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JUVENILE MYOCLONIC EPILEPSY

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ABSTRACT - Juvenile myoclonus epilepsy (JME) is a common epileptic syndrome, the etiology of which is genetically determined. Its onset occurs from 6 through 22 years of age, and affected patients present with myoclonic jerks, often associated with generalized tonic-clonic seizures - the most common association - and absence seizures. JME is non-progressive, and there are no abnormalities on clinical examination or intellectual deficits. Psychiatric disorders may coexist. Generalized polyspike-and-waves are the most characteristic electroencephalographic pattern. Usual neuroimaging studies show no abnormalities. Atypical presentations should be entertained, as they are likely to induce misdiagnosis. Prevention of precipitating factors and therapy with valproic acid (VPA) are able to control seizures in the great majority of patients. Whenever VPA is judged to be inappropriate, other antiepileptic drugs such as lamotrigine may be considered. Treatment should not be withdrawn, otherwise recurrences are frequent.

KEY WORDS: juvenile myoclonic epilepsy, diagnosis, etiology, treatment.

Epilepsia mioclônica juvenil

RESUMO - A epilepsia mioclônica juvenil é uma síndrome epiléptica comum, cuja etiologia é fundamentada na genética. Inicia-se entre 6 e 22 anos e os indivíduos apresentam mioclonias, que podem ser acompanhadas por crises tônico-clônicas generalizadas - associação mais comum - e crises de ausência. A doença não é progressiva, e não há alterações detectáveis no exame físico ou déficits intelectuais. Distúrbios psiquiátricos podem coexistir. Polipontas-ondas lentas generalizadas constituem o padrão eletrencefalográfico ictal típico. Não há anormalidades em exames de imagem convencionais. Apresentações atípicas devem ser consideradas, pois predispõem a erros de diagnóstico. A prevenção de fatores desencadeantes e o uso de ácido valpróico (VPA) controlam as crises epilépticas na grande maioria dos casos. Quando o VPA é inapropriado, outras drogas como a lamotrigina podem ser utilizadas. O tratamento não deve ser interrompido, visto que as recidivas são freqüentes.

PALAVRAS-CHAVE: epilepsia mioclônica juvenil, diagnóstico, etiologia, tratamento.

The first description of juvenile myoclonic epilepsy (JME) mounts to the 19th century[1]. During the 1950's, JME gained a wider projection with Janz, who called it "*Impulsiv Petit Mal*"[2]. Other terms have been used to define it, such as "myoclonic epilepsy of adolescence", "benign myoclonic juvenile epilepsy", and "Janz syndrome"[2]. The International League against Epilepsy (ILAE) currently classifies JME within the group of Idiopathic Generalized Epilepsies (IGE) with variable phenotypes[3].

Our goal is to review JME, including its clinical presentation and electroencephalography (EEG), and to underline the primary factors that contribute to frequent errors or delay in diagnosis[4]. Major advances in genetics and the most recent findings in neuroimaging studies are described as well. References for this review were identified by searches of Medline with the terms "juvenile myoclonic epilepsy" and "myoclonic epilepsy", limited to articles published in English since 2001. In another search, the authors utilized the terms "epilepsy", "practice guidelines", and "treatment" to select pertinent articles on treatment guidelines. In addition, an effort was made to search for studies on the Brazilian population through the online library SciELO, and a few references were also identified from relevant articles and books.

EPIDEMIOLOGY

JME is said to represent 5-11% of all epilepsy cases[4]. Its incidence has been estimated at approximately 1 per 100,000 population, while its prevalence varies from 10 to 20 per 100,000[5].

JME makes its clinical appearance between 6 and 22 years of age, but 50% of cases present at ages

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13-16 years[2]. Myoclonic seizures are present in all patients (appearing at 12-18 years) and are associated with generalized tonic-clonic seizures (GTCS) in 80-97%, the average age of onset the latter being 16-18 years, and with absence seizures (AS) in 12-54% of patients[6].

