Treatment of Juvenile Myoclonic Epilepsy

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Drug treatment of juvenile myoclonic epilepsy (JME) is mainly based on clinical experience and prospective and retrospective studies, with little evidence from randomized clinical trials. There are almost no head-to-head comparisons between old and new antiepileptic drugs (AEDs). Valproate is the drug of the first choice in men with JME. In women, lamotrigine (LTG) should be preferred regarding teratogenicity and side effects of valproate. Levetiracetam (LEV) is also effective. Recent data suggest that it may soon be used as first line treatment. Some AEDs can aggravate JME. In addition to AEDs, nonpharmacological treatments are important in JME. JME usually requires lifelong treatment because seizures nearly always return after withdrawal of therapy.

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Introduction

Juvenile myoclonic epilepsy (JME) is an idiopathic generalized epilepsy (IGE) [1]. It is a collection of seizure patterns that are clinically distinct from those in other forms of IGE, with the major characteristic being adolescence-onset myoclonic seizures. Although the pathogenesis is unknown, recent advances, especially in genetics, suggest several possible mechanisms [2]. JME is both genetically and clinically heterogeneous; some clinical variations may indicate differences in pathogenesis. The nosology and classification of IGE syndromes are currently under revision [3,4]. JME is characterized by a particular pharmacological sensitivity. Valproate has historically been described to have a specific potency. Other antiepileptic drugs (AEDs) are also efficient, such as clonazepam (CZP), lamotrigine (LTG), levetiracetam (LEV), and topiramate (TPM), while others may have aggravating effect. There is a lack of adequate powered study for JME [5].

Electroclinical Features of Juvenile Myoclonic Epilepsy

JME is a common IGE characterized by myoclonic seizures. It is the most common IGE in adults, espe-

cially in women. Isolated myoclonic jerks of the arms, especially shortly after awakening, are the characteristic feature. Generalized tonic-clonic seizures (GTCS) often occur, and one-third of individuals have absences. The GTCS are often preceded by a few minutes of generalized myoclonus of increasing frequency and intensity. They occur predominantly after awakening. Seizure occurrence is more likely related to sleep deprivation, fatigue, and alcohol withdrawal. Onset is usually in adolescence but seizures may begin or be diagnosed only in the early 20s. Eighty percent of patients with JME begin having seizures between ages 12 and 18 years. The mean age of onset for GTCS is 15.5 years. The most important element in the diagnosis of JME is the clinical history.

Misdiagnosis and delayed diagnosis remain common [6,7]. Patients frequently come to medical attention only after a GTCS, and the history of much earlier myoclonic jerks is then often obtained retrospectively [7].

The typical electroencephalographic abnormality is bilateral multiple spike or polyspike-wave complexes, which precede a myoclonic jerk. The EEG discharge includes 5–20 spikes with a frequency between 12 and 16 Hz. The amplitude of spikes is frequently maximal in anterior areas. An ictal recording is best obtained by polygraphic video-EEG performing a provoked early morning awakening during a full-night sleep recording or at

least after nocturnal sleep deprivation [8]. JME is one of the epileptic syndrome clearly associated with photosensitivity which occurs in about 30% [9,10]. Myoclonic seizures can be induced by intermittent luminous stimulation in photosensitive patients, but clinical photosensitivity is less frequent than during EEG recording. In some cases, focal clinical or EEG features or both in patients with JME can be observed [11–15]. These features include not only unilateral myoclonic jerks but also version and asymmetrical tonic limb posturing. These focal features lead sometimes to a erroneous diagnosis of partial epilepsy. The misdiagnosis can also be responsible for the prescription of an AED aggravating JME.

JME is usually described as a benign condition because of its particular pharmacological sensitivity. However, a distinctive set of personality features (i.e., lack of drive and endurance, unsteadiness, unreliability, an unstable self-concept, and rapidly changing affect and mood states), have been early described [16]. These observations have been confirmed by other studies [17–19]. In a study involving 25 JME patients and age-match controls, JME sample exhibited twice the amount of psychiatric symptoms than age-matched norms. Furthermore, psychopathological symptoms increased with duration of JME [20]. The frequency of psychiatric disorders was also evaluated in 100 patients with JME and compared with healthy controls. Psychiatric disorders were more frequent in JME ($n = 49$). Anxiety and mood disorders were diagnosed in 23 and 19 patients, respectively. Moreover, the disorders were more frequently observed in patients with higher seizure frequency [21]. These reports may have implications for clinical care. The evaluation of psychopathological comorbidity should be considered as a necessary part of clinical assessment.

