REVIEW

Juvenile myoclonic epilepsy: under-appreciated and under-diagnosed

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Juvenile myoclonic epilepsy (JME) is a hereditary, idiopathic, generalised epilepsy and is found in 5%–11% of patients with epilepsy. It is characterised by myoclonic jerks, occasional generalised tonic-clonic seizures, and sometimes absence seizures. JME continues to be under-appreciated and under-diagnosed. Accurate diagnosis is important as it usually responds well to treatment with appropriate anticonvulsants and misdiagnosis often results in unnecessary morbidity. In addition lifelong therapy is usually indicated as the natural history is one of relapse off treatment, even after a prolonged seizure-free period.

In 1822, "myoclonus" was described as "a symptom associated with epilepsy" by Pritchard.[1] Delasiave in 1854 termed it "petit mal moteur". In 1867, Herpin gave the first detailed description of a patient with juvenile myoclonic epilepsy (JME) calling the myoclonic jerks "secousses". In 1881, Gowers classified the jerks among the generalised "auras" and considered them to be epileptic. Unvericht described progressive myoclonic epilepsy in 1901 but failed to recognise the existence of more benign variants. In 1957, Janz and Christian published their article on 47 patients with "impulsive petit mal". Lund in 1975 introduced the term JME and this term was soon admitted into the international classification system thereafter.

DEFINITION

The original description by Janz and Christian distills the essential clinical features of this syndrome: "[epilepsy with] impulsive petit mal appears around puberty and is characterised 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 [generalised tonic-clonic seizures] and infrequent absences. The seizures usually occur after awakening and are often precipitated by sleep deprivation. Interictal and ictal EEG [electroencephalogram(s)] have rapid generalised, 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".[2]

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AETIOPATHOGENESIS

JME is an inherited disorder, but the exact mode of inheritance is not clear. There is a positive family history in 50% of cases or less. One study has confirmed a causative role of EJM1 in the pathogenesis of idiopathic generalised seizures in the majority of German families of JME patients. This study has refined a candidate region of 10.1 cM in the chromosomal region 6p21 between the flanking loci HLA-DQ and D6s1019.[3] However, some studies have revealed controversial results and genetic heterogeneity is suspected. Linkage to chromosome 15 has at most a minor role in JME.[4]

Few studies have focused on pathological findings in the brain of JME patients. Some studies suggest that microdysgenesis occurs more frequently in epileptic patients with idiopathic generalised epilepsy; if so, its pathological significance is unknown.[5]

CLINICAL FEATURES

JME may be responsible for about 10% of all epilepsies; exact figures may be higher as it is still an under-diagnosed syndrome. Studies show similar prevalence in males and females.[6] We commonly see patients with a non-specific diagnosis of a "seizure disorder" for many years before a definitive diagnosis is reached.

Eighty percent of patients with JME begin having seizures between ages 12 and 18 with a mean age of onset of 14.6 years. The mean age of onset for GTCS is 15.5 years, absence seizures 11.5 years, and myoclonic seizures 15.4 years.[7] Earlier onset is seen in photosensitive patients. Absence seizures typically begin between ages 5 and 16 years. Myoclonic jerks follow between one and nine years later followed by GTCS a few months later. Approximately 3%–8% of childhood absence epilepsies evolve into JME.

The most important element in the diagnosis of JME is the history. JME is still under-diagnosed because of lack of awareness of the syndrome by doctors who fail to ask patients about the occurrence of myoclonic jerks and about precipitating factors.[8] Atypical EEG findings in some patients also contribute to the misdiagnosis of patients with JME.[9] Myoclonic jerks are seen in 100% of cases of JME and are the *sine qua non* of diagnosis. They occur as the only seizure type in about 3%–5% of JME patients. Myoclonic jerks

Abbreviations: EEG, electroencephalogram; GTCS, generalised tonic-clonic seizures; JME, juvenile myoclonic epilepsy; MRI, magnetic resonance imaging

are characterised by short, bilateral, and usually symmetric synchronous muscle contractions predominantly involving the shoulders and arms. They can be single or repetitive and they are usually arrhythmic. The amplitude and the force of the jerks vary. Some jerks occur unilaterally. Sometimes myoclonic seizures of JME are perceived only as a subjective electric shock sensation inside the body. It is important to note that consciousness is preserved. Common symptoms used to describe myoclonic jerks are shakes, clumsiness, twitches, and nervousness. Patients may not volunteer information about their myoclonus unless specifically asked. Sometimes, the myoclonus is noticed only by the patient's family. GTCS occur in 90%–95% of patients with JME. GTCS are often preceded by a few minutes of generalised mild to moderate myoclonus of increasing frequency and intensity. GTCS occurring in JME are often characterised by lack of sensory aura, symmetry, remarkable violence, and a long duration of the tonic phase. They occur predominantly after awakening. Some patients may describe a brief dizziness or a funny sensation in the head beforehand.