JME affects both male and female patients equally[7], although a female predominance has been described[2]. Early onset of AS is more common in girls, while boys present with them at a later age, and in boys there is a predominance of asymptomatic AS, that is, a typical EEG not accompanied by symptoms[7]. A family history of epilepsy was present in 65.9% of 41 studied families, and 36% had at least two family members affected by JME[7].

JME patients have no intellectual or neurologic deficits, and the disease follows a non-progressive course[2]. In a study of 170 patients, overall mortality rate due to sudden death was estimated to be 0.9 per 1000 patient-years, and associated psychiatric disorders were considered to be risk factors for unexpected death[8].

In Brazil, a retrospective study was performed and showed results that were similar to those in the literature[9]. JME accounted for 2.8% of all epilepsy cases. There was a female predominance (73.1%), with age of onset between 7 and 18 years (average 13 years). All patients manifested myoclonic jerks, while 92.3% had GTCS and 19.2% had AS. A positive family history of epilepsy was present in 53.8%[9].

ETIOLOGY

JME etiology stems from genetics[2]. Its inheritance mode is unclear, as there have been reports of autosomal dominant, autosomal recessive modes, and multifactorial and complex models[10]. Although JME cases are genetically heterogeneous, patients within those various groups are not clinically distinguished by the current diagnostic methods[11].

Many studies tried to identify genes associated with JME. It was suggested that polymorphism of gene *KCNQ3* (8q24), responsible for the voltage-dependent potassium channel, may be an important predisposing factor for JME in Indian probands[11]. *KCNQ3* is expressed late, what might explain disease presentation during adolescence[11]. This potassium channel is implicated in the slow inhibitory post-synaptic potential and regulates the fast repolarization phase[12]. So, decreased activity of this potassium channel delays the repolarizing action potential and lowers the amount of excitation needed to produce subsequent action potentials, predisposing to undesirable discharges[12].

Another identified gene is *CLCN2* (3q26), responsible for the synthesis of voltage-gated chloride channel ClC-2, which is specially expressed in neurons inhibited by gamma-aminobutyric acid (GABA) and serves to maintain low intracellular concentrations of chloride, essential to the gabaergic inhibitory response[10,11,13,14]. The recognized mutation is a premature stop codon (M200fs x 231) and is associated with loss of function of channel ClC-2, resulting in chloride intracellular accumulation and, therefore, decrease in response to GABA or even inversion to an excitatory response[10,13].

Some studies demonstrated one *locus* in chromosome 6p that predisposes to JME[10]. An additional study extended these findings and detected five mutations of gene *EFHC1* (6p12)[10,11], whose protein interacts with type R voltage-dependent calcium channel ($Ca_V2.3$), inducing an increase in its current[13]. While mutations in this gene may suggest neuronal membrane electrical destabilization, another possibility was advanced[13]. A pro-apoptotic effect was attributed to gene *EFHC1*, mediated by the action of its protein on $Ca_v2.3$, interfering with intracellular calcium influx[13]. So, the presence of mutations in this topography might impair apoptosis during the process of central nervous system maturation, producing an increased density of neurons under deficient calcium control and consequently hyperexcitable circuits[11].

Some French-Canadian families exhibited autosomal dominant JME[10,11]. Those individuals were heterozygous for missense mutation Ala322Asp in gene *GABRA1* (5q34), responsible for the synthesis of alpha1 subunit of receptor $GABA_A$[11]. This receptor produces fast synaptic inhibition, and its dysfunction has long been suspected in epilepsy pathogenesis[10]. However, this mutation was not found among 83 patients with IGE, including JME patients[10].

Other genetic sites have also been studied, but their contribution to JME pathogenesis is incompletely understood[1]. While the list of genes implicated in epilepsy is ever growing, most researchers presume that several genes linked to epilepsy exert a modest effect, producing only a small functional change in their gene products, which is not detected by current analyses[14]. JME manifestation depends most likely on the interaction of one or more of the various identified genes with other genetic, epigenetic, or environmental factors[15].

