid lipofuscinosis, Unverricht Lundborg disease, myoclonic epilepsy with ragged red fibers (MERRF), Gaucher disease, and dentatorubral pallidoluysian atrophy. They can start in childhood, adolescence, or young adulthood and tend to be associated with multiple neurological and cognitive deficits. The myoclonus associated with these disorders can be induced by action or stimulation and tends to be multifocal. ILS tends to activate myoclonus at frequencies below 6 Hz. These diseases are associated with progressive neurological deterioration along with worsening seizure control. The diagnosis is more difficult to determine, primarily during the early stages of the disease when seizure severity is limited [78].

9. Treatment of JME

Response to treatment is drug-specific in the case of JME. Valproic acid (VPA) is considered the first line of therapy in patients with GGE, especially JME; however, it is not FDA approved for this condition [79, 80]. Rather than randomized control trials, evidence supporting the choice of VPA has primarily come from observational studies. While VPA is a broad spectrum

antiepileptic medication, it is very effective in 80% of patients [81]. Nonetheless, even in seizure-free patients, discontinuation of VPA leads to a very high rate of relapses [9]. A chart review from Duke University [82] of 33 JME patients identified resistance to VPA in 30%. The VPA refractory patients had a higher prevalence of EEG asymmetries (40% vs. 10%), atypical seizure characteristics including auras and postictal confusion (30% vs. 4%), and intellectual deficiency (20% vs. 0%). Clinical characteristics combined with EEG data may help in predicting which JME patients will respond favorably to VPA.

More recent support of VPA's relative efficacy over other antiepileptic medications was demonstrated The Standard and New Anti-Epileptic Drugs trials (SANAD) [83]. SANAD was a concurrent pragmatic parallel group, open-label, randomized trial which examined seizure control, tolerability, quality of life, and economic outcomes of standard antiepileptic medications used for GGE. VPA was compared with lamotrigine (LTG) and topiramate (TPM), and was significantly better for time to treatment failure (i.e., seizure control, side effects, addition of another AED). For time to 12-month remission, VPA was significantly better than LTG for GGE. Overall, VPA was better tolerated than TPM and more efficacious than LTG. In children with GGE, a retrospective observational study [84] examined the long-term effectiveness of LTG compared to VPA monotherapy in newly diagnosed patients. After 12 months of treatment, 69% patients continued LTG compared to 89% that adhered to their VPA regimen; after 24 months rates were 57% and 83%, respectively. Valproate showed equal efficacy in all GGE syndromes, whereas LTG showed better efficacy in CAE and JAE syndromes, than in JME.

Although VPA can be used safely by a number of patients, including those with comorbid psychiatric disease or underlying psychiatric vulnerability [85], there are some limitations. In particular, there is a high risk of teratogenicity as well as delayed cognitive development in children (pregnancy class D) [86, 87]. Exposure to VPA in utero has been associated with maladaptive behavior and decreased socialization skills in childhood [88, 89] as well. In cases where VPA is used during pregnancy, either because of unplanned pregnancy or because alternative treatment options of equivalent efficacy are unavailable, appropriate counseling, precautionary measures, and monitoring should be provided. Although LTG may have a lower efficacy, and has even been reported to increase myoclonic seizures in some patients, it is a popular alternative to VPA in women in childbearing age for the treatment of JME.

LTG and TPM have FDA approval for primary GTCS in the United States. Hence, more studies, albeit with small numbers of participants, have been conducted with those agents. An open-label study [90], designed to evaluate LTG monotherapy as a possible alternative in patients with JME who previously failed VPA, found LTG to be as effective and better tolerated compared with VPA. A small (N=28) randomized, controlled trial [91] compared TPM and VPA in adolescents and adults during a 12-week maintenance period, which resulted in 67% seizure freedom in the TPM group and 57% in the VPA group. The researchers concluded that TPM may be an effective, well-tolerated alternative to VPA as the groups had similar rates of adverse effects. Similarly, a prospective, open-label, randomized observational study in Korea [92] compared the efficacy and tolerability between TPM and VPA in patients with JME and did not find differences in efficacy, although the side effect profile of TPM was more favorable.

http://dx.doi.org/10.5772/58372

Clonazepam (CLN) was one of the first medications to be approved for myoclonic seizures and GTCS. While VPA is as an effective treatment for most patients with JME, one study showed [9] additional efficacy with CLN adjunctive therapy to control myoclonic seizures. However, CLN monotherapy did not consistently prevent GTCS. The authors concluded that adding CLN may allow the dose of VPA to be reduced in patients demonstrating dose-dependent VPA side effects. The addition of CLN can also be utilized in combination with other antiepileptic medications as well.

Levetiracetam (LVT) was more recently approved for the treatment of myoclonic seizures associated with JME. Similar to CLN, it can reduce the myoclonic seizures and GTCS [93], possibly with even better long-term efficacy and fewer side effects. Recently, several studies found LVT to be effective in all types of seizures in JME as concluded in a randomized double-blinded placebo controlled trial [94, 95]. Hence, LVT is another worthy alternative to VPA, especially in women of childbearing age. Other medications that may be effective in JME include zonisamide (ZNS), felbamate (FBM), lacosamide (LCM), and clobazam (CLB); however, systematic trials of those medications are lacking. Nonetheless, a retrospective chart review demonstrated that ZNS monotherapy was effective and well-tolerated in JME patients [96].

In contrast to effective AED treatments, there are a number of antiepileptic medications that may aggravate certain seizure types associated with JME, particularly myoclonic and absence seizures. Among commonly prescribed anticonvulsants, carbamazepine appears to have the strongest aggravating potential for myoclonic seizures, whereas the aggravating effect of phenytoin (PHT) is less prominent [97]. A retrospective study of patients with GGE, showed that oxcarbazepine (OXC) also aggravated myoclonic and absence seizures, and increased interictal epileptic discharges on EEG [98]. A retrospective study of adult GGE patients who developed video-EEG documented status epilepticus were all found to be taking either CBZ, PHT, vigabatrin (VGB), or gabapentin (GBP). Potential precipitating factors included dose increase of CBZ or PHT, or the initiation of CBZ, VGB, or GBP, as well as a decrease of phenobarbital (PB) dosage. Withdrawal of the aggravating agents and adjustment to medication resulted in full seizure control in that study. Therefore, it is important to make the appropriate diagnosis and medication selection to avoid potentially worsening certain seizure types. It is also important to consider the age, gender, comorbid conditions, and drug interactions when initiating antiepileptic therapy in JME patients.

10. Lifestyle modifications

As with a number of other chronic medical conditions (i.e., diabetes, hypertension, obesity), lifestyle factors have an important role to play in managing epilepsy disease burden. To illustrate the problems of how psychosocial factors influence the treatment of JME, Baykan et al. [30] followed 48 patients with JME for a mean of 20 years and found that 16.7% of patients had “pseudo-resistance” due to medication non-adherence and lifestyle related issues. Sharpe and Buchanan [99] studied 36 patients with JME at a tertiary referral hospital

and found that most patients with poor seizure control had provoked seizures only, which prompted the authors to emphasize the importance of lifestyle changes in managing seizures in JME.

Thus, perhaps the most obvious lifestyle factors worth noting in terms of JME pertain to patients' exposure to stimuli s associated with increased seizure frequency (i.e., fatigue, stress, sleep deprivation, alcohol intake, drug use, photic stimulation, stress, AED withdrawal/non-compliance) [9, 100-103]. From a disease management perspective, behavioral medicine strategies that are promoted by integrated, multidisciplinary teams may prove useful [104]. Elements of such programs often include steps to improve medication adherence, treat psychological problems and manage stress, implement sleep hygiene interventions, and develop methods to cope with exposure to possible seizure triggers [104-106]. Moreover, administration of psychoeducation should be considered a minimum standard of care by providing patients with information regarding identifiable triggers, risks of sleep deprivation, possible problems with exposure to stroboscopic flashes, relationship of alcohol intake and seizure control, as well as ways to increase AED adherence to prevent further seizures [107]. Although, some authors [103] have suggested that it is more efficient to use higher doses of AEDs in the initial treatment of JME, rather than implement behavior change strategies, systematic study of the effects of multidisciplinary treatment on lifestyle factors in epilepsy has remained an understudied area. However, initial studies in JME have suggested that there may be a desirable effect on seizure control, and likely improvements in quality of life. If some of these measures are put into place, it is likely that the number of patients with refractory seizures will be reduced [108, 109].

11. Cognitive and behavioral tasks

There have been studies suggesting that cognitive tasks can provoke or inhibit of epileptiform discharges in patients with JME [110]. These uncommon precipitating factors, such as mental and motor hand tasks, may be under-recognized in JME [35]. A Japanese study involving 480 patients with epilepsy tested the effect of cognitive tasks on EEG (i.e., neuropsychological EEG activation) consisting of reading, speaking, writing, written calculation, mental calculation, and spatial construction. They found that these cognitive tasks have an inhibitory effect on EEG discharges in the majority of epilepsy patients (64%), although they have a provocative effect in other patients (8%). The seizures caused by the provocative effect of these tasks were found to be precipitated by action programming or thinking activity (linguistic and praxic) [111]. Following this, Beniczky et al. [38] studied 60 patients with JME and found that the provocative effect of the cognitive tasks is task-specific, whereas the inhibitory effect seems to be related to cognitive activation in general. Another study involving 76 JME patients had similar results, suggesting that the inhibitory effect of these tasks support non-pharmacologic therapeutic interventions in JME [37].

http://dx.doi.org/10.5772/58372

12. Non-medical treatments

Alternative surgical therapies do not represent standard of care and are not approved for JME. However, in medically-refractory patients, clinicians often employ additional treatment options.

Vagal Nerve Stimulator: While vagal nerve stimulators (VNS) are approved for the treatment of medically refractory partial seizures, its use in JME has not been well documented. Nonetheless, the most recent AAN guidelines on VNS for epilepsy [112] asserted that VNS was effective in children with medically-refractory GGE. A greater than 50% reduction in seizure frequency was reported in 55% of the 470 children with partial or generalized epilepsy in the reviewed literature (13 class III studies). Based on those findings, the authors concluded that VNS could be considered adjunctive treatment. No such recommendations have been made regarding adult treatment as more trials are needed in that population.

One of the few JME specific studies of VNS [113] indicated that adjunctive therapy with VNS might be considered a favorable option for treatment of refractory cases of GGE, and may be the only alternative to refractory JME. A total of 12 cases with GGE and VNS implantation were followed for a mean of 23 months. It was found that the rate of seizure total reduction was 61%: a 62% reduction of GTCS, 58% reduction in absences, and 40% reduction of myoclonic seizures. Five of the seven patients in that study who had a JME diagnoses were responders, two of which became seizure free. One patient in that study was diagnosed with JME and failed conventional treatment that included 8 AEDs and the ketogenic diet. Subsequent to VNS implantation, she had >75% reduction in GTCS along with >50% reduction in absence and myoclonic seizures.

Corpus Callosotomy: There are even fewer studies that have examined the effectiveness of corpus callosotomy for medically refractory cases of JME. A case series (N=11) from Brazil [114] included GGE patients who underwent extensive one-stage callosal transections. At least 75% reduction in frequency of GTCS was noted in all patients; three patients had complete remission of absences and the other patients had a >90% reduction in the frequency of absence seizures. Only one patient who had myoclonic seizures prior to surgery remitted completely after surgery. Postoperative EEG recordings showed disruption of bilateral synchrony of interictal epileptic discharges in all patients, with minimal neurological deficits. While the authors reported that the patients only showed a decline of 4 points in mean FSIQ standard score, a more detailed examination of the patients' psychosocial status and cognitive functioning was not reported. A Japanese case report [115] of medically refractory JME showed that an anterior corpus callosotomy resulted in a desynchronization of generalized spike-and-wave discharges and a complete resolution of myoclonic seizures. An anterior corpus callosotomy may be effective for seizure reduction in some cases of refractory GGE due to the disruption of interhemispheric synchronization [116].

13. Prognosis

As with most GGE syndromes, JME responds well to an appropriate AED regimen, demonstrating a 70 to 80% response rate [117]. However, the long-term prognosis remains AED-dependent as there is an 80% recurrence risk after AED withdrawal. It is thought that CAE typically has a better prognosis and spontaneous remission that JME even when untreated, although this can be complicated by the development of myoclonus. In fact, a Canadian study [19] noted that 65% of children with CAE experienced remission after 10 to 18 years after their diagnosis, although 44% of patients who did not experience remission developed JME.

A long-term population-based study [14] that included 24 patients (majority women) who developed JME by 16 years of age were followed for up to 25 years after seizure onset. Eight patients (36%) developed convulsive status epilepticus and three patients (12.5%) had intractable seizures. In this cohort, 17% of patients had full remission of all seizure types and only myoclonic seizures persisted in 13%. Thus, about one-third of patients had remission of disabling seizures without the need for continuation of AEDs. Moreover, although JME rarely undergoes spontaneous remission, there may be an age effect that increases the probability of spontaneous remission as individuals reach the fourth decade of life. In another long-term study [30, 118] that followed 48 patients with JME (mean age of 40 years) for approximately 20 years, the authors indicated that seizure severity and myoclonic frequency seemed to change across the lifespan. For instance, myoclonia went into remission in the fifth decade of life in 54% of patients. Five patients discontinued AED treatment and six patients had lower AED dosage; 10 out of 11 of these patients did not relapse during the mean follow up of 8 years.

One of the longest outcome studies of JME [119] followed 31 patients for an average of 39 years. Over two-thirds became seizure free, a third of whom could be taken off AEDs altogether. Predictors of poor outcome were identified as presence of GTCS preceded by myoclonic seizures, longer duration of epilepsy, and the need for AED polytherapy. Predictors of seizure freedom included complete control of GTCS. Other factors may also influence remission as well. In a study of 32 JME patients in Japan, those with focal interictal epileptic discharges on EEG and or discharges activated by cognitive stimuli, had the least favorable outcome [120]. However, value of EEG in predicting outcome of JME remains controversial [121]. A study from Brazil [122] showed that patients with persistent seizures had an earlier age of onset, higher prevalence of personality disorders, and higher incidence of sensitivity to praxis-and verbally-induced ictal or interictal epileptic discharges.

