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Juvenile Myoclonic Epilepsy: An Update

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1. Introduction

We review the most important electroclinical aspects and possible subsyndromes of Juvenile myoclonic epilepsy (JME), as well as its genetic background, its pathophysiological and neuroimaging correlates, and treatment. JME is among the most common types of genetic epilepsies. The prevalence of JME in large cohorts has been estimated to be 5% to 10% of all epilepsies and around 18% of idiopathic generalized epilepsies but may be lower in some settings. There is a marked female predominance. Today JME is a widely recognized electro-clinical idiopathic generalized epilepsy syndrome. Onset is around the time of puberty. The most typical ictal phenomenon is bilateral myoclonia without loss of consciousness. Most patients also present with generalized tonic-clonic seizures (GTCS), and some with absence seizures. The typical circumstance at diagnosis is a first GTCS episode, after the patient has had myoclonia in the morning. Typically seizure episodes occur after awakening from a sleep period or in the evening relaxation period and are facilitated by sleep deprivation and sudden arousal. Diagnosis of JME can be made with the history of myoclonus plus a single GTCS plus generalized polyspike-waves or fast spike-waves on the EEG. The prevalence rate of photo-sensitivity (photoparoxysmal EEG response) in patients with JME ranges from 8 to 90%. Hyperventilation can induce absence seizures in patients with JME, while cognitive tasks are efficient in precipitating myoclonic seizures. Most patients have a good prognosis when treated with appropriate drugs, but with a well-known tendency to relapse after withdrawal. However, around 17% are able to discontinue medication and remain seizure-free thereafter. There is a small but still considerable subgroup of JME patients whose seizures are difficult to treat. Recent findings suggest that patients with JME have worse social adjustment in relevant aspects of their lives, works and familiar relationship. Differential diagnoses include the adolescent-onset progressive myoclonus epilepsies, or other forms of idiopathic generalized epilepsies of adolescence.

2. History of juvenile myoclonic epilepsy

Juvenile Myoclonic Epilepsy (JME) has been recognized by early distinguished physicians as Theodore Herpin in 1867 [1] and Robot in 1899 [2]. However, it was not until 1957 that Janz and Christian gave the first and precise description of JME in 47 German patients [3]. Later on, Castells and Mendilaharsu described JME in 70 Uruguayans patients [4]. Following that, Delgado-Escueta and Enrile-Bacsal reported 43 cases of uncontrolled convulsive seizures because the syndrome of JME was not recognized in those cases. [5]. Since then JME was reported in different ethnic groups around the world (Asia, Europe, North and Latin America, Oceania and Africa).

3. Classification and definition of JME

The ILAE Commission proposed and defined JME as a distinct syndrome of IGE: "Juvenile myoclonic epilepsy (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. The disorder may be inherited, and sex distribution is equal (but see Introduction!). Often, there are GTCS and less often infrequent absences. The seizures usually occur shortly after awakening and are often precipitated by sleep deprivation. Interictal and ictal EEG have rapid, generalized, often irregular spike-waves and polyspike-waves; there is no close phase correlation between EEG spikes and jerks. Frequently, the patients are photosensitive. Response to appropriate drugs is good" [6].

4. Incidence, prevalence, and sex ratio of JME

JME is the most common form of genetic/idiopathic generalized epilepsy (IGE): The IGEs comprises 40% of epilepsies in the US, 20% in Mexico, 8% in Central America [7] and is much higher (between 68–82.6%) in the Arab countries [8]. JME is responsible for 6 to 12 % up to 30% of all epilepsies in hospital and clinics records [3, 9-11] and for 3% according to a door-to-door population survey [12]. The incidence of JME varies from 0.5 to 6.3%/100.000. Based on 1% of population risk for epilepsy by age 20 [13], the risk of JME in the general population would be 1 per 1000 to 2000. The prevalence of JME has been estimated to be 5% to 10% of all epilepsies and 18% of IGEs [14, 15]. Gender differences are evident for JME with a marked female predominance [15, 16].