The neuropathologic finding described in JME patients is microdysgenesis[11,16], a mild malformation of cortical development whose role in epileptogenesis has not yet been clarified[17]. Recently, controversies were raised regarding the relationship of this cortical

malformation with the epilepsies, as it has also been found within other entities, and universal diagnostic criteria have not been established for microscopic analysis, making it difficult to compare studies in the literature[17].

DIAGNOSIS

JME diagnosis is based upon clinical criteria and typical electroencephalographic findings, such as: 1) presence of myoclonic jerks, AS, and GTCS with an age-dependent onset and well defined precipitating factors; 2) normal neurologic examination and head computerized tomography; 3) a generalized EEG pattern of spikes and/or polyspikes-and- waves; 4) complete remission of seizures in 80% of patients during valproic acid (VPA) therapy[4].

This clinical presentation is quite characteristic, but misdiagnosis and its attendant treatment delay are frequent[4,6,18,19]. In a study, the correct diagnosis was delayed by 8.3±5.5 years, and even in a tertiary center, patients were followed for 17.7±10.4 months until the diagnosis was established, corresponding to 6±4 clinic visits[4]. Sousa et al.[19] assessed 41 patients and detected a mean diagnostic delay of 8.2 years after onset of epileptic seizures; among the individuals whose epilepsy presented with myoclonias, mean delay was 6.1 years and among those who presented with AS and/or GTCS, 10.8 years.

The most common incorrect diagnosis was GTCS, followed by partial epilepsies[4,18]. There are a few factors contributing to these error rates, which may have a clinical or electroencephalographic substrate[19].

The primary clinical factor is the failure to detect myoclonic jerks[4,18,19]. Most patients do not complain of myoclonias[4], because either they find them to be unimportant or are ashamed by their occurrence, or else because myoclonic seizures are uncommon and not perceived as abnormal[19]. Patients interpret them in different ways, and many believe they are part of a GTCS[19]. In addition, clinicians frequently fail to ask about the occurrence of myoclonias during medical interview, a fact that was present in 14 out of 22 patients[4]. JME still appears to be a disease with which most physicians have no familiarity, therefore they interpret myoclonic jerks as stress or partial epileptic seizures[19].

Asymmetric myoclonias and the occurrence of GTCS at nighttime or as the first epileptic seizure have also been implicated as confounding factors[4,19].

Electroencephalographic factors include the presence of findings that are atypical but do not exclude JME[4,18,19]. Focal abnormalities deviated diagnosis toward partial seizures, particularly when AS are not recognized (misinterpreted as complex partial seizures) or when myoclonic jerks are predominantly unilateral (mistaken for motor partial seizures)[4]. Focal abnormalities on the EEG were found in 19.7-29.3% of patients[18,19]. Asymmetry of the recording amplitude with a generalized pattern also contributed to diagnostic error and was present in 38 out of 76 patients[18].

Finally, a normal recording was obtained on the initial EEG of 41% of patients, and 73.2% had at least one normal EEG recording during work-up[19]. Normal recordings were attributed to drug therapy, indicating that EEG should be performed before treatment onset[19]. Serial EEGs seem to be fundamental to confirm diagnosis: 3 recordings identified 84% of cases, and this figure increases to 94% when 4 to 8 recordings are obtained, but there is no significant increase with more than 8 recordings[19].

A correct diagnosis of JME has an important impact on treatment and outcome of patients[4]. Delay in disease identification hampers seizure control and may lead to status epilepticus, nonreversible brain damage, decreased school performance, social difficulties, and even death[4].

CLINICAL PRESENTATION

Identification of myoclonic jerks is critical to JME diagnosis[16]. They are characterized by single or repetitive, bilateral, abrupt, symmetric, arrhythmic, involuntary movements, predominantly involving the shoulders and arms; however, they can be unilateral[16,20]. One study showed involvement of upper extremities in 97.7% of patients and of lower extremities, trunk, and face in 46.5%, 23.3%, and 14%, respectively[21]. The most typical myoclonus is likely to be shoulder elevation with elbow flexion[20]. A myoclonic jerk is brief, but a duration of up to one second was described in association with an even slower relaxation phase[20]. The amplitude varies from violent movements to minimal twitchings, with the latter being called minipolymyoclonus[20]. At times, however, there are no visible movements, and the patient reports only a subjective electric shock sensation inside the body[16].