Hence, it appears that a subgroup of patients can be identified as being at a higher risk of refractory seizures. JME patients with an earlier onset of epilepsy, GTCS evolving after a build-up of myoclonic seizures, focal EEG abnormalities or sensitivity to cognitive activation, and cognitive or behavioral problems may be more likely to remain refractory to antiepileptic medications. Ideally, the significance of these factors needs to be validated prospectively by a multicenter, multinational study.

http://dx.doi.org/10.5772/58372

14. Cognitive dysfunction

Consideration of neuropsychological findings in JME has a brief history beginning with largely anecdotal reports suggesting patients displayed a combination of behaviors consistent with a "frontal syndrome" [3] in the context of normal intellectual functioning. As the following literature illustrates, the initial assertions that JME patients display a unitary "frontal syndrome" are challenged by data from a number of novel empirical designs. For instance, consideration of non-frontal factors is considered germane in light of the involvement of multiple brain regions that extend beyond structural frontal anatomy in JME [123]. Several themes of investigation have surfaced regarding cognition including delineation of neuropsychological profiles in JME, group performance differences, disease specific and non-disease factors that may affect cognitive functioning, along with neuroanatomical and functional correlates of task performance. Because of the idiopathic nature of JME and its strong genetic linkage, family studies of cognition have surfaced as well.

Given that JME has been conceptualized as a disorder affecting frontal brain regions, some of the first empirically-driven studies focused on the relationship of JME and performance on tasks that theoretically require significant frontal lobe recruitment. In this vein, JME groups have been assessed by a number of clinical and basic research cognitive measures that task frontal systems. For instance, a small study showed that a group of adult JME patients (n=9) demonstrated an abnormal number of errors and omissions on a task that requires individuals to identify previously learned complex visual information [124]. Such match-to-sample measures often have immediate and delayed portions that task visual working memory systems, which an aspect of executive functioning. The magnitude of abnormality was generally not as large as performance by a group of patients with frontal lobe epilepsy (FLE; n=15), although it was typically lower than control participants' (n=14) proficiency. In a follow-up study with a similar task, researchers from that group [125] reported that adult JME patients (n=9) had fewer correct responses than controls (n=14) on the same delayed match to sample paradigm. The JME patients performed normally on the immediate match to sample tasks, which generally relates to attentional functioning, but slower psychomotor speed performance than controls. However, it is not clear if the same patient and control groups were used across both of the studies, which decreases the generalizability of the findings. Nevertheless, these two projects served as stringboards for subsequent applied and experimental designs.

While it is important that the latter studies showed commonalities between theoretically similar patient groups (i.e., groups with suspected frontal lobe abnormalities) in order to provide additional validity evidence for a "frontal" construct, it is also relevant to include data from groups that are theoretically divergent (i.e., controls, various non-frontal clinical samples). As such, neurocognitive performance of a mixed sample [126] of patients diagnosed with temporal lobe epilepsy (TLE; n=15) and JME (n=15) was contrasted on a number of tasks related to frontal lobe functions. JME patients had impairments on a wide range of cognitive measures, as defined as >1.5 standard deviations below the mean for the normative comparison group. Of the 15 JME patients used in their analyses, one patient showed no impairment on testing, while half of the remaining sample had impairments on <3 tests and the other half was

impaired on >4 tests. Performance was most frequently impaired on a task that requires one to identify relationships between objects on a conceptual level, which was significantly discrepant from the TLE group. Additionally, patients were administered a task that requires individuals to quickly and sequentially alternate responses according to specific rules (i.e., Trailmaking Test Part B). On this task, the JME participants had lower scores than the TLE patients.

Additional studies have contrasted JME groups on test batteries that primarily include executive function tasks that have a relationship with frontal lobe involvement. Piazzini et al. [127] reported data from an adult sample of patients with JME (n=50), TLE (n=40), FLE (n=40), and controls (n=40). In that study, JME patients performed statistically significantly lower than TLE patients and controls, yet scored similarly to FLE on the Wisconsin Card Sorting Test and a semantic verbal fluency test. A group in Austria [128] published data from two studies [129, 130] that included a decision-making task and a number of neuropsychological variables in patients. Their results showed that JME patients performed similarly to mesial TLE patients on nearly all variables except they had lower semantic verbal fluency scores and slower psychomotor speed. The groups were otherwise similar on measures of verbal attention, verbal working memory, cognitive flexibility, planning, along with abstraction and categorization.

Other results [131] indicated that children with CAE (n=28), another GGE, largely performed worse than individuals with JME (n=11) on tasks of visual sustained attention, the Stroop Test, and Trailmaking Test. No differences were noted for verbal memory. Another group [132] sampled children and adolescents who had a similar level of normal intellectual functioning and were diagnosed with either recent-onset JME (n=20) or recent-onset benign childhood epilepsy with centrotemporal spikes (BCECTS; n=12). A sample of first-degree cousins (n=51) were also utilized as control participants. The researchers focused their cognitive assessment on objective measures of executive functioning that included subtests from the Delis-Kaplan Executive Function System (D-KEFS). They also examined behaviors that were subjectively rated by parents on the Behavior Rating Inventory of Executive Function (BRIEF). In their samples, the JME group performed significantly poorer than the control group on the D-KEFS Inhibition subtest. Parent report on the BRIEF indicated the JME group had more pathological ratings on the Behavioral Regulation and Metacognition scales than controls as well. However, there were no significant differences between the BCECTS and JME group on any measures. The latter study highlights that executive differences exist early in the disease course of JME, although the magnitude of executive dysfunction may not be larger than that in other genetic epilepsies.

There have also been reports [133] of cognitive functioning in mixed samples of children and adolescents with normal intellectual functioning diagnosed with GGE (i.e., JME & Absence) and genetic localization-related epilepsies (i.e., BECTS & non-BECTS). Although that study included 26 JME patients and a number of other patients with IPE, the JME group was compared only with the 72 healthy children, which indicated that the JME group performed below the mean of the control group in all cognitive domains (e.g., intelligence, academic, language, memory, executive functioning, fine motor dexterity and speed, cognitive processing speed). In particular, JME patients' lowest performance was in arithmetic, inhibition,

http://dx.doi.org/10.5772/58372

concept formation, psychomotor speed, and fine motor dexterity and speed. While visual inspection of the data suggested that JME patients performed lower than the group with absence seizures on a measure of language fluency, the group with absence seizures appeared to perform lower in all other domains. However, statistical group comparisons were not conducted to differentiate any of the clinical groups from one another.

Just as there has been variability in finding group differences between patient samples, findings from studies contrasting JME patients from healthy controls have been mixed and contradictory. In addition to the few clinical comparison group designs noted above, a number of other studies have shown that JME patients have statistically significantly lower proficiency than controls across a host of measures including intelligence [134, 135], verbal IQ [135], working memory [135], digit span [136-139], sustained attention [134], processing speed [134, 135], Trailmaking Parts A and B [137-139], Trailmaking Part B [140], mental flexibility [134, 137, 141, 142], response inhibition [134, 143], Stroop Test [137, 139, 140], Stroop Interference [136], speeded color reading [143], verbal abstraction [141], concept formation [136, 137, 142], perseverations[140], clock and cube drawing [143], sematic fluency [136, 138, 140, 143-145], phonemic fluency [137, 138, 140, 141, 144, 145], naming [135, 141], verbal learning and memory [138, 140, 143], visual memory [140, 141], and prospective memory [136]. On the other hand, a number of studies have also failed to find group differences on tasks of IQ [138, 143, 144], verbal intelligence [141, 145], auditory working memory and attention span [141, 143-146], spatial span [144, 145], spatial working memory [147], psychomotor speed [146], motor speed [134], mental flexibility [146], Trailmaking Parts A and B [145], response inhibition[141, 144, 145], figural fluency [134, 145], semantic fluency [141, 146], phonemic fluency [146], reading [134], naming [143], language comprehension[144], line orientation [143], facial recognition [143], memory [134], verbal learning [141, 144, 145], visual memory [144, 145], and design learning [141]. Another more recent study [148] reported no difference between JME patients and controls on a range of neuropsychological measures. Beyond functioning on objective cognitive tasks, another avenue for research is to examine patients' perceptions of cognitive dysfunction. Such a design has shown the JME patients rate a higher level of self-reported executive dysfunction than controls [144].

Given that the variability in findings across studies likely relates to a number of primary and secondary factors, the influence of the effects of such factors is also likely varied. For instance, one small study [128] showed that it may be important to consider the influence of seizure frequency on JME patients' abilities. In general, the JME patients in their sample did not perform differently from healthy controls on tasks of verbal attention, verbal working memory, or phonemic verbal fluency. On the other hand, controls consistently performed higher than JME patients on tasks related to psychomotor speed, cognitive flexibility, categorical verbal fluency, planning, along with abstraction and categorization. The patients who had been seizure free (n=11) for a year were also compared with patients who continued to have seizures (n=11). The groups showed no differences on any of the cognitive testing, although JME patients scored significantly lower on three of four indices of a decision-making task than controls; seizure status in the JME group was related to performance. However, when compared with controls, the patients who were not seizure-free also showed additional

significant differences on measures of cognitive flexibility, planning, and facets of a decision-making task than the seizure-free patients. Another study [146] examining performance on the same decision-making task reported no difference between controls and JME patients as a group, although fewer patients who were not seizure-free showed improvement and learning on the task over time. These findings suggest that seizure frequency may be an important modulator of cognitive abilities in JME patients.

Overall ability level, such as intelligence, has been shown to relate to performance across cognitive domains [149, 150]. This is likely to be the case with JME patients as well and may influence the significance level of research findings, particularly in small samples. As an example, heterogeneous cognitive performance in JME patients was noted in a published abstract [151], indicating that drug-resistant patients who performed in the impaired range on tasks of executive functioning had a high rate of impairments on tests in other domains. However, there were only limited published data available to review from that report. Other variables have been associated with cognitive performance in JME patients as well such as age of epilepsy onset [138], duration of epilepsy [135, 138], and educational level [135]. Additionally, JME patients on a regimen of multiple AEDs may perform worse than patients on monotherapy on tests of psychomotor speed, cognitive flexibility, and phonemic fluency [128]. On the other hand, some studies have shown no relationship with cognitive performance in JME groups related to duration of epilepsy [127], education level [138], the frequency of seizures [127, 138], treatment status [127], the type of seizures [127], age [138], sex [138], family history [138], or previous intake of an AED [138].

In addition to demography, there may be biological determinants of particular cognitive performance profiles in JME. In a magnetic resonance spectroscopy (MRS) study of the brain [152], researchers indicated JME patients with reduced frontal N-Acetylaspartic acid had lower mental flexibility compared with JME patients with normal levels. Other biological influences may relate to cognitive functioning as well. In JME patients, frontal and thalamic volumes have been associated with executive task performance [132]. Those researchers did not show similar anatomical relationships with cognitive performance in patients diagnosed with other epilepsies [132]. Similar work [141] has revealed an association of fractional anisotropy (FA), a measure of white matter integrity on diffusion tensor imaging (DTI), in anterior supplementary motor area (SMA) regions with scores on a picture naming task. FA values in the posterior cingulate region and corresponding gray matter volume (GMV) negatively predicted scores on the Trailmaking task. However, no other FA values were correlated with any other clinical variables or neuropsychological testing scores [141]. In terms of functional paradigms, fMRI patterns have differed for JME patients versus controls during tasks that require a high level of attention, concentration, and working memory, suggesting motor cortex involvement even though there were no group differences in the actual outcome of the task [147]. This suggests that there may be alterations in or pathological changes to cerebral regional recruitment during task performances as a function of disease state.

Regarding EEG studies, mixed findings have been demonstrated for the relationship of EEG patterns on cognitive performance. One group [143] examined the influence of paroxysmal EEG findings on task performance, but did not indicate a relationship. A non-significant

http://dx.doi.org/10.5772/58372

relationship between cognition and abnormal EEG findings has also been demonstrated elsewhere [137, 138]. In contrast, JME patients with at-rest epileptiform discharges (n=11) [142] have been shown to demonstrate worse abstract reasoning concept formation, and mental flexibility.

In addition to demonstrating divergence and convergence amongst clinic groups and anatomy considerations, the genetic involvement of JME may also elucidate predictable patterns of cognitive performance. In a unique approach to demonstrating potential genetic vulnerabilities that underlie cognitive performance, there is evidence [131] that first degree relatives of JME patients have lower performance on tasks of sustained attention than relatives of individuals diagnosed with CAE or TLE. Another small sample of young adults with JME performed similarly to their siblings on a number of tasks related to executive, language, verbal memory, phonemic and semantic fluency, and general intellectual functioning [144]. However, the JME group scored in a range suggesting more self-reported symptoms related to behavioral, motivational, cognitive, and emotional factors than their sibling [144]. Somnez et al. [143] also reported a number of similarities in cognitive performance for patients with JME who had a relative with epilepsy and those who did not have a relative with epilepsy. Nevertheless, the authors indicated that patients with a family history of seizures were found to be "less successful in general cognitive evaluation," in particular on a spatial perceptual task, forward auditory digit span repetition, and speeded reading measure. A more recent sibling study of cognitive differences in JME patients [136] included data indicating that a group of siblings showed no significant differences on any cognitive measure when compared with the JME group. Moreover, the siblings' performance was not discrepant from a group of healthy controls except for an aspect that indicates JME participants generated more responses that were counter to the test rules on a measure of prospective memory (i.e., remembering to remember). Taken together, findings in these studies may reflect a familial genetic vulnerability for subtle cognitive abnormalities in JME family members who do not have a history of seizures.

In general, the aggregate of cognitive studies in JME patients has indicated that JME patients do not typically perform at the same level as individuals from control or normative groups. Moreover, review of the literature suggests that more studies show JME patients have poorer performance on frontally mediated tasks (i.e., processing speed, response inhibition, and verbal fluency) Than those that do not show such difference. So, too, virtually no study has shown that JME groups perform better than controls on any number of tasks. However, the totality of results has not been consistent and a number of studies have shown that patients with JME sometimes display cognitive abnormalities in other neuropsychological domains as well. Additionally, the literature is weighted toward including mainly tasks related to frontal lobe functioning at the expense of investigating other cognitive domains, which results in literature bias. There are also conflicting data across the studies comparing controls with JME patients to the degree that it is difficult to definitively conclude there is a specific JME cognitive endophenotype, such as a "frontal syndrome." It is likely that, based on the number of inconsistent results for both fontal and non-frontal task performances, any given JME patient may display a range of cognitive abnormalities-the expression of which is likely dependent

upon various factors that have not been adequately described in the literature. As such, it will be important for researchers to continue to investigate etiological contributors to cognitive functioning in JME patients that account for the influence of psychosocial variables, neurobiological functions, and various other metrics of individual differences and disease characteristics.