5. Age of onset

As shown by Janz [17], one of its first investigators, JME has an age-related onset [Figure 1]. The seizures appear between 8 and 26 years with a mean age of onset at 14.2 years; the majority

of seizures occur between 12 and 18 years [17, 18]. Absence seizures (AS) are reported in 33.3% to 66.7%, myoclonic jerks (MJ) in 97%, and GTCS in 78.8% of the patients [14, 19]. In one study, AS antedated other types of seizures in all patients [20]. An earlier or later age of onset has also been reported [20-23]. Female preponderance for photosensitivity may explain an early onset of JME in female patients with photosensitivity [24, 25].
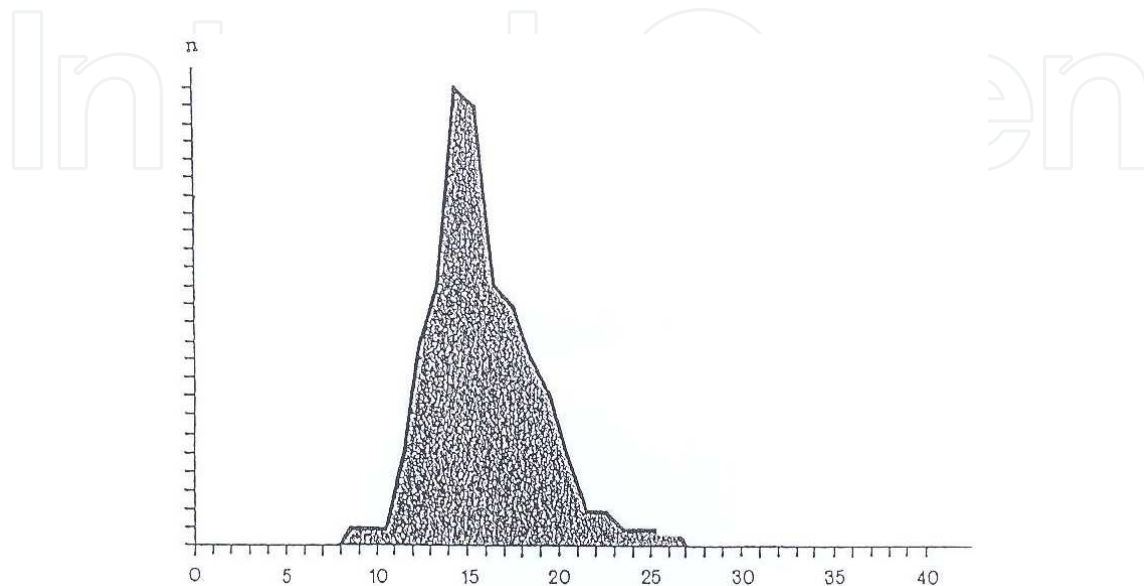

Figure 1. Age of onset of 139 patients with myoclonic seizures (i.e., beginning cases of juvenile myoclonic epilepsy). From Janz D et al. In: Epilepsy, J. Engel Jr and T A Pedley (ed), 1998. p.2391

6. Clinical presentation

JME is probably the most common and the most characteristic form of the IGE of adolescent-onset group. It is characterized by:

6.1. Myoclonic Jerks (MJ)

MJ occur prominently and spontaneously in the morning, after awakening; they are sudden, short-lasting, irregular, frequently symmetric; they may be self- limited (isolated) or may occur in clusters; if prolonged, these clusters may lead to a convulsive tonic-clonic seizure. MJ involve prominently the upper limbs; however the lower limbs and trunk are often not spared. Both distal and proximal jerky movements do occur; flexion of both forearms, flexion of both arms, flexion and abduction of the thighs and extension of the back, are typical. Patients may throw things out of their hands when the MJ involve or are restricted to the fingers; occasionally, the jerks are so intense that the patient falls to the ground (myoclonic-astatic seizures). Several authors reported some degree of asymmetry in MJ as well as focal features in the EEG, leading to the false diagnosis of focal epilepsy [26-28]. This issue will be discussed in the paragraph below (*Electroencephalography*)

Myoclonic status epilepticus (MSE) is not so rare. In MSE, consciousness may be intact. Drug withdrawal, sleep deprivation and alcohol intake are the main causes [29, 30].