During myoclonic jerks, consciousness is well preserved[16]. Most myoclonias occur when awakening from a night of sleep or a nap, a fact that was found in 62.8-87.5% of cases[7,21].

Only 3-5% of JME patients have just myoclonic jerks[16]. GTCS are present in 80-97% of patients[6] and appear months or years after onset of myoclonias[2]. They are often preceded by generalized mild to moderate myoclonic jerks of increasing frequency and intensity, which last a few minutes[16]. GTCS are charac-

terized by absent sensory aura, violent movements, and a long duration of the tonic phase[16]. They occur most commonly after awakening, and this feature was observed in 53.7% of cases[21] and in 11 out of 16 patients[7].

Absence seizures are present in a lower frequency, varying from 12 to 54%[6]. Age at onset is around 10.5 years (±3.4 years)[7]. Among 72 patients with AS followed throughout one year, 15% developed myoclonic seizures, leading to JME diagnosis[22]. Predictors of progression to JME were lack of response to antiepileptic drugs (AEDs) within the first year of treatment, absence status, family history of generalized seizures in first-degree relatives, and slowed background on initial EEG[22]. AS may occur several times a day, without any circadian variation, and are not associated with automatisms[16]. When AS appeared before 10 years of age, they were associated with a severe change in consciousness, a feature that was detected in 12.1% of patients[7].

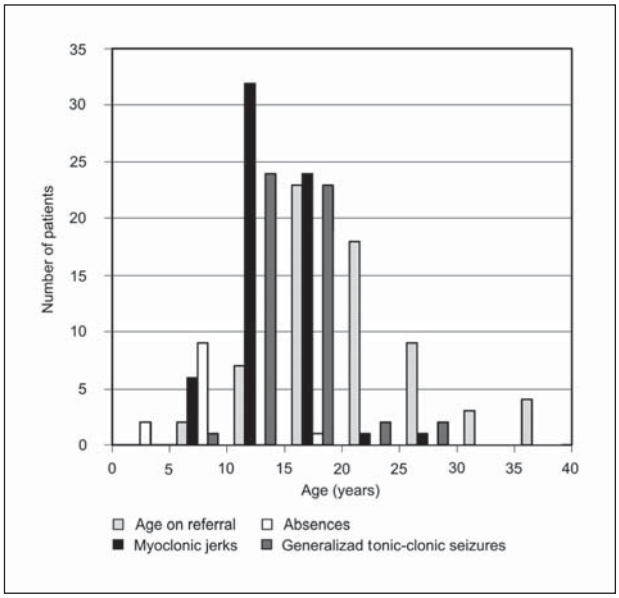

Fig 1. Age at onset and referral in juvenile myoclonic epilepsy.

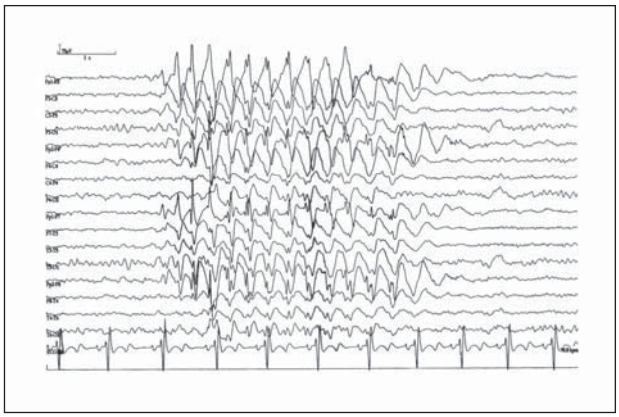

Fig 2. Twelve year-old female adolescent with recent onset of GTCS and myoclonic jerks. EEC shows generalized, irregular, 3.5 Hz spike-and-wave and polyspike-and-wave complexes, with frontocentral predominance. She is currently well controlled on VPA+LTG.

Fig 1 shows a chronologic sequence of the three epileptic seizure types in JME.