15. Psychiatric complications

Psychiatric disorders are common in the general population [153] and the presence of a neurological disorder has been associated with increased prevalence [154]. Patients with epilepsy, as a group, have a high rate of psychopathology [155] and present with unique psychiatric problems that may complicate proper diagnosis and treatment. For instance, patients with epilepsy may experience psychiatric symptoms that are caused by, maintained, or exacerbated by discrete epileptiform activity. The most striking incidence of this relates to peri-ictal states that cause intense psychiatric reactions that include any number of symptoms consistent with anxiety, fear and panic, negative emotionality, and even psychotic phenomena [156]. Moreover, psychiatric factors in epilepsy have been related to challenges that stem from the functional impact of the disease that serve to restrict, modify, or impair individuals' functional status [157]. In that regard, limitations, such as restricted job duties and driving cessation, have been related to a higher incidence of mental health and psychological adjustment challenges along with lower rated quality of life [158].

While much is known about the psychosocial aspects of some common epilepsy syndromes (i.e., TLE), there has been less prominent study in individuals who have been diagnosed with other less frequently occurring forms of epilepsy. Within the JME literature, there are oft mentioned assertions that individuals with JME possess characteristics including irresponsibility, labile behavior, poor discipline, quixotic temperaments, emotional regulation difficulties, and egocentrism, although few empirical data have directly addressed these psychological traits in a systematic fashion [159]. Early retrospective study identified that there was a high portion (36.4%) of "character neurosis disorder" in JME patients [160]. Other indications [161] were that approximately 29% had some type of psychiatric disorder. Applying personality typologies that are specific to epilepsy patients has proven challenging [162], although research-driven examinations have begun to more clearly identify the types of interictal psychiatric complications that frequently occur in patients with JME. Within that empirical approach, researchers have reported that a combination of personality features, psychiatric symptoms, and contemporary psychiatric disorders occur in JME patients. To a lesser extent, relationships with extra-disease factors, such as social functioning have also been investigated in JME patients.

In terms of research approaches, differential prevalence designs have shown that JME patients have a higher rate of psychiatric diagnoses than controls. Standardized diagnostic interviews, such as the Structured Clinical Interview for DSM-IV [163], have demonstrated rates of psychopathology in JME patient clinical samples ranging from 35 to 62% [164-167]. Lifetime

http://dx.doi.org/10.5772/58372

prevalence of Axis I (30%) and Axis II (26%) diagnoses has also been reported to be high, and a number (47%) have current or lifetime prevalence of some type of disorder. Concerning specific disorders in studies where standardized diagnostic interviews were used, results are as follows: anxiety disorders (21-23.8%) [165, 167], generalized anxiety disorder (19-23%) [165, 166, 168], depression (17-20.9%) [165-168], and somatoform disorders (5.6-7%) [165, 166, 168]. Those studies also indicated that less than 5% of patients have a substance abuse disorder, psychotic disorder, obsessive compulsive disorder, dysthymia, specific phobias, or attention deficit disorder [165-168]. Beyond Axis I disorders, it has been noted that 9 to 20% of samples have met criteria for a personality disorder according to structured diagnostic interview [166, 167]. Histrionic, paranoid personality, and borderline personality disorders were most prevalent. There has been a high rate of Axis I (11.3-19%) [164, 165] and Axis II (23%) [164] psychiatric comorbidity in those patients who have one diagnosis as well.

Across other various diagnostic schemes, such as retrospective chart review and clinical judgment, prevalence of any mental disorder varies from 26.5 to 34% [109, 169, 170]. Different researchers have also reported various combinations of mental disorders in samples such that 25.3% in one study were determined to have either an anxiety, phobia, or somatization disorder and 18.1% had a mood disorder [140]. Frequency of specific diagnoses for depression (8.6-14.5%) [109, 170] and anxiety disorders 15.5% [109] have also been reported. Similar to studies using structured diagnostic interviews, other designs have indicated a low prevalence (<5%) for psychotic disorders [169] and obsessive compulsive disorder [109, 169]. However, some data points have been outliers in that less than 5% of samples have been diagnosed with depression and anxiety disorders as well as depression [169]. In addition to diagnostic rates, patients with JME have scored significantly higher than controls on measures of symptoms related to depression, anxiety [171], internalization (24%), and externalization (16%) [172]. Prevalence of personality disorders in studies with less controlled diagnostic procedures have varied widely and have comprised 3 to 14% of samples [109, 169, 170]. Data from the aforementioned studies have indicated that groups of patients with JME have a higher incidence of mental disorders than members of control groups. Such studies have tended not to report comorbidity rates.

In addition to comparing control groups, research has been conducted examining differential prevalence of mental health problems in JME groups with that found in other groups of epilepsy patients. In a study of 157 patients with GGE [173], there were no significant differences in rates of psychiatric diagnoses between JME patients (23%) and diagnoses occurring in other GGE syndromes. In comparison to patients with partial epilepsies, varying degrees of concordance have been noted. In larger samples [168], similar numbers of psychiatric disorders have been found in JME patients (49%) and patients with refractory MTS (50%). In contrast, an early study using a structured diagnostic interview [174] found only 22% of the JME patients met criteria for a mental disorder, while 55% of patients with TLE met criteria for a mood disorder. Comparison of prevalence has suggested that JME patients have a lower rate of psychotic disorders than patients with MTS, although anxiety disorder may be more prevalent in JME groups (23%). That research group [165] also compared a larger cohort and did not find differing levels of psychiatric diagnoses (i.e., mood, anxiety or somatoform)

between JME patients and those with MTS, although the presence of psychotic disorders was associated with MTS group membership. Indeed, that group also published data [175] from the same sample that indicated significantly more MTS patients (11.6%) had at least two core symptoms of psychosis compared with 4.8% of those with JME. However, the proportion of individuals with post-ictal psychosis or interictal psychosis was similar between the groups. With regard to symptom severity, a sample of 20 JME and 20 TLE patients had scores on measures of stress and depression [176] that were similar.

Further research on various broad spectrum measures of personality traits [172] has revealed a number of disparate findings. Study on JME patients' responses on metrics of personality characteristics has indicated JME patients [172] experience significantly higher levels of a "repressive defensiveness" trait than the test normative sample, although a number of other variables were not significantly elevated. Other research [177] has compared responses of JME patients and controls on the Minnesota Multiphasic Personality Inventory [178], and another group [176] did not find group differences on a Five Factor personality inventory in JME and TLE patients. Another study [171] of personality features in JME explored possible endophenotypic expressions of personality features that are not part of contemporary psychiatric diagnostic categorization. As such, compared with controls, JME patients were shown to have a high rate of novelty seeking, low rate of harm avoidance, and low rate of self-directedness (e.g., lack of goal direction and incongruent habits). Taken together, these disparate and non-significant findings have led to conclusions that there may not be a specific personality profile associated with JME [172, 176].

Finding factors that influence or modify the expression of mental health problems in JME has also proven elusive. In a retrospective chart review [169] of 155 JME patients, it was shown that psychiatric disorders were more prevalent in patients with medically resistant seizures (58.3%) as opposed to non-resistant (19%). Similarly, anxiety disorders in JME patients have been associated with lack of seizure control and a history of having several lifetime GTCSs [167]. Moreover, other psychiatric and personality disorders have been associated with seizure frequency [166]. In contrast, others have not found associations of frequency of psychiatric diagnoses with duration of epilepsy [164, 168], type of seizures [164, 168], seizure frequency [164, 168], or number and type of AEDs [168]. Researchers [164] have also not found factors associated with psychiatric comorbidity including age and medication adherence.

Regarding personality features [177], patient endorsements on measures of personality have not been related to age of epilepsy, diagnosis onset, or seizure frequency. In JME patients with a personality disorder compared with JME patients without a personality disorder, there have been no group associations with disease duration [166], age of onset, or "adequate treatment" [179-181]. However, there have been significant associations of personality facets, such as novelty seeking, with early age of epilepsy onset and higher frequency of myoclonic seizures [171]. Disease chronicity has also been shown to relate to personality features, such as restraint [172].

In contrast to describing risk factors, researchers have identified potentially protective factors against anxiety and personality disorders that include being treated with an AED for more than 2 years [166, 168]. Although the direction of causality for this association is not known, it

http://dx.doi.org/10.5772/58372

is likely that lower psychological stress promotes adherence, and the effect of being adherent leads to better seizure control, which also likely results in better psychosocial functioning and fewer psychiatric symptoms. As psychological stress has been inconsistently shown to be related with seizure control, researchers have implemented psychological interventions expecting this will affect seizure outcome. In one such study [109], 58 JME patients with uncontrolled seizures receiving a "rational AED regimen" participated in psychological intervention with the goal to eliminate seizure precipitants. Treatment modalities in that study included an anti-stress program or Cognitive Behavioral Therapy intervention. The results from that study indicated that patients showed a reduction of seizure activity across three time epochs as treatment progressed and this also coincided with ratings of psychiatric functioning. This is particularly relevant as there are indications that psychological factors might relate to seizure control and perceptions of seizure control. For instance, in a survey of JME patients, 62 of 75 respondents (83%) reported that they viewed stress as the most frequent seizure precipitant [35]. These findings provide preliminary evidence that medication adherence and psychological treatment may have important roles in influencing emotional well-being in these patients.

Along with rates of psychiatric problems, other functional outcomes have been examined. For example, long-term follow-up of JME patients [14] has indicated that 65% to 77% of patients reported being "very satisfied" with their health, work, friendships, and social life. However, 61% were prescribed a psychiatric medication, nearly one third were unemployed, and 74% reported at least one "unfavorable" social outcome (i.e., school suspensions, truancy, fighting, criminal offense, social isolation, social impulsiveness, unplanned pregnancy). The authors noted that such outcomes occur at similar rates as other childhood onset epilepsies. Likewise, other data has indicated that only 22.9% of patients may find employment [140]. JME patients [182] also have adjustment challenges in work and family life. De Araujo Filho et al. [166] noted that JME patients, compared with controls, also had a lower DSM-IV Global Assessment of Functioning score and they reported a higher number of psychosocial problems.

As neurobiological theories of psychiatric disorders continue to be advanced [183, 184], there have also been more studies of cerebral functioning in patients with epilepsy and comorbid psychiatric conditions [185]. In that vein, a group from Brazil has been at the forefront of examining characteristics of brain structure and function in JME patients with and without psychiatric diagnoses. In particular, they [180] have shown small to medium correlations for NAA/Cr in the left medial primary motor region and right thalamus, and small to medium correlations for GLX/Cr in the right medial primary motor and left lateral primary motor areas for psychiatric JME patients. That group [179] also showed that 16 JME patients with a cluster B personality disorder had reduction of GMV in right thalamus compared with JME patients with no psychiatric problems. The JME group with personality disorders also had bilateral increases in GMV in the middle frontal gyrus and right orbitofrontal cortex, and decreased white matter in the posterior corpus callosum. Additional study [181] of cluster B personality disorders in patients with JME showed bilateral morphological changes in thalamic, frontal, and limbic structures compared with JME patients with no psychiatric disorder.

Overall, the current data do not consistently support a specific combination of behavioral or psychiatric symptoms among JME patients suggestive of a personality syndrome. In general, rates of psychiatric diagnoses in JME patients have been shown to be higher than the general population. Further, preliminary data suggest that JME patients have a higher rate of anxiety symptoms and less prevalence of psychotic symptoms compared with TLE patients. However, while there are a number of studies of psychiatric functioning in other epilepsies, such as TLE, psychiatric data in JME patients remain inadequate. Moreover, a number of studies typically lack satisfactory sample size, control and differing patients groups, psychosocial contributors, neuroimaging (i.e., structural and functional) studies, or neurophysiological metrics. Additionally, there is an absence in the literature regarding genetic, sibling, or family studies that address psychiatric variables. Such data will further help advance causal models of psychopathology and influence treatment implications. Although many details regarding psychiatric problems in JME are not well defined, the combined data has immediate implications for clinical care.

16. Pathophysiology

Based upon evidence of broad cognitive dysfunction and psychiatric problems along with the findings that there are various seizures triggers and EEG findings, mounting evidence has suggested that JME affects the brain in a generalized manner. Nonetheless, the contention that JME is a disease of the frontal lobe and or thalamus has been asserted consistently by the literature, even in the face of contradictory neuroimaging and neuropsychological findings. Recent developments in genetics and neuroimaging have opened new avenues to understand the mechanisms underlying GGEs and expand the conceptualization of JME.

Genetics: The genetic inheritance of JME is complex as about 20 chromosomal loci have been linked to the disease. While several channelopathies have been associated with multiple GGE phenotypes, particular mutations have also been specifically implicated in JME. For instance, GABRA1 mutation reducing GABA-receptor function and expression [186], and EFHC1 mutations affecting mitotic spindle organization [187, 188], are both candidate mechanisms.

Autosomal dominant inheritance of a GABRA-1 mutation was reported in a large French-Canadian family with seven members exhibiting JME [186]. GABRA1 on chromosome 5q34 encodes for the α_1-subunit of the γ-aminobutyric acid receptor subtype A ($GABA_A$-receptor), linked to a chloride-ionophore. Activation of this receptor allows chloride to enter the neuron, leading to hyperpolarization. The GABRA1 mutation leads to a loss of function of the $GABA_A$-receptor in vitro, either due to altered gating properties or decreased expression of receptors at the cell surface, resulting in decreased inhibition.

EFHC1 is located on chromosome 6p11 and was the first gene to be identified with specific linkage to JME [58]. EHFC1 mutations are more commonly associated with JME than channelopathies, accounting for 9% of JME cases [189]. They are inherited in an autosomal dominant fashion, but also account for singletons and sporadic cases. The putative role of EFHC1 is evolving, but appears to affect neuronal division and migration during corticogenesis [187,

http://dx.doi.org/10.5772/58372

190]. EFHC1 was originally shown to be a microtubule–associated protein (MAP), localized to the centrosome and the mitotic spindle. Loss of function of EFHC1 disrupts mitotic spindle organization and impairs radial migration of neurons to the developing cortex. Moreover, recent evidence points to impaired radial glia scaffold formation and altered morphology of both radially (mainly excitatory) and tangentially (mainly inhibitory) migrating neurons. This disruption of migration results in fewer neurons and impaired cortical migration of both excitatory and inhibitory neurons. Impaired morphology, i.e., the inability to transform from multipolar to bipolar cells, leads to the neurons remaining in the intermediate zone.