6.2. Generalized Tonic Clonic Seizures (GTCS)

Frequently, in the outpatient clinic or emergency unit, a young patient is examined because he/she was a victim of a generalized seizure upon awakening. Often, when asked, the family reports that the GTCS followed repeated, severe MJ (generalized clonic-tonic-clonic seizure type) [5].

6.3. Absence Seizures (AS)

As indicated above, AS are generally reported in one-third of patients with JME [31, 32]. However, their frequency might be much higher (66.7%) [19]. There is general agreement that AS associated with JME are mild and short, when compared to the childhood absences and absences of *Juvenile Absence Epilepsy.* They are less severe with age and are often unnoticed by the patient [33].

In a recent prospective study, with long-term follow up of 257 patients with JME, Martinez-Juarez IE and coworkers encountered four JME groups: (1) Classic JME (72%), (2) Childhood Absence Epilepsy (CAE) evolving to JME (18%), (3) JME with Adolescent Absence (7%), and (4) JME with Astatic Seizures (3%). There was a female preponderance in the second group (CAE evolving to JME); the authors concluded that all 4 subtypes are chronic and probably lifelong [34].

6.4. Precipitation of seizures

As reported above, occurrence of MJ in the early morning is one of the hallmarks of JME. MJ and GTCS are induced by sleep deprivation, fatigue and excessive alcohol intake [35]. Sleep deprivation is understood as falling asleep late at night and getting up or awaken early in the morning (short sleep).

Seizure-provoking factors in JME are numerous; among them are: stress, fatigue, fever, sleep, flashing sunlight, music, reading, thinking, and excessive alcohol intake. In JME, photosensitivity (photoparoxysmal EEG response), is age-related and it varies considerably [35]. However, only a small number of patients experiences seizures by photic stimulation in daily life. In patients with JME, absence seizures are induced by hyperventilation, while myoclonic seizures are provoked by cognitive tasks [35, 36].

7. Electroencephalography

JME is widely underdiagnosed despite a characteristic clinical picture and a distinct EEG profile. If a patient, who is suspected clinically to suffer from JME, has a normal EEG, a sleep EEG and an EEG on awakening should follow.

The background activity is usually normal; some authors report theta slowing during poor seizure control [37], others found an increase in *Absolute Power* of delta, alpha and beta bands, more evident in frontoparietal regions in patients with JME [38].

7.1. Interictal EEG

Interictal EEG shows diffuse or generalized spike-wave (SW) and polyspike-wave (PSW) discharges at 3-6 Hz [Figure 2].

Figure 2. Thirteen year-old girl with clinical JME since the age of 9 years showing interictal polyspike wave discharges not associated with clinical manifestations.

Localization related EEG abnormalities are found in 16.9-57.1 % of patients [14, 27, 28]. These focal abnormalities include unilateral discharges, paroxysms with unilateral onset, and frequently discharges with above 50% voltage asymmetries. In general these EEG changes are predominantly seen at sleep onset and after provoked awakening [26].

Photosensitivity (photoparoxysmal EEG response), with or without MJ, in patients with JME varies from 8 to 90% and is more frequent in females and adolescents [35] [Figure3]

As mentioned above, in patients with JME, absence seizures can be induced by hyperventilation [Figure 4],

while cognitive tasks can precipitate myoclonic seizures.

Figure 3. Photoparoxysmal response in a 20 year old female patient with JME since the age of 11 years accompanied by jerky movements of both upper extremities.

Figure 4. Same patient as in Figure 3 showing generalized polyspike-wave complexes accompanied by mild impairment of cognition during hyperventilation.

7.2. Ictal EEG

The characteristic ictal EEG manifestations of a MJ are a generalized burst of multiple spikes of short duration (0.5-2s). Frequently, however, the spikes are followed by slow waves with poorly structured spike-wave sequence [Figure 5].

Figure 5. Seventeen year-old male with JME suffering from mild MJ of the upper extremities accompanied by bursts of brief polyspike wave sequences.

Ictal EEG discharges of absences consist of multiple spikes usually preceding or superimposed on a slow wave. These discharges often show a characteristic fragmentation and last from 1-4 s.