Treatment

The goal of management is to render the individual seizure-free without the side effect(s) of antiepileptic drug(s). JME more frequently requires lifelong treatment because seizures nearly always return after withdrawal of therapy [22,23]. Late seizure recurrence in treated patients seems to be leading to AED withdrawal or erratic life style [24]. JME is difficult to treat in about 15% of patients. The predictors of pharmacoresistance include: (i) the coexistence of all three seizure types (myoclonic jerks, absence seizures, and GTCS), (ii) the existence of associated psychiatric problems, and (iii) focal clinical symptoms and/or focal EEG discharges [25–27].

Nonpharmacological Treatment

In JME, lack of sleep and alcohol intake can induce seizures. The sleep–wake rhythm has to be regulated. The

circumstances interfering with normal sleep and progressive awakening in the morning should be eliminated. If the patient stays up late at night, he should sleep longer in the next morning. Alcoholic drinks will only be permitted in small quantities, on social occasions. Patients should be advised not to drink in cases of lack of sleep. If the patient has photosensitivity, one should avoid relevant visual stimuli. Some maneuvers reduce the risk of photosensitive seizures, including monocular-complete occlusion, increased distance from a video-display terminal, and the provision of ambient back lighting [28]. We suggest these approaches to patients who show photosensitivity on EEG but do not know how successful these environmental alterations are in JME.

Valproate

Valproic acid (VPA) is a branched-chain fatty acid that markedly differs in structure from all other AED in clinical use. Its mechanism of action remains not fully understood. There are evidences that VPA increases GABA concentrations, the mechanism by which this occurs remains unknown. Multiple mechanisms have been proposed, including inhibition of GABA-T action, activation of GABA synthesis by an increase of GAD activity, and increased release of GABA into the synapse.

Based on clinical experience, VPA was first proposed as a treatment of myoclonic seizures. Twenty-three years ago, the sensitivity of JME to VPA was reported [22]. Although JME is an important syndrome, there have been almost no randomized clinical trials conducted using any medication for its treatment. However, there have been many open case studies conducted with VPA in JME management. The open series that have been published using VPA show a 41–88% seizure-free rate for patients receiving VPA, either as an add-on medication or as monotherapy [6,29]. Case studies have also shown that a low, once-daily dose (500 mg) of VPA can effectively control JME and keep patients seizure free for as long as 2 years [30,31]. Newer studies that examined the efficacy of LTG, TPM, and VPA in JME have all shown that VPA has the best efficacy of the three [32–35]. More recently, the SANAD study concluded for generalized epilepsy that VPA should remain the drug of first choice for many patients. The Standard and New Antiepileptic Drugs (SANAD) study was a randomized unblinded controlled trial involving 716 patients. Three AED were compared: VPA, LTG, and TPM. This study suggested that VPA was more effective than LTG and had a better tolerance than TPM [36].

VPA is today one of the most effective AED in JME. It should be considered the first line drug, at least for men. Taking into account the teratogenicity (possibly lessened

by the concurrent use of folic acid) and some side effects (weight gain), VPA is often considered unacceptable in young women of childbearing age.

Benzodiazepin

Benzodiazepines work by primarily enhancing gamma-aminobutyric acid (GABA)ergic inhibition by binding to the benzodiazepine receptor on GABAA receptors [37].

CZP can also be effective in the treatment of JME. Obeid et al. treated 17 JME patients with CZP [38]. All of them had myoclonic seizures before treatment, and 14 of the 17 had GTCS before treatment. After CZP treatment, myoclonic seizures were controlled in 15 (88%) of 17 patients, and the remaining two patients had a 75% reduction in seizure frequency. However, CZP did not produce effective results for reducing GTCS. The GTCS of 6 (43%) out of the 14 patients were controlled. In addition, two patients sustained injuries during GTCS because CZP eliminated their myoclonic seizures, which had served as a warning, and they went directly into a GTCS. The authors concluded that CZP, while effective in treating myoclonic seizures, probably should not be used to control GTCS.

Lamotrigine

LTG is a phenyltriazine derivative. LTG acts through inhibition of voltage-activated sodium channels and possibly calcium channels, so that it prevents the release of glutamate [39].

LTG is effective in controlling GTCS and absence while there are some reports of myoclonic seizures exacerbation [40,41].