Susceptibility genes may also play an important role in the expression of epilepsy phenotypes. Although channelopathies only account for 3% of JME [187], their genetic associations with epilepsy are likely important markers for disease characteristics. GABRA2 mutations, in addition to SCN1A and SCN1B mutations, have been liked to pedigrees with generalized epilepsy with febrile seizures, whose members may present with many types of epilepsy syndromes, including JME [186].

There are also several susceptibility single-nucleotide polymorphism (SNP) loci that contribute to the risk of developing GGE and JME, which has been suggested by genome-wide association analyses. For GGE, in general, at least three candidate genes have been noted: 1) VRK (2p16.1): a loci that may affect cortical development, 2) SCNA1 (2q24.3): a loci for coding the α-subunit of the neuronal voltage-gated sodium channel, mutations of which are the most common cause of channelopathy-related epilepsy, and 3) PNPO (17q21.32): a loci that is involved in pyridoxine oxidation to an active-cofactor involved in neurotransmitter metabolism. Susceptibility candidates for specific GGE syndromes, such as absence epilepsy or JME, were also identified. The linkage associated with JME is at 1q43, flanked by two regions with high recombination rates and covering the CHRM3 gene, which codes for the M3 muscarinic acetylcholine receptor. While nicotinic acetylcholine receptor mutations have been linked to autosomal dominant frontal lobe epilepsy, it is not clear how muscarinic receptors contribute to epileptogenesis.

In summary, the genetic effects of JME are manifold and various genotypes can result in the same epilepsy syndrome. This may be due to a combination of factors, including the lack of accurate epilepsy syndrome differences in subphenotypes or failure to identify epigenetic mechanisms.

Pathology: Brain pathology studies in cases of JME are rare (i.e., approximately 20 cases) as patients usually have an average life expectancy. Meencke and Janz [191] published brain pathology in eight patients with GGE, most of whom had myoclonic seizures. They found microdysgenesis in seven patients, defined as persistent uni-or bipolar cells in the subpial region, increased cell density in the stratum moleculare, portrusions of neurons against the pial membrane, containing well-differentiated neurons, columnar neuronal architecture, and increased neurons in the subcortical white matter. Atypical neurons were also found in the hippocampus and cerebellum [192]. There was no evidence of gliosis or chronic neuronal loss. Those findings were criticized for a lack of control group pathology samples [193], and the authors [191] published an additional number of brains from a mixed group of GGE. Using that latter group of specimens, the authors reported that there was a frontal-to-parietal decrease of “microdysplasia”, which was absent in the occipital lobes. In 2000, another group

compared five GGE patients, who died of SUDEP, to a nonepileptic control group [194]. This study did not find an increase of the "microdysplasia". Based upon the small numbers of patients with heterogeneous electroclinical features and syndromal diagnoses, it is difficult to draw any conclusions regarding pathology findings that are specific to JME.

Neuroimaging: In contrast to pathology studies, a number of morphometric imaging approaches since the 1990s have contributed to the neurobiological understanding of GGE and JME. Such studies have demonstrated differences between JME patients and normal controls, and suggest that there are subtle pathological changes difficult to assess by routine histology. Further, while JME manifests as generalized electroclinical activity, structural imaging has indicated circumscribed, multiregional abnormalities. Similarly, functional imaging studies have also demonstrated a predominance of symmetrical multiregional involvement (i.e., cerebral blood flow [CBF] or blood oxygen level dependent [BOLD] changes) prior to and during absence seizures or prolonged spike-and-wave discharges.

Structural Neuroimaging: Routine clinical structural imaging scans, whether computerized tomography (CT) or magnetic resonance imaging (MRI), are considered normal in individuals with JME. In contrast, more sensitive techniques, such as voxel-based morphometry (VBM), can show subtle variations in gray matter concentration or volume that differ in JME patients compared with healthy controls. An early quantitative MRI volumetric study in GGE participants showed increases in normalized gray matter volume (GMV) compared to healthy controls, but also possible differences between other epilepsy syndromes as well [195]. In a subsequent VBM study, statistical parametric mapping demonstrated increased mesial frontal GMV in JME patients. Individual patients also demonstrated additional changes in parietotemporal regions along with decreases frontally in individual patients analyzed by a volume of interest method [195].

More recent VBM studies in JME patients have demonstrated multiregional volumetric and morphometric brain changes [196, 197]. Lin et al. [196] showed increased right frontal GMV and but reduced bilateral thalami, insula, and cerebellar hemisphere volume. Differences in GMV as a function of photosensitivity were also detected, as there were decreases in occipital lobe, left inferior frontal lobe, and hippocampal GMV in photosensitive patients compared with non-photosensitive JME patients. Altered cortical morphology differences in terms of surface area metrics, and not cortical thickness, was noted in the left hemisphere: insula, cingulate, occipital pole, middle temporal, and fusiform gyri [197]. Similar differences were also noted in the right hemisphere: insula, inferior temporal gyrus, and precuneus. Mean cortical curvature measurements in JME patients were also different from controls in the bilateral insula, left cingulate, and right inferior temporal gyrus.

Diffusion tensor imaging (DTI) provides a complementary approach to traditional morphometric and volumetric analyses, as it accounts for white matter connectivity in cortical and subcortical regions. The most important parameters assessed by DTI are fractional anisotropy (FA) and mean diffusivity (MD), which provide information about the microstructural integrity of the white matter pathways. In particular, FA is influenced by myelin integrity and fiber density, whereas MD is correlated with microscopic membrane disruption and extracellular fluid accumulation.

http://dx.doi.org/10.5772/58372

It has been shown that JME patients have symmetric FA reductions in the bilateral superior and anterior corona radiata, genu and body of the corpus callosum, along and with middle and superior frontal tracts [139]. White matter tract MD increases coincided with the FA reduction, although the left superior parietal lobe was also affected. There were no increases in FA or decreases in MD found in JME patients. Frequency of GTCS was correlated with the severity of the microstructural changes.

Several studies have shown similar reductions of FA [141] and increases in MD [198], mainly concentrated in thalamocortical pathways and the corpus callosum; pathways that are responsible for propagation and synchronization of spike-and-wave discharges. These DTI changes have been correlated with GMV reduction in the supplementary motor area (SMA) and posterior cingulate cortices. The SMA FA was correlated with deficits for word naming tasks and expression, while the posterior cingulate changes predicted cognitive inhibition scores [141] and deficits in frontal lobe executive motor functioning. A subsequent study by the same group demonstrated a correlation between DTI and fMRI-based measures of structural and functional connectivity between prefrontal cognitive cortex and motor cortices [198]. Connectivity was decreased between prefrontal and frontopolar regions and increased between occipital cortex and SMA. The authors suggested that the frontal connectivity changes may be related to cognitive deficits seen in JME, and occipitomotor connectivity may be related to photosensitivity, although association with these clinical phenotypes were not investigated.

The neuroanatomic basis of GMV and DTI changes is not clear. It is suspected that the decreased connectivity may be due to altered cortical organization, but as many of these changes are correlated with disease activity, degenerative changes cannot be ruled out. So far, the studies have shown disparate findings, thus, leading to an inconclusive picture of cerebral differences in JME. However, the aggregate of study results suggests diffuse abnormalities with morphological changes that include regions beyond the frontal lobes. Moreover, pathological studies are needed to confirm changes in cortical organization and connectivity. To improve on this knowledge base, an animal model of JME could be utilized to investigate a number of clinicopathological data points including morphometric changes and histopathologic findings.

Functional – Interictal PET, MRS, EEG-fMRI: Interictal PET studies using flourodeoxyglucose (FDG) evaluate metabolism over a 40-minute uptake time. While FDG-PET is not ideal for evaluating transient ictal state or interictal discharges it does evaluate a more chronic functional status. In an early study, Swartz et al. [125] indicated that JME patients showed decreased metabolism in the prefrontal and premotor cortices, which was associated with behavioral and cognitive dysfunction. Increased metabolism in the bilateral thalami was correlated with increased ictal or interictal epileptic discharges in another study of JME patients [199]. These studies demonstrated predominantly frontal lobe dysfunction, and an obvious activation of the thalami by ictal and interictal epileptic discharges. The absence of cortical activations suggests more fluctuation in metabolism due to epileptic discharges, decreased neuronal activity in the interictal state, or a general decrease of metabolism due to the disruptive effect of epileptic discharges on cognitive activity.

Magnetic resonance spectroscopy (MRS) can be used to measure neuronal function and concentrations of neurotransmitters in the cerebral cortex and subcortical structures. One study showed reduced N-acetyl aspartate (NAA) in the medial frontal lobes (and not in the occipital lobes) of individuals with JME [200]. The same group [152] showed NAA reduction was specific to JME as compared to individuals diagnosed with GTCS upon Awakening, but was similar to patients with CAE and JAE, [201]. However, investigation of cortical regions was limited and did not involve the lateral frontal, sensorimotor, or parietal areas.

Functional connectivity is a novel method evaluating regional covariance of BOLD signal over time. Most of the functional connectivity data is derived from generalized spike-and-wave discharges in individuals with absence epilepsy. Such studies have examined BOLD changes before, during, and after spike-and-wave discharges. While the thalamocortical networks projecting mainly to the medial frontal lobe are briefly activated during these discharges, more sustained activations occur in the parietal lobes prior to the discharges. As the discharges evolve, increases in BOLD dissipate, resulting in decreased frontoparietal BOLD signal. The brief discharges associated with JME are less likely to cause similar degrees of BOLD changes. Therefore, evaluating more stable measures such as functional connectivity, can provide more information regarding the networks.

One group has contributed greatly to evaluating connectivity both structurally and functionally in individuals with JME [141, 198]. As mentioned above, they have demonstrated that functional connectivity is closely correlated with structural connectivity in the medial frontal cortices in individuals with JME [198]. They showed that during verbal fluency tasks, there is diffuse symmetrical activation of the SMA, bilateral inferior frontal gyri, left premotor area, left thalamus and bilateral putamen, as well as bilateral ventral visual areas. The thalamic region, showing altered connectivity on DTI, was connected to cortices largely overlapping the areas of functional activation. Overall, the individuals with JME showed increased task-dependent connectivity with respect to the frontal cortices compared to controls. Based upon these findings, the authors concluded that the thalamus serves an important function in increased frontal connectivity and coherence.

However, another study of functional connectivity in GGE, which included a large number of patients with JME, showed that there was no alteration of thalamic or mesial frontal connectivity when no discharges occurred [202]. Although the investigative techniques have differed between studies and selection biases may be present, the latter study suggests that generalized spike-and-wave discharges may be generated by healthy networks in response to abnormal connectivity and cortical synchronization in disparate brain regions. Indeed, another study showed alterations in default mode network (DMN) connectivity (in the absence of ictal or interictal epileptic discharges) between posterior and anterior nodes in patients with GGE [203]. Given the current limitations, additional methods, such as intracranial electrophysiological recordings and subsequent pathological examination would help elucidate the mechanisms underlying the CBF changes.

Transcranial Magnetic Stimulation: Transcranial magnetic stimulation (TMS) leads to a brief depolarization of cortical neurons, and can target brain regions such as the motor and language cortices. Motor cortex stimulation, such as the primary hand motor area, is conducted

http://dx.doi.org/10.5772/58372

frequently as the stimulus direction and intensity can be optimized to specifically activate hand muscles. TMS can be applied using single or paired pulses. Single pulse TMS is used to measure the resting motor threshold and the cortical silent period (CSP). Furthermore, the paired pulse stimulation paradigm is used measure short-latency intracortical inhibition and facilitation.

Early studies demonstrated an increase in CSP in individuals with GGE, suggesting increased intracortical inhibition [204]. Sleep deprivation in individuals with GGE resulted in a greater change in cortical excitability compared to patients with partial epilepsies or controls, based upon paired-pulse studies [205]. ILS appears to decrease CSP in healthy controls, but not in photosensitive or nonphotosensitive individuals with GGE [206]. These findings are somewhat counterintuitive, as it would be expected that hyperexcitability would be observed in the motor cortices of GGE patients.

Antiepileptic medications can reduce cortical excitability, but there also seems to be variable findings across studies of various GGE syndromes and stimulation protocols. A meta-analysis, showed normal rMT threshold in all GGE patients, except for individuals with JME, who had decreased motor thresholds compared to healthy controls [207], suggesting a degree of cortical excitability in the patients. In a subsequent study, the same group showed that rMT was decreased for photosensitive individuals with GGE compared to those without, although this may be due to syndrome-specific bias, as photosensitivity is most commonly associated with JME [208].

Animal Models: Due to its high rate of photosensitivity, the bamboo species, *Papio hamadryas papio*, has long been investigated as a model for epileptic photosensitivity [209]. Researchers established the electrophysiological mechanisms of the model by intracranial depth electrode recordings during photoepileptic responses that occurred with or without lesioned pathways. The ictal and interictal epileptic discharges have been shown to conform to a generalized cerebral distribution, and photic stimulation in the baboons elicits both myoclonic seizures and GTCS. Unlike humans, who respond to ILS at different frequencies (i.e., 12-18Hz), this species is maximally photosensitive at frequencies of 20-25 Hz. However, like humans, they are the most sensitivity to seizure activity in mornings, shortly after awakening. In order to study the seizures in a controlled way, researchers typically elicit activation by ILS, often after pretreatment with allylglycine, a GABA synthesis inhibitor, or by administering proconvulsants (e.g., pentylenetetrazol) [210].

Observations of the baboon's photoparoxysmal responses have indicated that there are generalized spike-and-wave complexes that occur maximally in the frontocentral regions, particularly in the mesial frontal surfaces [43]. During ILS, the occipital driving responses remain localized to occipito-parietal areas with occipital IEDs being rare and temporally unsustained. Fischer-Williams's et al. [43] early study showed that subcortical structures, thalamus, basal ganglia, and brainstem were only secondarily affected by frontocentral IEDs, usually in association with high-amplitude or repetitive discharges. The amygdala, hippocampus, and uncus were not involved in the photoepileptic responses.