8. Genetics of JME

JME is the most common cause of hereditary grand mal seizures in people with epilepsy in the population at large [5, 17]. It has both Mendelian inheritance and complex genetic inheritance [12, 39]. 49% of JME families have clinical and EEG traits suggesting an autosomal dominant inherited disease. Variants of JME genes, with small to modest effects, contribute to risk/susceptibility in the remaining 51% [5, 12, 39]. Linkage disequilibrium is understood as the occurrence, in a specific population, of both DNA markers (DNA microsatellites or SNPs, single nucleotide polymorphisms) and a JME mutation at a higher frequency than would be predicted by random chance. With the passage of time, linkage disequilibrium decays through recombinations and transmissions into thousands of generations resulting in the fact that the

epilepsy allele will have smaller and smaller genetic effects and will require other epilepsy alleles or environment to produce the epilepsy phenotype [40]. However, linkage disequilibrium is strongest and covers the widest region of a chromosome when the epilepsy allele is of recent origin, and has large genetic effects, e.g., Mendelian dominant or recessive effects.

Chromosome locus	HGNC gene symbol[a] or phenotype	Gene/encoded protein	Country/ethnic group/ancestral origin	Mode of inheritance
1p36.22	Absence and JME	*Suggestive linkage*	Europe (Germany, Netherlands, UK, France, Italy, and Greece)	AD/oligogenic: meta analysis of 235 absence families and 118 JME families
1p36.33	**EJM7**	**GABRD**[b]	Australian families incl GEFS +	AD
2q23.3	**EJM6**	**CACNB4**[b]	One family (father and son with absences and tonic–clonic) from Germany; one woman with JME and a daughter with 3-Hz spike waves	AD
2q34	JME	Unknown	Europe (Germany, Netherlands, UK, France, Italy, and Greece)	AD/oligogenic: meta analysis of 118 JME families
2q23.3 and 2q24.1	JME	Unknown	Tunisia — one large consanguineous family	AR
2q33–36	**EJM9**	Unknown	India — one large 4 generation family	AD
3p14.2	JME/absence	*Suggestive linkage*	Europe(Germany, Netherlands, UK, France, Italy, and Greece)	AD/oligogenic: meta analysis of 235 absence families and 118 JME families
3q21.1	JME	**CASR** (*calcium sensor receptor gene*)[b]	One large Indian family; 5 of 96 unrelated JME patients from Bangalore, India	AD
5q12–14	**EJM4**	Unknown	India	AD
5q35.3	JME with PPR (photosensitivity)	Unknown	Netherlands	AD
5q34	**EJM5**	**GABRA1**[b]	French Canadian (Quebec, Canada) — one family; one absence patient from Germany; one absence patient from France	AD
5q34	(Absence and JME)	Unknown	Europe — Germany, Netherlands, UK, France, Italy, and Greece	AD/oligogenic: meta analysis of 235 absence families and 118 JME families
6p12	**EJM1**	**Myoclonin1/EFHC1**[b]	Hispanics [LA, California] Hispanics [Belize] Hispanics [Mexico[c]] Hispanics [Honduras and Mexico] Japan Italy and Brazil Tennessee Austria	AD
6p12	JME	Unknown	Netherlands	AD
6p21.3	**EJM3**	**BRD2**[c] (bromodomain-containing gene)	European descent [Los Angeles, California] European descent [NY[c]]; Germany	AD/oligogenic
6p20	JME	–	Germany	AD
6p21.2	JME	–	Germany	AR
6q24	JME	–	Saudi Arabia	AR
7q32	Photoparoxysmal response 3 (PPR3), with or without myoclonic epilepsy	Unknown	Netherlands 16 multiplex families	AD
8q21.13	JME with PPR (photosensitivity)	JRK, glutamate receptor GRIN2A are suspected	Netherlands	AD
10q25–q26	JME with PPR	–	India (New Delhi), 5 families	AD
13q13	JME with PPR (photosensitivity)	–	Netherlands	AD
13q31.3	CAE	–	Europe and Australia (Germany, Netherlands, UK, France, Italy and Greece)	AR/meta analysis of 235 absence families
13q31	JME with PPR (photosensitivity)		Netherlands, United Kingdom, Denmark, France, Greece, Portugal, Sweden	AD
15q14		**Cx36**[c] (connexin36) or a gap junction protein2 or GJP2	European descent (New York)	AR
15q14	**EJM2**	CHRNA7 is candidate gene	UK, Sweden families	AR
18q21	JME	**ME2**[c] (malic enzyme2)	European descent (New York)	Association studies with JME
19q13	Generalized epilepsy with febrile seizures plus, including JME (GEFS + 1)	SCN1B	Europe and Australia (Germany, Netherlands, UK, France, Italy, and Greece)	Meta analysis of 235 absence and 118 JME families AR
Xp11.4–11.3	JME	EFHC2	Germany, 81 patients	Association study with JME