Many studies performed over recent years have demonstrated clinical utility for the treatment of JME. An open-label study to evaluate LTG as an alternative to valproate (63 patients switched from valproate to LTG) demonstrated an improvement in 67 % of patients. No aggravation of clinical symptoms was also reported [42]. Buchanan conducted a study of 12 patients with JME who were treated with LTG monotherapy [43]. Five (41%) of these 12 patients became seizure free while receiving LTG monotherapy, and the authors concluded that LTG might be effective in the management of JME. In a retrospective study, VPA monotherapy (n = 36) and LTG monotherapy (n = 14) were compared, as well VPA (n = 22), LTG (n = 21), and TPM polytherapy (n = 15) were compared. The results suggested that LTG were an effective option as monotherapy and polytherapy [34]. Furthermore, the efficacy of LTG in JME was evaluated in bitherapy. The polytherapy is especially interesting in case of drug resistance. The combination of LTG with VPA

appears synergistic in many types of epilepsy. However, the same combination is lead to an increased risk to develop a rash [44,45]. LTG monotherapy is usually described as AED that is not associated with an increased risk for major fetal malformation in most of the available studies [46,47]. The data from the UK Epilepsy and Pregnancy Register suggested a positive dose–response relationship for malformations in LTG monotherapy, particularly at doses higher than 200 mg/day [48].

Levetiracetam

LEV is a pyrrolidone derivative, and is the S-enantiomer of the ethyl analogue of piracetam. While the exact mechanism of action of LEV is not known, it appears to act via a specific binding site within the brain (but neither directly affect GABA or glutamate nor alter sodium channel properties), produces a limited reduction in high-voltage-activated calcium currents, and possibly modulates intracellular calcium transients [49,50]. Molecular studies involving transgenic mice suggest that LEV binds to a synaptic vesicle protein (SVA2) that is involved in vesicle neurotransmitter exocytosis, and that the binding affinity to SVA2 is directly proportional to seizure protection [51].

LEV is probably the best new AED in the treatment of JME and may replace VPA for the treatment of the disorder because of high and sustained efficacy, fast action, and an excellent safety profile. Preliminary safety data in human pregnancy suggest that LEV did not frequently induce major congenital malformations. Using a UK pregnancy register, 117 pregnancies exposed to LEV were analyzed. Three of them had major congenital malformations (2.7%; 95%CI: 0.9–7.7). All three were exposed to other AEDs. Further study need to confirm this result [52].

The recent data suggest that it can be used as first line treatment. Noachtar et al. evaluated LEV in 122 patients (113 with JME and 9 with juvenile absence epilepsy). This study was a double-blind multicenter placebo controlled trial conducted in patients without control on one AED. The responder rate was 58.3% with LEV versus 23.3% with placebo [53]. Specchio et al. conducted a multicenter, prospective open-label study in patients with JME [54]. Ten patients had newly diagnosed and 38 had refractory resistant and/or were intolerant to previous AED. Five dropped out. Eighteen (37.5%) had myoclonia control and 35 (73%) had no GTCS.

More recently, two studies evaluated efficacy and tolerability of LEV monotherapy. Verrotti et al. reported 32 JME patients treated by LEV as first administered drug. At 6-month evaluation, 15 patients were seizure free; 14 patients were responders (>50% reduction

in seizures) while 29 patients were seizure free after 12 months of treatment. No patients reported adverse events [55]. In a retrospective study, Scharpe et al. registered 12 patients with LEV as the first therapy and 16 as the initial appropriate agent. Eighty percent (24/30) of patients became seizure free with LEV monotherapy and two additional patients showed improved seizure control. Treatment failure with VPA also did not predict failure of LEV [56].

Finally, LEV was evaluated as effective and well-tolerated drug for treating GTCS in patients with IGE. Berkovic et al. conducted a multicenter, randomized, double-blind, placebo-controlled study of 164 patients (LEV, $n = 80$; placebo, $n = 84$), including 54 patients with JME ($n = 24$ in LEV group, $n = 30$ in placebo group). LEV produced a greater mean reduction in GTCS frequency per week over the treatment period (56.5%) than placebo (28.2%). The percentage of patients who had >50% reduction of GTCS frequency per week (responders) during the treatment period was 72.2% for LEV and 45.2% for placebo (OR: 3.28; 95% CI: 1.68–6.38). The percentage of patients free of GTCS (34.2% vs. 10.7%) and all seizure types (24.1% vs. 8.3%) was also greater for LEV than placebo. LEV was well tolerated with 1.3% of patients discontinuing therapy [57].

Topiramate

TPM is a sulphamate-substituted monosaccharide that exhibits some inhibition of carbonic anhydrase. Its AED activity is independent of this effect. TPM has multiple modes of action, including modulation of voltage-dependent sodium channels, potentiation of GABAergic inhibition at a novel site on the GABAA receptor, and possible action at non-Nmethyl-D-aspartate (NMDA) receptors [58–60].