In addition, paroxysmal visually evoked potential (PVEP) studies, using single flash stimuli administered after a 10 second train of 25 Hz ILS, have enabled researchers to track discrete

electrophysiological events through cortical-subcortical networks. In one study, earliest activation of frontocentral IEDs occurred 20 to 30 milliseconds after the flash, with a subsequent eyelid or facial myoclonus occurring 10 to 12 milliseconds later [211]. Motor symptoms tend to occur only when the amplitude of the cortical discharges exceeded 200 microvolts [212]. Following a PVEP, activation of thalamic nuclei (e.g., ventralis lateralis, centrum medianum, & lateralis posterior) occurs at cortical discharge amplitudes exceeding 400 microvolts. Silva-Barrat et al. [213] also demonstrated that photosensitive and asymptomatic control baboons show difference PVEP responses in peristriate and parietal regions, but not in the striate or cortical responses. It was also shown that frontocentral ictal or interictal epileptic discharges were not activated by ILS following bilateral occipital lobe ablation, while destruction of the superior colliculus or pulvinar unilaterally caused only transient suppression of photoepileptic responses [214]. In terms of other lesion study, corpus callosum sectioning in combination with unilateral stimulation of the occipital lobe resulted in frontocentral discharges and seizures that remained ipsilateral to the activated occipital lobe [215].

Although the epilepsy in these baboons appears similar to JME in many ways, early researchers failed to establish a model for JME from characteristics seen with the baboons. However, the phenotypic expression of several hundred baboons has recently been described clinically and with scalp EEG [216]. The onset of the syndrome typically occurs in adolescence, there is a preponderance of myoclonic and GTCS, and there is a similar diurnal pattern (i.e., predominately in the morning) to JME [217]. The myoclonic seizures tend to affect the face and arms. The GTCS tend to occur in a sporadic fashion, and can be triggered by handling or ketamine. The interictal epileptic discharges are generalized in distribution with 4-6 Hz in frequency, although 2-3 Hz discharges have been noted in younger baboons [218]. Younger baboons can also present with absence seizures, and even spike-and-wave stupor [216]. Although the baboon model of epilepsy and JME share many clinical characteristics, including a genetic etiology, the mode of inheritance and underlying genotypes are not known.

Szabó et al. [219, 220] have also evaluated structural and functional neuroimaging in a large baboon colony. Their findings indicated that while routine structural MRI studies are normal, morphometric analyses revealed decreased central and intraparietal sulci along with cingulate sulci in baboons that showed IEDs [221]. The smaller sulcal areas may reflect an underlying developmental anomaly, resulting in decreased U-fibers, rather than a process due to aging or degenerative disease.

Functional studies have aimed to describe epileptic neuronal networks. IED rate and associated cerebral blood flow changes on $H_2{}^{15}O$-PET have demonstrated co-activations of the premotor, perirolandic, insular-parietal, and occipital cortices, areas that are also observed in human GGE networks [222]. Resting state fMRI has shown altered connectivity of the motor, but not the visual cortices, and DMN connectivity was altered in the epileptic baboons as well [223]. This group has also used intracranial video-EEG in combination with depth, grid, and strip electrodes in order to improve spatial resolution [224]. Results from this approach indicated that frequent multiregional IEDs occur, which appears to trigger generalized discharges. The researchers also recorded myoclonic and GTCS, most of which were triggered multifocally. The focal regions that were most active, according to invasive monitoring,

http://dx.doi.org/10.5772/58372

included the parieto-occipital region, parietal lobe, premotor area, and orbitofrontal cortex. This was unexpected as the scalp EEG demonstrated only generalized discharges, and the multifocal discharges appeared to occur both parietally and frontally, reflecting a more diffuse pathology.

Previous examinations of pathology have not shown cortical abnormalities in these animals, suggesting developmental changes or seizure-induced injury [225]. Comparison of neuronal counts from the molecular layer, cortical layer 6 and subcortically, in three sulci, namely the cingulate, intraparietal, and lunate sulcus between asymptomatic photosensitive and healthy control baboons did not demonstrate cortical neuronal reductions, but did detect increased numbers of neurons in the subcortical white matter of the anterior cingulate sulcus [226]. Neuronal flow cytometry, on the other hand, demonstrated cortical neuronal reductions, particularly in the frontal regions related to motor functions and somatosensory cortex [227]. The motor cortices most involved were the face and hand regions, areas most commonly involved in the manifestation of myoclonic seizures. The decreased cell counts are likely to result in decreased functional connectivity, especially in the motor cortices. The electrophysiological effects of the neuron reductions are unclear, but may be related to the extent that inhibitory and excitatory neurons are affected. More detailed pathology for specific types of neurons needs to be pursued, and a qualitative evaluation of cortical organization also needs to be considered.

17. Conclusions

JME is a commonly occurring and electroclinically well-defined neurological disease. As with most GGEs, it is relatively straightforward to diagnose and treat; however, there is still uncertainty regarding features which may influence a poor response to antiepileptic medications and complicate overall prognosis. Compared to other types of GGE, JME appears to have a structural etiology. Thus, although it shares commonalities with other GGEs, JME breaks that mold, as the condition has been associated with multiregional and/or asymmetric electroclinical findings. While the nature and development of that structural and functional etiology does not appear to be frontal lobe specific, research has yet to define a replicable model for the disease. Moreover, as JME sub-syndromes [228] may have overlapping features with other epilepsies, establishment of cognitive signs and symptoms that are specific to JME has continued to elude researchers.

As a result of the apparent time-course of syndrome onset along with differing prevalence and prognosis across the lifespan, in conjunction with the subtle cerebral abnormalities as noted above, some cases of JME likely reflect a set of underlying neurodevelopmental processes. Nevertheless, there remains a lack of knowledge regarding histopathology, electroclinicial characteristics and propagation patterns, genetic contributors to phenotypic expression, and disease biomarkers. Given its similarities to human GGE syndromes (i.e., similar seizure types and electrophysiological characteristics) and methodical constraints in human research, recent contributions from the animal literature suggest that continued investigation of these factors

in a baboon population will offer a unique avenue to further refine human models of JME, particularly in the setting of photosensitivity. Furthermore, pharmacological development would likely be assisted by employing trials of agents in animals that show behaviors consistent with human phenotypes.

In terms of treatment, various combinations of agents have been shown effective, although some cases of JME result in intractability. Overall, regardless of intractability, JME has the potential for negatively impacting quality of life. For instance, recent studies indicated discernible interictal effects on cognition and behavior, even in patients that are relatively well-controlled. Thus, contrary to previous assertions and clinical lore, JME does not appear to be a "benign" disease.

Author details

Russell D. Pella, Lakshmi Mukundan and C. Akos Szabo*

*Address all correspondence to: szabo@uthscsa.edu

University of Texas Health Science Center at San Antonio, USA

References

[1] Herpin TH. Des asces incomplets de l'epilepsie. Paris, France: J Balliere et Fils; 1867.

[2] Rabot LDL. De la myoclonie épileptique. Paris, France: Thèse; 1899.

[3] Janz D, Christian W. Impulsiv-petit mal. Deutsche Zeitschrift fu°r Nervenheilkunde 1957;176:346–86.

[4] Delgado-Escueta AV, Enrile-Bacsal F. Juvenile myoclonic epilepsy of Janz. Neurology. 1984;34(3):285-94.

[5] Lund M, Reintoft H, Simonsen N. [A controlled social and psychological investigation of patients with juvenile myoclonic epilepsy]. Ugeskrift For Laeger. 1975;137(41): 2415-8.

[6] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia. 1989;30(4):389-99.

[7] Genton P, Gelisse P. Juvenile myoclonic epilepsy. Archives of Neurology. 2001;58(9): 1487-90.

[8] Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. Mayo Clinic Proceedings Mayo Clinic. 1996;71(6):576-86.

[9] Panayiotopoulos CP, Obeid T, Tahan AR. Juvenile myoclonic epilepsy: a 5-year prospective study. Epilepsia. 1994;35(2):285-96.

[10] Figueredo R, Trevisol-Bittencourt PC, Ferro JB. [Clinical-epidemiological study of patients with juvenile myoclonic epilepsy in Santa Catarina State, Brazil]. Arquivos De Neuro-Psiquiatria. 1999;57(2B):401-4.

[11] Kun LN, Ling LW, Wah YW, Lian TT. Epidemiologic study of epilepsy in young Singaporean men. Epilepsia. 1999;40(10):1384-7.

[12] Murthy JM, Yangala R, Srinivas M. The syndromic classification of the International League Against Epilepsy: a hospital-based study from South India. Epilepsia. 1998;39(1):48-54.

[13] Janz D, Durner M. Juvenile Myoclonic Epilepsy. In: Engel J, Pedley, T.A., editor. Epilepsy: a comprehensive textbook. Philadelphia, PA: Lippincott-Raven Press; 1998. p. 2389–400.

[14] Camfield CS, Camfield PR. Juvenile myoclonic epilepsy 25 years after seizure onset: a population-based study. Neurology. 2009;73(13):1041-5.

[15] Camfield CS, Striano P, Camfield PR. Epidemiology of juvenile myoclonic epilepsy. Epilepsy & Behavior. 2013;28(Suppl 1):S15-S7.

[16] Mullins GM, O'Sullivan SS, Neligan A, McCarthy A, McNamara B, Galvin RJ, et al. A study of idiopathic generalised epilepsy in an Irish population. Seizure. 2007;16(3): 204-10.

[17] Manonmani V, Tan CT. A study of newly diagnosed epilepsy in Malaysia. Singapore Medical Journal. 1999;40(1):32-5.

[18] Asadi-Pooya AA, Emami M, Sperling MR. A clinical study of syndromes of idiopathic (genetic) generalized epilepsy. Journal of the Neurological Sciences. 2013;324(1-2): 113-7.

[19] Wirrell EC, Camfield CS, Camfield PR, Gordon KE, Dooley JM. Long-term prognosis of typical childhood absence epilepsy: remission or progression to juvenile myoclonic epilepsy. Neurology. 1996;47(4):912-8.

[20] Obeid T, Panayiotopoulos CP. Juvenile myoclonic epilepsy: a study in Saudi Arabia. Epilepsia. 1988;29(3):280-2.

[21] Sozmen V, Baybas S, Dirican A, Koksal A, Ozturk M. Frequency of epilepsies in family members of patients with different epileptic syndromes. European Neurology. 2011;65(1):4-9.

[22] Grünewald RA, Chroni E, Panayiotopoulos CP. Delayed diagnosis of juvenile myoclonic epilepsy. Journal of Neurology, Neurosurgery & Psychiatry. 1992;55(6):497-9.

[23] Gunatilake SB, Seneviratne SL. Juvenile myoclonic epilepsy: a study in Sri Lanka. Seizure. 2000;9(3):221-3.

[24] Genton P, Gelisse P, Thomas P. Juvenile myoclonic epilepsy today. In: Schmitz B, Sander, T, editor. Juvenile Myoclonic Epilepsy: The Janz Syndrome. Berlin, Germany: Hippokrates-Verlag; 2000. p. 11-32.

[25] Serratosa JM, Delgado-Escueta AV. Juvenile Myoclonic Epilepsy. In: Wyllie E, editor. The treatment of epilepsy: principles and practices. Philadelphia, PA: Lea & Febiger; 1993. p. 552-70.

[26] Tóth V, Rásonyi G, Fogarasi A, Kovács N, Auer T, Janszky J. Juvenile myoclonic epilepsy starting in the eighth decade. Epileptic Disorders: International Epilepsy Journal With Videotape. 2007;9(3):341-5.

[27] Hirano Y, Oguni H, Funatsuka M, Imai K, Osawa M. Differentiation of myoclonic seizures in epileptic syndromes: A video-polygraphic study of 26 patients. Epilepsia. 2009;50(6):1525-35.

[28] Kasteleijn-Nolst Trenité DGA, de Weerd A, Beniczky S. Chronodependency and provocative factors in juvenile myoclonic epilepsy. Epilepsy & Behavior. 2013;28(Suppl 1):S25-S9.

[29] Badawy RA, Macdonell RA, Jackson GD, Berkovic SF. Why do seizures in generalized epilepsy often occur in the morning? Neurology. 2009;73(3):218-22.

[30] Baykan B, Altindag EA, Bebek N, Ozturk AY, Aslantas B, Gurses C, et al. Myoclonic seizures subside in the fourth decade in juvenile myoclonic epilepsy. Neurology. 2008;70(22 Part 2):2123-9.

[31] Genton P, Thomas P, Kasteleijn-Nolst Trenité DGA, Medina MT, Salas-Puig J. Clinical aspects of juvenile myoclonic epilepsy. Epilepsy & Behavior. 2013;28(Suppl 1):S8-S14.

[32] Sadleir LG, Scheffer IE, Smith S, Carstensen B, Carlin J, Connolly MB, et al. Factors influencing clinical features of absence seizures. Epilepsia. 2008;49(12):2100-7.

[33] Larch J, Unterberger I, Bauer G, Reichsoellner J, Kuchukhidze G, Trinka E. Myoclonic status epilepticus in juvenile myoclonic epilepsy. Epileptic Disorders: International Epilepsy Journal With Videotape. 2009;11(4):309-14.

[34] Crespel A, Velizarova R, Genton P, Gélisse P. [Juvenile myoclonic epilepsy with recurrent myoclonic status: efficacy of valproate]. Thérapie. 2009;64(5):321-3.

[35] da Silva Sousa P, Lin K, Garzon E, Sakamoto AC, Yacubian EMT. Self-perception of factors that precipitate or inhibit seizures in juvenile myoclonic epilepsy. Seizure. 2005;14(5):340-6.

[36] Wolf P. From precipitation to inhibition of seizures: rationale of a therapeutic paradigm. Epilepsia. 2005;46 Suppl 1:15-6.

[37] Guaranha MS, da Silva Sousa P, de Araújo-Filho GM, Lin K, Guilhoto LM, Caboclo LO, et al. Provocative and inhibitory effects of a video-EEG neuropsychologic protocol in juvenile myoclonic epilepsy. Epilepsia. 2009;50(11):2446-55.

[38] Beniczky S, Guaranha MSB, Conradsen I, Singh MB, Rutar V, Lorber B, et al. Modulation of epileptiform EEG discharges in juvenile myoclonic epilepsy: an investigation of reflex epileptic traits. Epilepsia. 2012;53(5):832-9.