[a]Human Genome Nomenclature Committee gene symbol in bold letters.

[b]Mutation segregate with epilepsy affected members across 2 to 4 generation families or in singletons.

[c]SNP-associated variants of BRD2, Cx36 and ME2; AD, autosomal dominant; AR, autosomal recessive; JME, juvenile myoclonic epilepsy; and pCAE, pyknoleptic childhood absence epilepsy.

Table 1. Juvenile myoclonic epilepsy genes and chromosome loci. (Modified from Delgado-Escueta AV,2004,2007)

5 Mendelian JME genes have been reported (http://omim.org and http://www.ncbi.nlm.nih.gov/omim/). These are as follows: CACNB4 (calcium channel beta4 subunit) [41], CASR (calcium channel sensory receptor) [42], GABRA1 (GABA receptor alpha one subunit) [43], GABRD (GABA receptor delta subunit) [44], and Myoclonin1/EFHC1 (myoclonin1/one EF-hand containing gene) [45] [Table 1].

Also, three SNP susceptibility alleles of putative JME genes that contribute to the complex genetics of JME have been reported [12, 39, 46]: bromodomain-containing 2 (BRD2) [47], connexin 36 (Cx-36) [48], and malic enzyme2 (ME2) [49]. Additionally, more than 22 chromosome loci linked to JME have been described [Table 1] [46].

Familial segregation or association with disease identifies putative JME disease genes. In autosomal dominant JME, a candidate epilepsy gene should show at least one variant per affected individual; each candidate epilepsy gene should show homozygous mutations or compound heterozygous mutations in autosomal recessive JME [50-52]. Contributions of de novo mutations in the epilepsies have been demonstrated through studies of copy number variations (CNVs) which in fact contribute to genetic generalized epilepsies with complex inheritance, including JME. Consequently, pathogenic de novo mutations could be identified in JME patients [51, 52].

It has been shown that mutations in Cchb4, the mouse homologue of human CACNB4 or mutations in GABRA1 are sufficient to produce the absence phenotype while mutations in Myoclonin1/EFHC1 or BRD2 are sufficient to produce a convulsive phenotype (myoclonic or clonic or tonic-clonic seizures).[41, 53-55].

The identification of epilepsy alleles that cause JME could lead to new AED discoveries, to early diagnosis and curative treatment of JME.

9. Neuropsychological and behavioral studies in JME

There is an increasing interest in the behavioral and neuropsychological aspects of JME patients. Several studies have suggested specific cognitive deficits that explain some of the clinical and special behavioral findings in patients with JME. They also reported an increased incidence in psychiatric comorbidity in patients with JME. Pung and coworkers reported a circadian dysrhythmia in patients with JME which might explain the poor social outcome observed in those patients [56]. Several recent neuropsychological studies suggest that JME has a specific cognitive profile, with some deficiencies in areas related to the frontal lobes. These studies report impairment in word fluency and interference as well as dysfunctional planning abilities [57-59]. JME patients often show intolerance towards multiple tasks under time pressure. This might explain the occurrence of seizures in some of these patients during cognitive tasks. Also, patients with JME often fail to adhere to treatment plans. This might be linked to impairment in prospective memory. Interestingly Wandschneider and coworkers found this impairment also in their siblings indicating that it might be genetically determined [60].