Absence seizures are a feature in 40% of patients. These seizures are relatively infrequent, brief, and not associated with automatisms. They may occur several times a day without circadian variation. Severity is age dependent with absence seizures of later onset (>10 years) being less severe. Seizures of JME are often precipitated by sleep deprivation, fatigue, emotional stress, menses, and moderate to heavy intake of alcohol. They tend to occur just after morning awakening. Thirty to forty percent of patients with JME are photosensitive. Seizures are precipitated by flashing strobe lights or flickering sunlight (for example, through a line of trees) in patients with photosensitivity. Drugs such as cocaine and amitryptiline, which reduce the seizure threshold can precipitate seizures of JME. Physical examination is usually normal. Intelligence is preserved.

INVESTIGATIONS

An interictal EEG from a sleep deprived patient characteristically shows discharges of diffuse bilaterally symmetrical and synchronous 4–6 Hz polyspike and wave complexes lasting between 0.5–10 seconds; these may be predominantly seen over the frontocentral region. The resting awake EEG background activity shows normal alpha rhythm. Continuous video-EEG monitoring reveals 10–16 Hz polyspike discharges often associated with myoclonic jerks. These may be preceded by asymptomatic spike and wave activity and often are followed by 1–3 Hz slow waves. The number of spikes range from 5–20 and is evidently more closely related to the intensity than to the duration of the jerks. Absence seizures are associated with 3 Hz spike and wave activity. Intermittent photic stimulation frequently precipitates spike and wave pattern more so in females than males. Subtle focal abnormalities may be seen in 30%–50% of JME patients.[10] These may present as focal slow waves, spikes, or sharp waves or a focal onset of a generalised discharge. If clinical and EEG data are consistent with JME, there is no need for imaging. High resolution magnetic resonance imaging (MRI) is normal in patients with JME. It may be reasonable to obtain MRI in those with refractory JME.

Electrophysiological studies have shown higher P25 and N33 amplitudes in somatosensory evoked potentials.[11] Voxel based analysis MRI data are only a research tool at present. Some studies using this technique have shown abnormal cerebral structure in JME with involvement of mesiofrontal cortical structures.[12] Magnetic resonance spectroscopy studies show reduced frontal lobe concentration of *N*-acetyl aspartate in JME, which may suggest prefrontal neuronal dysfunction in JME.[13] Positron emission tomography studies indicate that patients with JME may have cortical disorganisation that affects both the epileptogenic potential and frontal lobe cognitive functioning.[14] Such patients may exhibit abnormal patterns of cortical activation that are associated with subtle cognitive dysfunction. However, magnetic resonance spectroscopy and positron emission tomography studies are currently only research tools.

Learning points

- JME is an idiopathic generalised epilepsy characterised by myoclonic jerks, generalised tonic-clonic seizures, and sometimes absence seizures.
- JME is frequently under-diagnosed and under-appreciated.
- Myoclonic jerks are seen in 100% cases of JME and are the *sine qua non* of diagnosis.
- JME responds to treatment with sodium valproate. Newer broad spectrum drugs such as topiramate, and possibly levetiracetam, may also be of benefit.
- Lifelong treatment is needed.

DIFFERENTIAL DIAGNOSIS

JME should be distinguished from hypnagogic myoclonus, which is a normal phenomenon. The progressive myoclonic epilepsies are symptomatic generalised epilepsies which are characterised by progressive neurological deterioration, dementia, and ataxia. Epilepsy with grand mal seizures upon awakening is an important condition that should be considered in the differential diagnosis. This syndrome is closely related to JME, but myoclonic seizures are not present. Non-epileptic seizures may sometimes resemble seizures of JME.

MANAGEMENT

The goal of pharmacological management is to render the individual seizure-free without side effects of the medication. Sodium valproate has traditionally been the drug of choice. Eighty five to ninety percent of patients with JME become seizure-free with valproate monotherapy. All patients with JME require lifelong treatment because seizures invariably return after withdrawal of therapy. Absence seizures alone may be treated with ethosuximide. Myoclonic jerks respond well to clonazepam. Primidone, vigabatrin, gabapentin, and tiagabine have been unsuccessful in treatment of JME. Phenytoin and carbamazepine have shown to aggravate the myoclonic and absence seizures of JME and therefore should be avoided.[15] The response to lamotrigine has shown unpredictable results.[16 17] Topiramate appears to be of benefit in JME, and levetericetam is currently being investigated.[18 19] Vagal nerve stimulation has been used as in refractory JME.[20] JME is difficult to treat in about 15% of patients. The predictors of pharmacoresistance include (1) the coexistence of all three seizure types (myoclonic jerks, absence seizures, and GTCS) and (2) the existence of associated psychiatric problems.[21]

Precipitating factors for seizures should be avoided. These include avoiding moderate to heavy consumption of alcohol, fatigue, and photosensitising lights. Patients should be encouraged to develop regular sleeping habits. Advice regarding driving restrictions, working at height, and supervised swimming is appropriate. During pregnancy, the risks of discontinuing treatment outweigh the benefits. The importance of pre-pregnancy counselling and the addition of folic acid is an essential part of management in women of childbearing potential.

PROGNOSIS

Although JME has been described as a benign condition, it should be borne in mind that any condition that places the patient at risk for GTCS increases morbidity and mortality.

Failure to diagnose the condition increases the patient's morbidity. All patients require lifelong treatment. As mentioned, patients with JME are at increased risk of relapse if treatment is discontinued.

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