[39] Matsuoka H, Takahashi T, Sasaki M, Matsumoto K, Yoshida S, Numachi Y, et al. Neuropsychological EEG activation in patients with epilepsy. Brain: A Journal of Neurology. 2000;123(2):318-30.

[40] Kasteleijn-Nolst Trenité DGA. Provoked and reflex seizures: surprising or common? Epilepsia. 2012;53 Suppl 4:105-13.

[41] Mayer T, Wolf P. Perioral reflex myoclonias in reading epilepsy and juvenile myoclonic epilepsy. In: Wolf P IY, Zifkin B editor. Reflex Epilepsies: Progress in Understanding. New Barnet, Herts, UK: John Libbey; 2004. p. 62–3.

[42] Kasteleijn-Nolst Trenité DG. Photosensitivity in epilepsy. Electrophysiological and clinical correlates. Acta Neurologica Scandinavica Supplementum. 1989;125:3-149.

[43] Fischer-Williams M, Poncet M, Riche D, Naquet R. Light-induced epilepsy in the baboon, Papio papio: Cortical and depth recordings. Electroencephalography & Clinical Neurophysiology. 1968;25(6):557-69.

[44] Parra J, Kalitzin SN, Iriarte J, Blanes W, Velis DN, Lopes da Silva FH. Gamma-band phase clustering and photosensitivity: is there an underlying mechanism common to photosensitive epilepsy and visual perception? Brain: A Journal of Neurology. 2003;126(Pt 5):1164-72.

[45] Varotto GELSGF. Enhanced frontocentral EEG connectivity in photosensitive generalized epilepsies: A partial directed coherence study. Epilepsia. 2012;53(2):359-67.

[46] Moeller F, Siebner HR, Ahlgrimm N, Wolff S, Muhle H, Granert O, et al. fMRI activation during spike and wave discharges evoked by photic stimulation. NeuroImage. 2009;48(4):682-95.

[47] Bai X, Vestal M, Berman R, Negishi M, Spann M, Vega C, et al. Dynamic time course of typical childhood absence seizures: EEG, behavior, and functional magnetic resonance imaging. The Journal of Neuroscience: The Official Journal of The Society for Neuroscience. 2010;30(17):5884-93.

[48] Benuzzi F, Mirandola L, Pugnaghi M, Farinelli V, Tassinari CA, Capovilla G, et al. Increased cortical BOLD signal anticipates generalized spike and wave discharges in

adolescents and adults with idiopathic generalized epilepsies. Epilepsia. 2012;53(4): 622-30.

[49] Ferlazzo E, Zifkin BG, Andermann E, Andermann F. Cortical triggers in generalized reflex seizures and epilepsies. Brain: A Journal of Neurology. 2005;128(Part 4):700-10.

[50] Asconapé J, Penry JK. Some clinical and EEG aspects of benign juvenile myoclonic epilepsy. Epilepsia. 1984;25(1):108-14.

[51] So GM, Thiele EA, Sanger T, Schmid R, Riviello JJ, Jr. Electroencephalogram and clinical focalities in juvenile myoclonic epilepsy. Journal of Child Neurology. 1998;13(11): 541-5.

[52] Genton P, Gonzalez Sanchez MS, Saltarelli A, Bureau M, Dravet C, Roger J. [Misleading aspects of the standard electroencephalogram in juvenile myoclonic epilepsy: a retrospective study of 56 consecutive cases]. Neurophysiologie clinique=Clinical neurophysiology. 1995;25(5):283-90. Epub 1995.

[53] Baise-Zung C, Guilhoto LMFF, Grossmann RM. Juvenile myoclonic epilepsy: nonclassic electroencephalographical presentation in adult patients. European Journal of Neurology. 2006;13(2):171-5.

[54] Syvertsen MR, Markhus R, Selmer KK, Nakken KO. [Juvenile myoclonic epilepsy]. Tidsskr Nor Laegeforen. 2012;132(14):1610-3.

[55] Genton P, Puig A, Tunon C, Lahoz CH, Sanchez M. Juvenile myoclonic epilepsy and related syndromes: clinical and neurophysiological aspects. In: Malafosse A, Genton, P, Hirsch, E, Marescaux, C, Broglin, D, Bernasconi, R, editor. Idiopathic generalized epilepsies: clinical, experimental and genetic aspects. London, UK: John Libbey and Company Ltd; 1994. p. 253–65.

[56] Fittipaldi F, Currà A, Fusco L, Ruggieri S, Manfredi M. EEG discharges on awakening: a marker of idiopathic generalized epilepsy. Neurology. 2001;56(1):123-6.

[57] Janz D. Epilepsy with impulsive petit mal (juvenile myoclonic epilepsy). Acta Neurologica Scandinavica. 1985;72(5):449-59.

[58] Delgado-Escueta AV, Greenberg DA, Treiman L, Liu A, Sparkes RS, Barbetti A, et al. Mapping the gene for juvenile myoclonic epilepsy. Epilepsia. 1989;30 Suppl 4:S8.

[59] Koeleman BPC, de Kovel CGF, Kasteleijn-Nolst Trenité DGA. Photoparoxysmal EEG response and genetic dissection of juvenile myoclonic epilepsy. Epilepsy & Behavior. 2013;28(Suppl 1):S69-S71.

[60] Serafini A, Rubboli G, Gigli GL, Koutroumanidis M, Gelisse P. Neurophysiology of juvenile myoclonic epilepsy. Epilepsy & Behavior. 2013;28(Suppl 1):S30-S9.

[61] Panayiotopoulos CP. A clinical guide to epileptic syndromes and their treatment 2nd ed. United Kingdom: Springer; 2007.

http://dx.doi.org/10.5772/58372

[62] Lancman ME, Asconapé JJ, Penry JK. Clinical and EEG asymmetries in juvenile myoclonic epilepsy. Epilepsia. 1994;35(2):302-6.

[63] Lancman ME, Asconapé JJ, Golimstok A. Circling seizures in a case of juvenile myoclonic epilepsy. Epilepsia. 1994;35(2):317-8.

[64] Ferrie CD. Idiopathic Generalized Epilepsies Imitating Focal Epilepsies. Epilepsia. 2005;46:91-5.

[65] Aliberti V, Grünewald RA, Panayiotopoulos CP, Chroni E. Focal electroencephalographic abnormalities in juvenile myoclonic epilepsy. Epilepsia. 1994;35(2):297-301.

[66] Niedzielska K, Kuran W, Romaniak A. [Clinical-electrophysiological pattern of juvenile myoclonic epilepsy]. Neurologia I Neurochirurgia Polska. 1995;29(5):675-85.

[67] Jayalakshmi SS, Srinivasa Rao B, Sailaja S. Focal clinical and electroencephalographic features in patients with juvenile myoclonic epilepsy. Acta Neurologica Scandinavica. 2010;122(2):115-23.

[68] Usui N, Kotagal P, Matsumoto R, Kellinghaus C, Lüders HO. Focal Semiologic and Electroencephalographic Features in Patients with Juvenile Myoclonic Epilepsy. Epilepsia. 2005;46(10):1668-76.

[69] Létourneau K, Cieuta-Walti C, Deacon C. Epileptiform asymetries and treatment response in juvenile myoclonic epilepsy. The Canadian Journal of Neurological Sciences Le Journal Canadien Des Sciences Neurologiques. 2010;37(6):826-30.

[70] Kelley SA, Kossoff EH. Doose syndrome (myoclonic-astatic epilepsy): 40 years of progress. Developmental Medicine & Child Neurology. 2010;52(11):988-93.

[71] Caraballo RH, Chamorro N, Darra F, Fortini S, Arroyo H. Epilepsy with myoclonic atonic seizures: an electroclinical study of 69 patients. Pediatric Neurology. 2013;48(5):355-62.

[72] Fisher RS, Boas WvE, Blume W, Elger C, Genton P, Lee P, et al. Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46(4):470-2.

[73] Adie WJ. Pyknolepsy: a form of epilepsy in children, with a good prognosis. Sect Neur. 1924;17:19-25.

[74] Panayiotopoulos CP. Typical absence seizures and related epileptic syndromes: Assessment of current state and directions for future research. Epilepsia. 2008;49(12): 2131-9.

[75] Tassinari CA, Bureau M. Epilepsy with myoclonic absences. In: Roger J DC, Bureau M, Dreifuss FE, Wolf P, editor. Epileptic syndromes in infancy, childhood and adolescence. London, England: John Libbery Eurotext; 1985. p. 121-9.

[76] Durner M, Sander T, Greenberg DA, Johnson K, Beck-Mannagetta G, Janz D. Localization of idiopathic generalized epilepsy on chromosome 6p in families of juvenile myoclonic epilepsy patients. Neurology. 1991;41(10):1651-5.

[77] Berkovic SF, So NK, Andermann F. Progressive myoclonus epilepsies: clinical and neurophysiological diagnosis. Journal of Clinical Neurophysiology. 1991;8(3):261-71.

[78] Shahwan A, Farrell M, Delanty N. Progressive myoclonic epilepsies: a review of genetic and therapeutic aspects. Lancet Neurology. 2005;4(4):239-48.

[79] French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2004;62(8):1252-60.

[80] Auvin S. Treatment of Juvenile Myoclonic Epilepsy. CNS Neuroscience & Therapeutics. 2008;14(3):227-33.

[81] Calleja S, Salas-Puig J, Ribacoba R, Lahoz CH. Evolution of juvenile myoclonic epilepsy treated from the outset with sodium valproate. Seizure. 2001;10(6):424-7.

[82] Fernando-Dongas MC, Radtke RA, VanLandingham KE, Husain AM. Characteristics of valproic acid resistant juvenile myoclonic epilepsy. Seizure. 2000;9(6):385-8.

[83] Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: An unblinded randomised controlled trial. The Lancet. 2007;369(9566):1016-26.

[84] Mazurkiewicz-Bełdzińska M, Szmuda M, Matheisel A. Long-term efficacy of valproate versus lamotrigine in treatment of idiopathic generalized epilepsies in children and adolescents. Seizure. 2010;19(3):195-7.

[85] Ben-Menachem E, Schmitz B, Tomson T, Vajda F. Role of valproate across the ages. Treatment of epilepsy in adults. Acta Neurologica Scandinavica. 2006;114:14-27.

[86] Adab N, Kini U, Vinten J, Ayres J, Baker G, Clayton-Smith J, et al. The longer term outcome of children born to mothers with epilepsy. Journal of Neurology, Neurosurgery & Psychiatry. 2004;75(11):1575-83.

[87] Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. Journal of Neurology, Neurosurgery & Psychiatry. 2006;77(2):193-8.

[88] Vinten J, Bromley RL, Taylor J, Adab N, Kini U, Baker GA. The behavioral consequences of exposure to antiepileptic drugs in utero. Epilepsy & Behavior. 2009;14(1): 197-201.

[89] Duncan S. Teratogenesis of sodium valproate. Current Opinion in Neurology. 2007;20(2):175-80.

[90] Morris GL, Hammer AE, Kustra RP, Messenheimer JA. Lamotrigine for patients with juvenile myoclonic epilepsy following prior treatment with valproate: results of an open-label study. Epilepsy & Behavior. 2004;5(4):509-12.

[91] Levisohn PM, Holland KD. Topiramate or valproate in patients with juvenile myoclonic epilepsy: A randomized open-label comparison. Epilepsy & Behavior. 2007;10(4):547-52.

[92] Park KM, Kim SH, Nho SK, Shin KJ, Park J, Ha SY, et al. A randomized open-label observational study to compare the efficacy and tolerability between topiramate and valproate in juvenile myoclonic epilepsy. Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia. 2013;20(8):1079-82.

[93] Specchio LM, Gambardella A, Giallonardo AT, Michelucci R, Specchio N, Boero G, et al. Open label, long-term, pragmatic study on levetiracetam in the treatment of juvenile myoclonic epilepsy. Epilepsy Research. 2006;71(1):32-9.

[94] Noachtar S, Andermann E, Meyvisch P, Andermann F, Gough WB, Schiemann-Delgado J. Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. Neurology. 2008;70(8):607-16.

[95] Rosenfeld WE, Benbadis S, Edrich P, Tassinari CA, Hirsch E. Levetiracetam as add-on therapy for idiopathic generalized epilepsy syndromes with onset during adolescence: analysis of two randomized, double-blind, placebo-controlled studies. Epilepsy Research. 2009;85(1):72-80.

[96] Kothare SV, Valencia I, Khurana DS, Hardison H, Melvin JJ, Legido A. Efficacy and tolerability of zonisamide in juvenile myoclonic epilepsy. Epileptic Disorders: International Epilepsy Journal With Videotape. 2004;6(4):267-70.

[97] Genton P, Gelisse P, Thomas P, Dravet C. Do carbamazepine and phenytoin aggravate juvenile myoclonic epilepsy? Neurology. 2000;55(8):1106-9.

[98] Gelisse P, Genton P, Kuate C, Pesenti A, Baldy-Moulinier M, Crespel A. Worsening of Seizures by Oxcarbazepine in Juvenile Idiopathic Generalized Epilepsies. Epilepsia. 2004;45(10):1282-6.

[99] Sharpe C, Buchanan N. Juvenile myoclonic epilepsy: diagnosis, management and outcome. The Medical Journal of Australia. 1995;162(3):133-4.

[100] Mantoan L, Walker M. Treatment options in juvenile myoclonic epilepsy. Current Treatment Options In Neurology. 2011;13(4):355-70.

[101] Penry JK, Dean JC, Riela AR. Juvenile myoclonic epilepsy: long-term response to therapy. Epilepsia. 1989;30 Suppl 4:S19.

[102] Shian WJ, Chi CS. Juvenile myoclonic epilepsy. Zhonghua Yi Xue Za Zhi=Chinese Medical Journal; Free China Ed. 1994;53(6):375-8.

[103] Sokic D, Ristic AJ, Vojvodic N, Jankovic S, Sindjelic AR. Frequency, causes and phenomenology of late seizure recurrence in patients with juvenile myoclonic epilepsy after a long period of remission. Seizure. 2007;16(6):533-7.

[104] Dahl JC. A Behaviour Medicine Approach to Epilepsy-Time for a Paradigm Shift? Scandinavian Journal of Behaviour Therapy. 1999;28(3):97.