10. Neuroimaging findings in JME

A particular personality profile is associated with JME. Behavioral studies suggest a possible frontal lobe dysfunction [57]. Modern neuroimaging techniques have proven to be very useful in understanding the underlying mechanisms of JME. A PET study using H215O to measure cerebral blood flow in patients with IGE and a history of absence seizures showed that there was a significant focal increase in thalamic blood flow during absence seizures. This result suggests that the thalamus plays a key role in the pathogenesis of typical absence seizures [61]. In another study using 18F-FDG PET and a visual working memory paradigm in nine JME patients and 14 controls, in which pairs of abstract images were presented and subjects had to indicate (by pressing a button) whether the images were matching or not, Swartz and colleagues showed that JME patients' performance was impaired during the working memory condition. The authors concluded that dysfunction in thalamo-fronto-cortical networks might account for poor working memory performance in JME patients. The decreased uptake of 18F-FDG in the ventral premotor cortex, the caudate, the dorsolateral prefrontal cortex bilaterally, and the left premotor area, was in favor of a widespread frontal impairment [62]. Using PET and the radioligand 11C-WAY-100635, Meschaks and colleagues observed reduced WAY-100635 binding potential in the dorsolateral prefrontal cortex, the raphe nuclei, and the hippocampus, but not in motor cortex. The observed reductions in serotonin 1A receptor binding suggest that the serotonin system is affected in JME, and also that serotonergic processes are involved in the pathophysiology of myoclonus in JME [63]. In another PET study, Ciumas and coworkers compared JME patients with patients suffering from generalized tonic-clonic seizures (GTCS): alterations in the dopamine system were found in both GTCS and JME [64].

One study using Magnetic Resonance Spectroscopy (proton MRS) found that N-acetyl aspartate (NAA) levels are reduced in the thalami of JME patients. This finding supports the idea that thalamic dysfunction is part of the underlying mechanism of epileptogenesis in JME [65]. Moreover, other interesting studies using 1H-MRS demonstrated a significantly reduced prefrontal concentration of NAA in JME patients compared with controls [66, 67]. This finding seems to be specific to JME, compared with other forms of IGE [67].

Using Functional MRI (fMRI), Vollmar et al. [68] investigated 30 JME patients with a challenging working memory fMRI paradigm. The authors found an increased functional connectivity within the frontal and parietal lobes, between the motor system and areas of higher cognitive functions. They correlated those findings with the well-known fact that cognitive tasks can precipitate MJ in some JME patients [69].

Quantitative MRI has been used to demonstrate subtle but widespread cerebral structural changes in patients with IGE, particularly in patients with JME [70]. In a related study, Woermann and coworkers have shown that patients with JME have an increase in cortical gray matter in the mesial frontal lobes compared with healthy subjects [71].

Using T1weighted MRI and diffusion tensor imaging (DTI) O'Muircheartaigh et al. found a decreased mesial frontal gray matter volume and a reduced fractional anisotropy (FA) in the underlying white matter tracts. These findings may represent the anatomical basis for the reported neuropsychological and psychiatric changes seen in patients with JME [72].

11. Animal model of JME

Genetic Absence Epilepsy Rats from Strasbourg (GAERS) is a well-established genetic model of absence epilepsy [73]; however, the baboon represents a more advanced non-human primate model of epilepsy, specifically of IGE [74]. It offers a natural model of photosensitive epilepsy with myoclonic and generalized tonic clonic seizures occurring spontaneously or provoked by intermittent photic stimulation [74]. In the baboon, seizures occur spontaneously or are triggered by ketamine or under other circumstances, such for example, fighting among baboons; also, baboons with seizures have normal brain anatomy [75].

In a recent study by Szabó and coworkers [76] involving a pedigree baboon colony, seizures were defined as generalized myoclonic or tonic-clonic; characteristically two thirds of the seizures occurred in the morning. Also, seizure onset occurred in adolescence (age, 5 y), the prevalence of recurrent seizures in this pedigree was 15%. Contrary to human recent findings, seizures in the baboon were more prevalent in male baboons, with a tendency of an early onset and more frequent seizures compared with female baboons. Electroencephalographically, on the baboon scalp, interictal epileptic discharges present as generalized spike-and-wave discharges of 4-6 Hz frequency. All the above clinical and EEG features in the baboon suggest similarities to juvenile myoclonic epilepsy in humans. The baboon also represents an excellent model for testing the efficacy and electrophysiological mechanisms of action of future AEDs for IGEs [77, 78].