Precipitating factors of epileptic seizures are varied, and the most often one is sleep deprivation, reported in 58.3-89.5% of cases[6,7]. Other triggers that have been identified include fatigue (73.7%), photosensitivity (36.8%), menses (24.1%), mental concentration (22.8%), and stress, excitement, or frustration (12.3%)[7]. Alcohol ingestion was also found to be a precipitating factor in 51.2% of cases[21].

PSYCHIATRIC EVALUATION

In a study[23], 49% of JME patients were diagnosed with psychiatric disorders. Anxiety (46.9%) and mood (38,7%) disorders were most frequently observed, and generalized anxiety and major depression were the most common in each group, respectively. Personality disorders were detected in 20 patients and included, in decreasing order of frequency, histrionic, passive-aggressive, *borderline*, dependent, and obsessive-compulsive personalities. On the other hand, it is important to acknowledge the potential contribution of AEDs in patients with a predisposition to psychiatric disorders[23].

ELECTROENCEPHALOGRAPHY

Patients with JME typically present with an EEG that has a background rhythm within the limits of normal[2]. However, the presence of moderately excessive theta activity and/or alpha rhythm slowness have been described in 28 individuals[7]. Interictal findings include bursts of generalized and irregular spike-and-waves and polyspike-and-waves, in a frequency of 3-5 Hz and frontocentral dominance[24] (Fig 2). The polyspikes are not necessarily followed by slow waves. These bursts may be fragmentary and are usually confined to the frontal regions[24].

The typical ictal EEG of a myoclonic seizure displays the pattern of polyspike-and-wave, which consists of a group of 5 to 20 generalized, almost always symmetrical and high frequency (10-16 Hz) spikes, usually followed by slow waves in a frequency of 2,5-5 Hz[2,24,25]. The onset and maximal voltage are seen in the frontocentral regions, then spreading to the parietal, temporal, and occipital regions[2]. This finding may be present in 22.2% to 51.4% of patients[6,19,21].

The myoclonic jerk occurs simultaneously with the

polyspike-and-wave pattern, but the latter continues beyond the termination of the jerk, and may persist for several seconds[24]. There appears to be a correlation between the number of spikes in a given complex and the severity of the associated myoclonic seizure[2].

However, other patterns may be observed in ictal EEGs. The main alternative pattern is generalized and irregular spike-and-wave (3-5 Hz), reported among 25.2-78.4% of cases[6,19]. In addition, the clinician may find slow sharp waves, bursts of slow waves, groups of sharp waves, groups of spikes, and a fast rhythm[25].

Focal discharges were more frequent in the frontal regions[19,25]. They may be isolated spikes, sharp waves, slow waves, or spike-and-wave complexes[7,16,21]. Asymmetry of the recording was found in 9.8-33.3% of cases[1,19,21], and its frequency was increased in EEGs with sleep deprivation[25].

Hyperventilation made the EEG abnormalities more obvious in all patients that were analyzed by Panayiotopoulos et al[7]. Besides, photic stimulation produced a paroxysmal response in 30-40% of patients[1]. Sousa et al[25] assessed the effect of sleep deprivation, which increased the EEG sensitivity in 73.3%, increased three-fold the global index of discharges, and prolonged their duration.

NEUROIMAGING STUDIES

JME usually causes no abnormalities in neuroimaging studies[4,6,26]. However, recently developed neuroimaging techniques have detected structural abnormalities. An increase in cortical gray matter was identified in mesial frontal lobes[16,26], frontobasal regions, and anterior portion of the thalamus[26]. Magnetic resonance spectroscopy found a reduced N-acetylaspartate in the temporal lobe[16].

DIFFERENTIAL DIAGNOSIS

Epilepsy with generalized tonic-clonic seizures on awakening and juvenile absence epilepsy rank high in the list of differential diagnoses[2]. Both may present all three seizure types that are common in JME, however in different proportions, which may disguise the correct diagnosis[2]. Other epilepsies that should be considered are absences with eyelid myoclonias and epilepsy with myoclonic absences[1].