[105] Guilfoyle SM, Follansbee-Junger K, Modi AC. Development and preliminary implementation of a psychosocial service into standard medical care for pediatric epilepsy. Clinical Practice in Pediatric Psychology. 2013;1(3):276-88.

[106] Lundgren T, Dahl J, Hayes S. Evaluation of mediators of change in the treatment of epilepsy with acceptance and commitment therapy. Journal of Behavioral Medicine. 2008;31(3):225-35.

[107] Kasteleijn-Nolst Trenité DGA, Schmitz B, Janz D, Delgado-Escueta AV, Thomas P, Hirsch E, et al. Consensus on diagnosis and management of JME: From founder's observations to current trends. Epilepsy & Behavior. 2013;28(Suppl 1):S87-S90.

[108] Crespel A, Gelisse P, Reed RC, Ferlazzo E, Jerney J, Schmitz B, et al. Management of juvenile myoclonic epilepsy. Epilepsy & Behavior. 2013;28(Suppl 1):S81-S6.

[109] Martinović Z. Adjunctive behavioural treatment in adolescents and young adults with juvenile myoclonic epilepsy. Seizure. 2001;10(1):42-7.

[110] da Silva Sousa P, Lin K, Garzon E, Ceiki Sakamoto A, Yacubian EMT. Language-and praxis-induced jerks in patients with juvenile myoclonic epilepsy. Epileptic Disorders: International Epilepsy Journal with Videotape. 2005;7(2):115-21.

[111] Matsuoka H, Nakamura M, Ohno T, Shimabukuro J, Suzuki T, Numachi Y, et al. The Role of Cognitive–Motor Function in Precipitation and Inhibition of Epileptic Seizures. Epilepsia. 2005;46:17-20.

[112] Morris GL, 3rd, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: Vagus nerve stimulation for the treatment of epilepsy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013;81(16):1453-9.

[113] Kostov H, Larsson PG, Røste GK. Is vagus nerve stimulation a treatment option for patients with drug-resistant idiopathic generalized epilepsy? Acta Neurologica Scandinavica. 2007;115:55-8.

[114] Cukiert A, Burattini JA, Mariani PP, Cukiert CM, Argentoni-Baldochi M, Baise-Zung C, et al. Outcome after extended callosal section in patients with primary idiopathic generalized epilepsy. Epilepsia. 2009;50(6):1377-80.

[115] Iimura Y, Sugano H, Nakajima M, Arai H. Stepwise synchronization through the corpus callosum is one cause of myoclonic jerks. World Neurosurgery. 2012;77(2): 399.E5-8.

[116] Jenssen S, Sperling MR, Tracy JI, Nei M, Joyce L, David G, et al. Corpus callosotomy in refractory idiopathic generalized epilepsy. Seizure. 2006;15(8):621-9.

[117] Faught E. Treatment of refractory primary generalized epilepsy. Reviews In Neurological Diseases. 2004;1 Suppl 1:S34-S43.

[118] Baykan B, Martínez-Juárez IE, Altindag EA, Camfield CS, Camfield PR. Lifetime prognosis of juvenile myoclonic epilepsy. Epilepsy & Behavior. 2013;28(Suppl 1):S18-S24.

[119] Geithner JFZJRCU. Predictors for long-term seizure outcome in juvenile myoclonic epilepsy: 25-63 years of follow-up. Epilepsia. 2012;53(8):1379-86.

[120] Matsuoka H. The seizure prognosis of juvenile myoclonic epilepsy. The Japanese Journal of Psychiatry and Neurology. 1992;46(2):293-6.

[121] Seneviratne U, Cook M, D'Souza W. The prognosis of idiopathic generalized epilepsy. Epilepsia. 2012;53(12):2079-90.

[122] Guaranha MSB, Filho GMdA, Lin K, Guilhoto LMFF, Caboclo LOSF, Yacubian EMT. Prognosis of juvenile myoclonic epilepsy is related to endophenotypes. Seizure. 2011;20(1):42-8.

[123] Ristić AJ, Ostojić J, Kozić D, Vojvodić NM, Popović LM, Janković S, et al. Hippocampal metabolic dysfunction in juvenile myoclonic epilepsy: 3D multivoxel spectroscopy study. Journal of the Neurological Sciences. 2011;305(1-2):139-42.

[124] Swartz BE, Halagren E, Simpkins F, Syndulko K. Primary memory in patients with frontal and primary generalized epilepsy. Journal of Epilepsy. 1994;7(3):232-41.

[125] Swartz BE, Simpkins F, Halgren E, Mandelkern M, Brown C, Krisdakumtorn T, et al. Visual working memory in primary generalized epilepsy: an 18FDG-PET study. Neurology. 1996;47(5):1203-12.

[126] Devinsky O, Gershengorn J, Brown E, Perrine K, Vazquez B, Luciano D. Frontal functions in juvenile myoclonic epilepsy. Neuropsychiatry, Neuropsychology, & Behavioral Neurology. 1997;10(4):243-6.

[127] Piazzini A, Turner K, Vignoli A, Canger R, Canevini MP. Frontal cognitive dysfunction in juvenile myoclonic epilepsy. Epilepsia. 2008;49(4):657-62.

[128] Zamarian L, Höfler J, Kuchukhidze G, Delazer M, Bonatti E, Kemmler G, et al. Decision making in juvenile myoclonic epilepsy. Journal of Neurology. 2013;260(3): 839-46.

[129] Zamarian L, Trinka E, Bonatti E, Kuchukhidze G, Bodner T, Benke T, et al. Executive functions in chronic mesial temporal lobe epilepsy. Epilepsy Research and Treatment. 2011;Vol. 2011(ArtileID 596174):11 pages.

[130] Delazer M, Zamarian L, Bonatti E, Kuchukhidze G, Koppelstaetter F, Bodner T, et al. Decision making under ambiguity and under risk in mesial temporal lobe epilepsy. Neuropsychologia. 2010;48(194-200).

[131] Levav M, Mirsky AF, Herault J, Xiong L, Amir N, Andermann E. Familial association of neuropsychological traits in patients with generalized and partial seizure disorders. Journal of Clinical and Experimental Neuropsychology. 2002;24(3):311-26.

[132] Pulsipher DT, Seidenberg M, Guidotti L, Tuchscherer VN, Morton J, Sheth RD, et al. Thalamofrontal circuitry and executive dysfunction in recent-onset juvenile myoclonic epilepsy. Epilepsia. 2009;50(5):1210-9.

[133] Jackson DC, Dabbs K, Walker NM, Jones JE, Hsu DA, Stafstrom CE, et al. The neuropsychological and academic substrate of new/recent-onset epilepsies. The Journal of Pediatrics. 2013;162(5):1047-53.e1.

[134] Guidotti L, Seidenberg M, Pulsipher DT, Morton J, Dow C, Sheth RD, et al. Cognition and MRI volumetrics in children with recent onset juvenile myoclonic epilepsy. Epilepsia. 2006;47:110.

[135] Pascalicchio TF, de Araujo Filho GM, da Silva Noffs MH, Lin K, Caboclo LOSF, Vidal-Dourado M, et al. Neuropsychological profile of patients with juvenile myoclonic epilepsy: a controlled study of 50 patients. Epilepsy & Behavior. 2007;10(2):263-7.

[136] Wandschneider B, Kopp UA, Kliegel M, Stephani U, Kurlemann G, Janz D, et al. Prospective memory in patients with juvenile myoclonic epilepsy and their healthy siblings. Neurology. 2010;75(24):2161-7.

[137] Moschetta SP, Valente KD. Juvenile myoclonic epilepsy: the impact of clinical variables and psychiatric disorders on executive profile assessed with a comprehensive neuropsychological battery. Epilepsy & Behavior. 2012;25(4):682-6.

[138] Kim S-Y, Hwang Y-H, Lee H-W, Suh C-K, Kwon S-H, Park S-P. Cognitive impairment in juvenile myoclonic epilepsy. Journal of Clinical Neurology (Seoul, Korea). 2007;3(2):86-92.

[139] Kim JH, Suh S-i, Park S-Y, Seo W-K, Koh I, Koh S-B, et al. Microstructural white matter abnormality and frontal cognitive dysfunctions in juvenile myoclonic epilepsy. Epilepsia. 2012;53(8):1371-8.

[140] Jovic NJ, Vucinic DM, Ignjatovic PM, Kosac A. Cognitive and psychiatric issues in juvenile myoclonic epilepsy. Epilepsy & Behavior. 2013;28(2):324.

[141] O'Muircheartaigh J, Vollmar C, Barker GJ, Kumari V, Symms MR, Thompson P, et al. Focal structural changes and cognitive dysfunction in juvenile myoclonic epilepsy. Neurology. 2011;76(1):34-40.

[142] Lavandier N, de Toffol B, Gillet P, Hommet C, Corcia P, Autret A. Syndrome dysexe ´cutif, e´pilepie myoclonique juve´nile et anomalies paroxystiques intercritiques. Rev Neurol. 2002;158(Suppl. 1):164.

[143] Sonmez F, Atakli D, Sari H, Atay T, Arpaci B. Cognitive function in juvenile myoclonic epilepsy. Epilepsy & Behavior. 2004;5(3):329-36.

[144] Iqbal N, Caswell HL, Hare DJ, Pilkington O, Mercer S, Duncan S. Neuropsychological profiles of patients with juvenile myoclonic epilepsy and their siblings: a preliminary controlled experimental video-EEG case series. Epilepsy & Behavior. 2009;14(3): 516-21.

[145] Roebling R, Scheerer N, Uttner I, Gruber O, Kraft E, Lerche H. Evaluation of cognition, structural, and functional MRI in juvenile myoclonic epilepsy. Epilepsia. 2009;50(11):2456-65.

[146] Wandschneider B, Centeno M, Vollmar C, Stretton J, O'Muircheartaigh J, Thompson PJ, et al. Risk-taking behavior in juvenile myoclonic epilepsy. Epilepsia. 2013.

[147] Vollmar C, O'Muircheartaigh J, Barker GJ, Symms MR, Thompson P, Kumari V, et al. Motor system hyperconnectivity in juvenile myoclonic epilepsy: a cognitive functional magnetic resonance imaging study. Brain: A Journal of Neurology. 2011;134(Pt 6): 1710-9.

[148] Lin K, de Araujo Filho GM, Pascalicchio TF, Silva I, Tudesco ISS, Guaranha MSB, et al. Hippocampal atrophy and memory dysfunction in patients with juvenile myoclonic epilepsy. Epilepsy & Behavior. 2013;29(1):247-51.

[149] Brooks BL. A Study of low scores in Canadian children and adolescents on the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV). Child Neuropsychology. 2011;17(3):281-9.

[150] Steinberg BA, Bieliauskas LA, Smith GE, Langellotti C, Ivnik RJ. Mayo's Older Americans Normative Studies: Age-and IQ-Adjusted Norms for the Boston Naming Test, the MAE Token Test, and the Judgment of Line Orientation Test. The Clinical Neuropsychologist. 2005;19(3-4):280-328.

[151] Walsh J, Marson AG, Smith PEM, Rees MI, Baker GA, Thomas RH. Neuroticism and executive function in drug-refractory juvenile myoclonic epilepsy. Epilepsy & Behavior. 2013;28(Suppl 1).

[152] Savic I, Österman Y, Helms G. MRS shows syndrome differentiated metabolite changes in human-generalized epilepsies. NeuroImage. 2004;21(1):163.

[153] Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-anset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry. 2005;62(6):593-602.

[154] Marrie RA, Fisk JD, Bo Nancy Y, Stella L, Elliott L, Caetano P, et al. Mental comorbidity and multiple sclerosis: validating administrative data to support population-based surveillance. BMC Neurology. 2013;13(1):1-8.

[155] Kessler RC, Lane MC, Shahly V, Stang PE. Accounting for comorbidity in assessing the burden of epilepsy among US adults: results from the National Comorbidity Survey Replication (NCS-R). Molecular Psychiatry. 2012;17(7):748-58.

[156] Mula M. Epilepsy-induced behavioral changes during the ictal phase. Epilepsy & Behavior. 2013.

[157] Gandy M, Sharpe L, Perry KN, Miller L, Thayer Z, Boserio J, et al. The psychosocial correlates of depressive disorders and suicide risk in people with epilepsy. Journal of Psychosomatic Research. 2013;74(3):227-32.

[158] Gilliam F, Hecimovic H, Sheline Y. Psychiatric comorbidity, health, and function in epilepsy. Epilepsy & Behavior. 2003;4 Suppl 4:S26-S30.

[159] de Araújo Filho GM, Yacubian EMT. Juvenile myoclonic epilepsy: psychiatric comorbidity and impact on outcome. Epilepsy & Behavior. 2013;28(Suppl 1):S74-S80.

[160] Lund M, Reintoft H, Simonsen N. [A controlled sociological and psychological study on patients with juvenile myoclonus epilepsy]. Der Nervenarzt. 1976;47(12):708-12.

[161] Tsuboi T. Primary generalized epilepsy with sporadic myoclonias of myoclonic petit mal type. Stuttgart: Thieme Medical Publishers; 1977.

[162] Devinsky O, Najjar S. Evidence against the existence of a temporal lobe epilepsy personality syndrome. Neurology. 1999;53(5, Suppl 2):S13-S25.

[163] First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute; 2002.

[164] Trinka E, Kienpointner G, Unterberger I, Luef G, Bauer G, Doering LB, et al. Psychiatric comorbidity in juvenile myoclonic epilepsy. Epilepsia. 2006;47(12):2086-91.

[165] de Araujo Filho G, Mazetto L, da Silva JM, Caboclo LO, Yacubian EM. Psychiatric comorbidity in patients with two prototypes of focal versus generalized epilepsy syndromes. Seizure. 2011;20(5):383-6.

[166] de Araújo Filho GM, Pascalicchio TF, Sousa PdS, Lin K, Ferreira Guilhoto LMF, Yacubian EMT. Psychiatric disorders in juvenile myoclonic epilepsy: a controlled study of 100 patients. Epilepsy & Behavior. 2007;10(3):437-41.

[167] de Araujo Filho GM, Pascalicchio TF, Lin K, Sousa PS, Yacubian EMT. Neuropsychiatric profiles of patients with juvenile myoclonic epilepsy treated with valproate or topiramate. Epilepsy & Behavior. 2006;8(3):606-9.