Several studies have shown the usefulness of TPM in patients with JME. There is one randomized-controlled study on the efficacy of TPM in patients with GTCS including patients with JME [61]. A reduction of more than 50% of GTCS were reported in 8/11 patients treated by TPM compare to 2/11 in placebo-treated patients. A reduction in myoclonic and absence seizures was also reported but did not achieve statistical significance. TPM efficacy and tolerability were evaluated in 22 patients with JME [62]. Sixteen patients completed the first year of the follow-up, while four left the study because of poor seizure control and two because of low compliance. Myoclonic seizures were controlled in 11 patients and persisted in 5 patients. GTCS were completely controlled in 10 patients, 4 patients had more than 50% reduction of seizures and 2 had reduction less than 50%. In a randomized open-label treatment, 28 patients with a recent

diagnosed JME received TPM or VPA [63]. Twelve of 19 patients treated with TPM and 7 of 9 patients treated by VPA completed the study. Generalized tonic-clonic, myoclonic and absence seizures were totally controlled in 10/12, 9/14, and 2/2 TPM-treated patients, respectively, and 3/4, 7/9 and 1/2 valproate-treated patients. In a retrospective cohort, TPM monotherapy and polytherapy were considered as an alternative to VPA [34].

Zonisamide

By blocking the voltage-sensitive sodium channels, zonisamide (ZNS) prevents repetitive neuronal firing. It also reduces voltage-dependent T-type calcium channels, facilitates dopaminergic and serotonergic neurotransmission, weakly inhibits carbonic anhydrase and may protect neurones from free-radical damage, thereby stabilizing neuronal membranes [64,65].

Few studies focused on the effects of ZNS are available. A retrospective study analyzing 15 patients (monotherapy in 13 patients and added to valproate in 2 patients) reported a good control of seizures. About 69%, 62%, and 38% were free for generalized tonic-clonic, myoclonic, and absence seizures, respectively. Side effects were reported in 20% of patients [66]. In a neurophysiological study of one patient, ZNS permits almost complete disappearance of generalized spike and wave discharges [67]. These data suggest the possible usefulness of this AED in JME.

AED Aggravating JME

It is now well known that AEDs can aggravate epilepsy. Phenytoin (PHT), carbamazepine (CBZ) and oxcarbazepine have shown to aggravate the myoclonic and absence seizures of JME and therefore should be avoided [68–70]. Genton et al. conducted a study with CBZ and PHT to determine the risk of seizure aggravation in 40 patients with JME [68]. In the CBZ group, 19 (68%) of 28 patients had a seizure aggravation, usually affecting the myoclonic seizure, and only 6 (21%) of 28 patients improved. In the PHT group, six (38%) of 16 patients had a seizure aggravation, and only 2 (12%) of 16 patients improved. Aggravation mostly was in the form of increased myoclonic jerks. The authors concluded that among commonly prescribed AED, CBZ appears to have the strongest aggravating potential in patients with JME, whereas the aggravating effect of PHT is less prominent.

There have been isolated series of reports indicating that LTG can exacerbate or aggravate myoclonic seizures. Biraben et al. reported four patients with JME receiving LTG therapy that experienced myoclonus seizure aggravation [40]. Carrazana et al. also found two patients

with JME (2/24) developed dramatic exacerbation of myoclonus and two others (2/24) had mild transient increases in morning myoclonus with LTG [41].

Antiepileptic Drug Selection

When presented with a patient with epilepsy, physicians should prescribe the medication that will effectively control the seizures yet not endanger the patient with adverse events or seizure aggravation. Although JME is an important syndrome, there have been no randomized clinical trials conducted using any medication for its treatment. Drug treatment of JME is mainly based on clinical experience and prospective and retrospective studies. There are almost no head-to-head comparisons between old and new AEDs [5].

The 2001 and 2005 expert consensus surveys on adult epilepsies [71,72] ranked valproate as the treatment of choice for IGE when the patient's sex was not specified. However, in the 2005 survey adult epilepsy, when it was specified that the patient was a woman, the experts rated LTG as treatment of choice. In the 2005 expert opinion and 2007 European expert opinion about pediatric epilepsy treatment, VPA and LTG were the for 15-year-old male with JME, while LTG was the only choice for 15-year-old female with JME [73,74]. ZNS was rated as high second line by the experts on pediatric epilepsy while European experts rate it as third-line reflecting lack of familiarity with this AED and its limited availability in Europe [74]. In the 2007 pediatric expert opinion, LEV was rated sometimes appropriate in both sexes reflecting the recent data [73]. This rating may reflect the recent studies on JME and IGE.

VPA is historically the drug of the first choice in men with JME. In women, in whom considerations of teratogenicity, weight gain, and polycystic ovary syndrome are relevant, other options include LEV, LTG, TPM, and perhaps ZNS. In patients with symptoms refractory to treatment with one drug, VPA associated with small doses of LTG is often an effective combination. Recent data suggest that LEV can be used as second-line but may also be used as first line treatment.

Conflict of Interest

The authors have no conflict of interest.

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