12. Management of JME

12.1. AEDs treatment

According to the international League Against Epilepsy, "In JME, response to appropriate drugs is good" [6]. However, 15 % of patients with JME might be drug resistant [79]. Today, with the available new AEDs the rate of drug resistance might be lower. The choice of AEDs is based on clinical experience and the available studies and trials. Several AEDs can be used with success in patients with JME. However, it is important to know, that some AEDs can aggravate myoclonic jerks. Valproate is still considered the first-line treatment in JME in male and females without childbearing potential. The dosage in adults varies from 1000mg to 2000mg/day. The control rate varies from 84.5% to 90% in different studies [5,,80-82].

Several studies have shown the efficacy of Lamotrigine (LTG) in the treatment of JME [83,84]. LTG is useful in younger women because of the potential teratogenicity of VPA [85], in patients with migraine (with aura) [86] and in patients with bipolar depression [87]. However, LTG appears to be less effective than VPA [82] and has the potential to exacerbate seizures in IGE and can aggravate MJ or GTCS [88]. The same authors [88] reported de novo appearance of MJ in IGE in five women among 93 patients treated with LTG (5.4%) with a phenotype close to JME at the time of aggravation.

Levetiracetam (LEV) is highly effective in controlling seizures in JME as shown by the studies by Berkovic and co-workers [89], Noachtar and colleagues [90] and Rosenfeld and colleagues [91]. These randomized, double-blind, placebo-controlled studies showed a responder rate of 61% in patients with JME, with 20.8% of them becoming seizure-free. LEV should be one of the options in the treatment of JME [92] as a first line or add on, particularly in women of childbearing potential. However, LEV also may exaggerate myoclonus [93].

If tolerated, Topiramate (TPM) can be useful in the treatment of JME particularly in overweight patients and in patients with associated migraine. Several authors have shown its efficacy as an add-on therapy in JME [94-96]. TPM was even reported as slightly more efficacious then VPA in a study by Levisohn and Holland in 2007 [97]. TPM may produce neuropsychiatric side effects particularly alteration of attention, and verbal fluency [98] and therefore may lead to treatment failure [82].

Few studies showed good efficacy of Zonisamide (ZNS) in patients with JME. One particular study by Kothare and colleagues looked at 15 patients with JME: 13 patients received ZNS as first monotherapy and 2 as add-on therapy. There were 80% of responders in the monotherapy group. 69% of patients were GTCS-free, 62% were seizure-free for MJ, and 38% were seizure-free for absences. The daily dose ranged between 200 and 500 mg [99].

Another study showed that ZNS treatment led to more than 50% reduction of seizure frequency in 83.3% of treated patients for GTCS and in 100% for MJ and absences [100].

Obeid and colleagues reported that Clonazepam was effective in controlling myoclonic jerks, but not the GTCS in JME patients [101]. In a later study, Panayiotopoulos [102] found both Clonazepam and Acetazolamide useful adjunctive drugs in JME, particularly if absences and myoclonus are associated. Mantoan and colleagues [92] found that Clonazepam can be combined with LTG in JME in order to avoid the myoclonic effects of LTG. The same authors, among others, have shown that few AEDs like Carbamazepine, Oxcarbazepine, and Phenytoin can exacerbate absences and myoclonus and even induce status epilepticus and should not be used in JME, although these drugs are able to control tonic-clonic seizures associated with JME when these are refractory to other medication [92,103-105].

Lacosamide may be effective in JME. However, larger, controlled studies confirming the usefulness of this AED are lacking [106].