Although rare, the progressive myoclonic epilepsies, such as Unverricht-Lundborg disease and Lafora disease, should be ruled out. They usually affect patients in a similar age range, but they also include neurologic deficits, worsening of myoclonic seizures, and a slow background rhythm in the EEG[2].

Other causes of myoclonias should be included in JME's differential diagnosis, such as hypnagogic myoclonia - a normal phenomenon[16] - and acquired forms of myoclonic jerks, which may be associated with post-anoxia and lipid storage disease[1].

TREATMENT

JME treatment is based on AEDs and control of precipitating factors[1]. As JME is a lifelong disorder, its treatment should be continued indefinitely, otherwise recurrences are rather frequent, occurring within a variable period of months to years after AED discontinuation[2]; seizure recurrence may even lead to status epilepticus[1].

Given JME high prevalence, it is surprising that there is no randomized controlled clinical trial assessing its initial monotherapy[27]. Based on anecdotal clinical experience and case series, VPA was established as the first-choice AED[27]. It controls all three seizure types in 85% of cases[2]. A good therapeutic response occurs even in patients who have a significant family history[28]. Some studies reported a favorable response in adult patients that were treated with VPA dosages as low as 500 mg per day, and a double-blind crossover study found no significant difference in seizure frequency between 1000 mg or 2000 mg daily of VPA[29]. A reasonable approach may be to start with a single daily dosage after dinner of 500 mg with an extended-release VPA formulation and then adjusting it to response, but increasing daily dosage to 2000 mg does not improve seizure control[1,32]. VPA therapy may be limited by adverse effects or by drug interactions, as VPA inhibits uridine diphosphate-glucuronosyltransferase and cytochrome P450 isoenzymes[1]. In addition, a subgroup of patients that are refractory to VPA has been identified[30]. Independent clinical factors thought to be involved in inadequate control of epileptic seizures were the coexistence of all three seizure types and the presence of psychiatric disorders[30].

When a patient does not respond to VPA, the 2004 *National Institute for Health and Clinical Excellence* (NICE) guidelines suggest lamotrigine (LTG) as the first choice. Second choice AEDs include clobazam, levetiracetam, and topiramate[31].

LTG may be able to accomplish remission of epileptic seizures, however there are also reports of worsening of myoclonic seizures and GTCS[1,32], primarily at higher doses[31]. Combination therapy with VPA+LTG appears to have a synergistic effect, but one should be aware of the possibility of the patient developing a severe skin rash[32].

Clobazam has long been used in the treatment of partial and generalized epilepsies[31]. Among 16 female

patients that had intolerable adverse effects to VPA, substitution of clobazam for VPA as monotherapy gained control of epileptic seizures in nine (56.3%), yet clobazam is more frequently prescribed as adjunctive therapy[33].

Levetiracetam is an alternative to VPA due to its low incidence of adverse effects and lack of known drug interactions[1]. Response rate for myoclonias was 58.3% versus 23.3% for placebo, and 80% of cases were reported to be free of epileptic seizures[32].

Topiramate therapy during one year was able to control GTCS in 62.5% of patients and myoclonic jerks in 68.8%, although 13.6% had an increase in frequency of absence seizures[34].

Clonazepam may also be utilized[4], as it helps to control myoclonic jerks in association with VPA, although it has a lesser effect on GTCS[1,32]. It is considered to be a sound option as an add-on medication during epileptic seizure exacerbations, however its prolonged use is inappropriate in the long run given its sedative effect and tachyphylaxis[1].

Carbamazepine and phenytoin may worsen myoclonic seizures[1]. Other AEDs that should no be used include gabapentin, tiagabine, and vigabatrin[1,32].

CONCLUSION

JME is a common yet underdiagnosed epileptic syndrome. The clinician should inquire a patient suspected with epilepsy regarding the occurrence of myoclonic jerks and, in addition, he or she should consider atypical presentations, otherwise JME diagnosis might be omitted. Its etiology is still surrounded by many unsolved issues, however recent advances in genetic and neuroimaging studies will be helpful to clarify JME's physiopathogenesis.

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