[168] de Araújo Filho GM, Rosa VP, Lin K, Caboclo LOSF, Sakamoto AC, Yacubian EMT. Psychiatric comorbidity in epilepsy: a study comparing patients with mesial temporal sclerosis and juvenile myoclonic epilepsy. Epilepsy & Behavior. 2008;13(1): 196-201.

[169] Gélisse P, Genton P, Thomas P, Rey M, Samuelian JC, Dravet C. Clinical factors of drug resistance in juvenile myoclonic epilepsy. Journal of Neurology, Neurosurgery & Psychiatry. 2001;70(2):240-3.

[170] Salas-Puig J, Camara da Silva A, Davet C, J R. L´épilepsie myoclonique juvenile dans la population du centre. Saint-Paul Epilepsies 1990;2:108–13.

[171] Moschetta S, Fiore LA, Fuentes D, Gois J, Valente KD. Personality traits in patients with juvenile myoclonic epilepsy. Epilepsy & Behavior. 2011;21(4):473-7.

[172] Plattner B, Pahs G, Kindler J, Williams RP, Hall RE, Mayer H, et al. Juvenile myoclonic epilepsy: a benign disorder? Personality traits and psychiatric symptoms. Epilepsy & Behavior. 2007;10(4):560-4.

[173] Akanuma N, Hara E, Adachi N, Hara K, Koutroumanidis M. Psychiatric comorbidity in adult patients with idiopathic generalized epilepsy. Epilepsy & Behavior. 2008;13(1):248-51.

[174] Perini GI, Tosin C, Carraro C, Bernasconi G, Canevini MP, Canger R, et al. Interictal mood and personality disorders in temporal lobe epilepsy and juvenile myoclonic epilepsy. Journal of Neurology, Neurosurgery & Psychiatry. 1996;61(6):601-5.

[175] de Araújo Filho GM, da Silva JM, Mazetto L, Marchetti RL, Yacubian EMT. Psychoses of epilepsy: A study comparing the clinical features of patients with focal versus generalized epilepsies. Epilepsy & Behavior. 2011;20(4):655-8.

[176] Pung T, Schmitz B. Circadian rhythm and personality profile in juvenile myoclonic epilepsy. Epilepsia. 2006;47:111-4.

[177] Karachristianou S, Katsarou Z, Bostantjopoulou S, Economou A, Garyfallos G, Delinikopoulou E. Personality profile of patients with juvenile myoclonic epilepsy. Epilepsy & Behavior. 2008;13(4):654-7.

[178] Butcher JN, Dahlstrom WG, Graham JR, Tellegen A, Kaemmer B. Manual for the restandardized Minnesota Multiphasic Personality Inventory: MMPI—2. An administrative and interpretive guide. Minneapolis: University of Minnesota Press; 1989.

[179] de Araújo Filho GM, Jackowski AP, Lin K, Guaranha MSB, Guilhoto LMFF, da Silva HH, et al. Personality traits related to juvenile myoclonic epilepsy: MRI reveals pre-

frontal abnormalities through a voxel-based morphometry study. Epilepsy & Behavior. 2009;15(2):202-7.

[180] de Araújo Filho GM, Lin K, Lin J, Peruchi MM, Caboclo LOSF, Guaranha MSB, et al. Are personality traits of juvenile myoclonic epilepsy related to frontal lobe dysfunctions? A proton MRS study. Epilepsia. 2009;50(5):1201-9.

[181] de Araujo Filho GM, de Araujo TB, Sato JR, Silva Id, Lin K, Júnior HC, et al. Personality traits in juvenile myoclonic epilepsy: evidence of cortical abnormalities from a surface morphometry study. Epilepsy & Behavior. 2013;27(2):385-92.

[182] Moschetta S, Valente KD. Impulsivity and seizure frequency, but not cognitive deficits, impact social adjustment in patients with juvenile myoclonic epilepsy. Epilepsia. 2013;54(5):866-70.

[183] Staufenbiel SM, Penninx BWJH, Spijker AT, Elzinga BM, van Rossum EFC. Hair cortisol, stress exposure, and mental health in humans: A systematic review. Psychoneuroendocrinology. 2013;38(8):1220-35.

[184] Vargas C, López-Jaramillo C, Vieta E. A systematic literature review of resting state network--functional MRI in bipolar disorder. Journal of Affective Disorders. 2013;150(3):727-35.

[185] Busch RM, Frazier T, Chapin JS, Hamrahian AH, Diehl B, Alexopoulos A, et al. Role of cortisol in mood and memory in patients with intractable temporal lobe epilepsy. Neurology. 2012;78(14):1064-8.

[186] Cossette P, Liu L, Brisebois K, Dong H, Lortie A, Vanasse M, et al. Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. Nature Genetics. 2002;31(2):184.

[187] de Nijs L, Wolkoff N, Coumans B, Delgado-Escueta AV, Grisar T, Lakaye B. Mutations of EFHC1, linked to juvenile myoclonic epilepsy, disrupt radial and tangential migrations during brain development. Human Molecular Genetics. 2012;21(23): 5106-17.

[188] de Nijs L, Wolkoff N, Grisar T, Lakaye B. Juvenile myoclonic epilepsy as a possible neurodevelopmental disease: Role of EFHC1 or Myoclonin1. Epilepsy & Behavior. 2013;28(s1):S58-S60.

[189] Delgado-Escueta AV. Advances in Genetics of Juvenile Myoclonic Epilepsies. Epilepsy Currents. 2007;7(3):61-7.

[190] de Nijs L, Léon C, Nguyen L, LoTurco JJ, Delgado-Escueta AV, Grisar T, et al. EFHC1 interacts with microtubules to regulate cell division and cortical development. Nature Neuroscience. 2009;12(10):1266-74.

[191] Meencke HJ, Janz D. The significance of microdysgenesia in primary generalized epilepsy: an answer to the considerations of Lyon and Gastaut. Epilepsia. 1985;26(4): 368-71.

[192] Veith G, Wicke R. Cerebrale Differenzierungsstorungen bei Epilepsie. Westdtsch Ver. 1968:515-34.

[193] Lyon G, Gastaut H. Considerations on the significance attributed to unusual cerebral histological findings recently described in eight patients with primary generalized epilepsy. Epilepsia. 1985;26:365-7.

[194] Opeskin K, Kalnins RM, Halliday G, Cartwright H, Berkovic SF. Idiopathic generalized epilepsy: lack of significant microdysgenesis. Neurology. 2000;55(8):1101-6.

[195] Woermann FG, Free SL, Koepp MJ, Sisodiya SM, Duncan JS. Abnormal cerebral structure in juvenile myoclonic epilepsy demonstrated with voxel-based analysis of MRI. Brain: A Journal of Neurology. 1999;122 (Pt 11):2101-8.

[196] Lin K, Jackowski AP, Carrete H, Jr., de Araújo Filho GM, Silva HH, Guaranha MSB, et al. Voxel-based morphometry evaluation of patients with photosensitive juvenile myoclonic epilepsy. Epilepsy Research. 2009;86(2-3):138-45.

[197] Ronan L, Alhusaini S, Scanlon C, Doherty CP, Delanty N, Fitzsimons M. Widespread cortical morphologic changes in juvenile myoclonic epilepsy: evidence from structural MRI. Epilepsia. 2012;53(4):651-8.

[198] Vollmar C, O'Muircheartaigh J, Symms MR, Barker GJ, Thompson P, Kumari V, et al. Altered microstructural connectivity in juvenile myoclonic epilepsy: The missing link. Neurology. 2012;78(20):1555-9.

[199] Kim JH, Im KC, Kim JS, Lee S-A, Kang JK. Correlation of interictal spike-wave with thalamic glucose metabolism in juvenile myoclonic epilepsy. Neuroreport. 2005;16(11):1151-5.

[200] Savic I, Lekvall A, Greitz D, Helms G. MR spectroscopy shows reduced frontal lobe concentrations of N-acetyl aspartate in patients with juvenile myoclonic epilepsy. Epilepsia. 2000;41(3):290-6.

[201] Simister RJ, McLean MA, Barker GJ, Duncan JS. Proton MRS reveals frontal lobe metabolite abnormalities in idiopathic generalized epilepsy. Neurology. 2003;61(7): 897-902.

[202] Moeller F, Maneshi M, Pittau F, Gholipour T, Bellec P, Dubeau F, et al. Functional connectivity in patients with idiopathic generalized epilepsy. Epilepsia. 2011;52(3): 515-22.

[203] McGill ML, Devinsky O, Kelly C, Milham M, Castellanos FX, Quinn BT, et al. Default mode network abnormalities in idiopathic generalized epilepsy. Epilepsy & Behavior. 2012;23(3):353-9.

[204] Macdonell RA. Prolonged cortical silent period after transcranial magnetic stimulation in generalized epilepsy. Neurology. 2001;57:706-8.

[205] Badawy RA, Curatolo JM, Newton M, Berkovic SF, Macdonell RA. Changes in cortical excitability differentiate generalized and focal epilepsy. Annals of Neurology. 2007;61(4):324-31.

[206] Groppa S, Siebner HR, Kurth C, Stephani U, Siniatchkin M. Abnormal response of motor cortex to photic stimulation in idiopathic generalized epilepsy. Epilepsia. 2008;49(12):2022-9.

[207] Brigo F, Storti M, Benedetti MD, Rossini F, Nardone R, Tezzon F, et al. Resting motor threshold in idiopathic generalized epilepsies: a systematic review with meta-analysis. Epilepsy Research. 2012;101(1-2):3-13.

[208] Brigo F, Igwe SC. Corticospinal excitability in juvenile myoclonic epilepsy: The story so far. Seizure. 2013.

[209] Killam EK. Photomyoclonic seizures in the baboon, Papio papio. Federation Proceedings. 1979;38(10):2429-33.

[210] Meldrum BS, Anlezark G, Balzamo E, Horton RW, Trimble M. Photically induced epilepsy in Papio papio as a model for drug studies. Advances In Neurology. 1975;10:119-32.

[211] Menini C, Stutzmann JM, Laurent H, Naquet R. Paroxysmal visual evoked potentials (PVEPs) in Papio papio. I. Morphological and topographical characteristics. Comparison with paroxysmal discharges. Electroencephalography & Clinical Neurophysiology. 1980;50(5-6):356-64.

[212] Silva-Barrat C, Ménini C, Bryère P, Naquet R. Multiunitary activity analysis of cortical and subcortical structures in paroxysmal discharges and grand mal seizures in photosensitive baboons. Electroencephalography & Clinical Neurophysiology. 1986;64(5):455-68.

[213] Silva-Barrat C, Ménini C. The influence of intermittent light stimulation on potentials evoked by single flashes in photosensitive and non-photosensitive Papio papio. Electroencephalography & Clinical Neurophysiology. 1984;57(5):448-61.

[214] Menini C, Silva-Barrat C. The photosensitive epilepsy of the baboon. A model of generalized reflex epilepsy. Advances In Neurology. 1998;75:29-47.

[215] Fukuda H, Valin A, Bryère P, Riche D, Wada JA, Naquet R. Role of the forebrain commissure and hemispheric independence in photosensitive response of epileptic baboon, Papio papio. Electroencephalography & Clinical Neurophysiology. 1988;69(4):363-70.

[216] Szabó CÁ, Knape KD, Leland MM, Williams JT. Electroclinical phenotypes in a pedigreed baboon colony. Epilepsy Research. 2013;105(1-2):77-85.

[217] Szabó CÁ, Knape KD, Leland MM, Cwikla DJ, Williams-Blangero S, Williams JT. Epidemiology and characterization of seizures in a pedigreed baboon colony. Comparative Medicine. 2012;62(6):535-8.

[218] Szabó CA, Leland MM, Knape K, Elliott JJ, Haines V, Williams JT. Clinical and EEG phenotypes of epilepsy in the baboon (Papio hamadryas spp.). Epilepsy Research. 2005;65(1-2):71-80.

[219] Szabó CÁ, Salinas FS, Narayana S. Functional PET Evaluation of the Photosensitive Baboon. The Open Neuroimaging Journal. 2011;5:206-15.

[220] Szabó CÁ, Narayana S, Kochunov PV, Franklin C, Knape K, Davis MD, et al. PET imaging in the photosensitive baboon: Case-controlled study. Epilepsia. 2007;48(2): 245-53.

[221] Szabó CA, Kochunov P, Knape KD, McCoy KJM, Leland MM, Lancaster JL, et al. Cortical sulcal areas in baboons (Papio hamadryas spp.) with generalized interictal epileptic discharges on scalp EEG. Epilepsy Research. 2011;93(2/3):91-5.

[222] Szabó CÁ, Narayana S, Franklin C, Knape KD, Davis MD, Fox PT, et al. "Resting" CBF in the epileptic baboon: Correlation with ketamine dose and interictal epileptic discharges. Epilepsy Research. 2008;82(1):59-65.

[223] Salinas FS, Fox PT, Szabó CA. Using resting-state fMRI to demonstrate functional connectivity differences between epileptic and control non-human primates. Presentation at: NC3R Primate Welfare Meeting; 2013; London, UK.

[224] Szabó CÁ, Salinas FS, Leland MM, Caron J-L, Hanes MA, Knape KD, et al. Baboon model of generalized epilepsy: Continuous intracranial video-EEG monitoring with subdural electrodes. Epilepsy Research. 2012;101(1/2):46-55.

[225] Ticku MK, Lee JC, Murk S, Mhatre MC, Story JL, Kagan-Hallet K, et al. Inhibitory and excitatory amino acid receptors, c-fos expression, and calcium-binding proteins in the brain of baboons (Papio hamadryas) that exhibit 'spontaneous' grand mal epilepsy. Epilepsy Research Supplement. 1992;9:141-9.

[226] Phelix CF, Szabó CÁ. Quantification of heterotopic neurons in baboons with generalized interictal epileptic discharges. Poster session presented at: American Epilepsy Society 66th Annual Meeting; 2012; San Diego, CA.

[227] Young NA, Szabó CÁ, Phelix CF, Flaherty DK, Balaram P, Foust-Yeoman KB, et al. Epileptic baboons have lower numbers of neurons in specific areas of cortex. Proceedings of the National Academy of Sciences of the United States of America. 2013.

[228] Martínez-Juárez IE, Alonso ME, Medina MT, Durón RM, Bailey JN, López-Ruiz M, et al. Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up. Brain: A Journal of Neurology. 2006;129(Pt 5):1269-80.