12.2. Discontinuing AEDs in patients with JME

In a recent interesting study, Geithner and colleaguers [107] followed 31 patients with JME for as long as 25 years: Of these 31 patients, 67.7 % became seizure free. In 6 of these patients (28.6%), AEDs were discontinued with no more seizures. The most important factor that increased the chance for complete seizure freedom after stopping the AED was complete remission of the GTCS under a single anti-epileptic drug. However, the occurrence of a photo-paroxysmal response increased the risk of seizure recurrence after stopping AEDs. The authors concluded that in order to maintain seizure freedom, lifelong antiepileptic drug treatment is not necessarily required by all patients with JME.

13. Other treatments and approaches

13.1. Dietary therapy for JME

Ketogenic diet has been utilized for a number of conditions. Recently, Kossoff and colleagues [108] have looked at the effectiveness of the use of diet for treatment for AED-resistant JME. The investigators used a modified Atkins diet as an adjunct therapy to treat 8 adolescents and adults patients with JME. Six (75%) of these patients had more than 50% seizure reduction after one month, five patients (63%), had a greater than 50% seizure improvement after three months; three patients reported increasing seizures frequency during periods of noncompliance. The authors concluded that the modified Atkins diet can be a useful therapy for young patients with AED-resistant JME. However, more patients need to be studied to assess which JME patients may benefit from this therapy.

13.2. Vagal Nerve Stimulation (VNS)

Only one study [109] reported on the role of VNS in drug resistant JME. In this study, 12 patients with drug resistant IGE were offered VNS. Among these patients 7 patients had JME: 5 of them responded to VNS and had reduced AED-treatment at follow up. Kostov and colleagues [109] concluded that adjunctive VNS therapy is a favourable treatment option for drug-resistant IGE patients.

13.3. Lifestyle, psychiatric treatment

In managing JME, life style is considered an important part of the treatment and this aspect should be discussed with the patient in order to obtain good seizure control. Patients should avoid all precipitating factors such as fatigue, sleep deprivation, alcohol and unnecessary drug intake. In particular, patients should avoid any potentially dangerous activities in the awakening period, such as taking a bath without observation, for example.

There is also a high prevalence of psychiatric disorders in patients with JME, such as mood, anxiety, and personality disorders. Early recognition and treatment of these disturbances and psychosocial difficulties play an important role in the prognosis of JME [110].

14. Conclusion

JME is a common form of IGE with a characteristic clinical and electroencephalographic profile. Usually, a sleep EEG or an EEG on awakening confirm the clinical suspicion. Despite this distinct clinical and EEG trait, JME is often not recognized as such; this might result in serious consequences for the sufferers: in particular, if potentially aggravating AEDs are used, especially Carbamazepine, Oxcarbazepine, Phenytoin; but also, in some patients, Lamotrigine, which might exacerbate absences and myoclonus. These AEDs are therefore contraindicated, although they can improve control of tonic-clonic seizures when these are refractory to other

medications. The following AEDs should not be used in JME: Gabapentin, Pregabalin, Tiagabine, and Vigabatrin; they can worsen seizures (Tiagabine and Vigabatrin might induce absence status epilepticus).

Beside the pharmacological treatment, management of JME should also include the patient's lifestyle, with avoidance of sleep deprivation, alcohol excess and the treatment of the cognitive and psychiatric problems that is often associated with JME.

With correct diagnosis and appropriate AED treatment (such as Valproate, Levetiracetam), a small but important group of patients will be able to come off medication not requiring therefore lifelong AED medications.

In refractory cases of JME, modified Atkins diet might be useful. Vagus Nerve Stimulation, Callosotomy and Deep brain stimulation are rarely contemplated.

Neuroimaging, using advanced imaging techniques, suggests subtle structural and functional changes, mainly within the frontal lobes, in patients with JME.

These changes correlate with the observed neuropsychological deficits (frontal lobe dysfunction) in patients with JME.

Genetically, JME is the most common cause of hereditary grand mal seizures and has both Mendelien (dominant or recessive trait) and complex genetic inheritance. During the last two decades a lot of discoveries have been made in this field. Finding more chromosome loci and more epilepsy-causing mutations for JME will continue to provide definitive evidence of the complex nature of this disease and of the existence of specific diseases within JME. Future

AEDs should be designed to counter major genes that cause JME.

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