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Juvenile myoclonic epilepsy refractory to treatment in a tertiary referral center

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ABSTRACT

Introduction: Juvenile myoclonic epilepsy (JME) is an epileptic syndrome often regarded as one in which seizures are relatively easy to control. Individuals with JME, however, often require lifelong therapy to remain seizure-free, and a few have refractory epilepsy. We ascertained a population with JME and characterized a subgroup with refractory epilepsy.
Material and methods: We audited and reviewed clinical records of individuals diagnosed with JME identified via a sample of 6600 individuals in a clinical database from a specialized epilepsy clinic at a tertiary referral center.
Results: We identified 240 people with a diagnosis of JME (146 females), with a mean age at seizure onset of 14.2 years (SD: 4.5), and a mean age at diagnosis of 15.6 years (SD: 4.9). Clinical phenotypes seen were classic JME phenotype (88%), childhood absence epilepsy evolving into JME (6%), JME with adolescent absences (4%), and JME with astatic seizures (2%). More than a quarter (28%) had a family history of epilepsy. The most commonly used antiepileptic drug (AED) was sodium valproate in 78% of individuals, followed by levetiracetam (64%) and lamotrigine (55%). In the previous year, 47.5% were seizure-free. Using the International League against Epilepsy (ILAE) definitions and considering National Institute for Health and Care Excellence (NICE)-recommended AEDs for this syndrome, 121 individuals (50.4%) were identified as having refractory epilepsy.
Discussion: Juvenile myoclonic epilepsy is often regarded as a benign epileptic syndrome, but in this setting, half of the individuals with JME have refractory epilepsy with only about a quarter of those seizure-free in the previous year. Despite some advances in the understanding of this syndrome, there is still much to do before we can offer all the best outcomes.

1. Introduction

The International League against Epilepsy (ILAE) [1] fully recognized juvenile myoclonic epilepsy (JME) in 1985, almost 120 years after the first clinical report [2] and 30 years after it was described [3]. Juvenile myoclonic epilepsy is defined by the ILAE [4] as an epilepsy syndrome, a subgroup of genetic generalized epilepsies (GGE), characterized by myoclonic jerks (MJ), which occur in a fully conscious state and predominate in the upper limbs, usually on awakening. Absence and generalized tonic–clonic seizures (GTCS) may occur in 50–80% of individuals. In 2013, an international experts panel proposed two sets of criteria for JME diagnosis [5], both relying on a clear history of myoclonic jerks predominantly after awakening and an electroencephalograph (EEG) with generalized epileptiform discharges supporting a diagnosis of idiopathic generalized epilepsy (Box 1). Clinical phenotypes in JME were reported in the first descriptions [6–8], but only later [9] was a classification proposed with four subgroups: classic JME, childhood absence epilepsy (CAE) evolving to JME, JME with adolescent absence, and JME with astatic seizures (see Box 1).

Seizures in JME are often regarded as relatively easy to control. However, individuals frequently require lifelong therapy to remain seizure-free. A few present with refractory epilepsy, defined by the ILAE as failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to attain sustained seizure freedom [10]. The UK National Institute for Health and Care Excellence (NICE) guidelines on the diagnosis and management of epilepsies [11] included recommendations for the pharmacological treatment of JME. Sodium valproate was recommended as first-line treatment, and lamotrigine, levetiracetam, and topiramate were considered first-line if sodium valproate was unsuitable or not tolerable. If first-line treatments were

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Box 1
Juvenile myoclonic epilepsy (JME) diagnostic criteria and clinical phenotypes.

Diagnostic criteria for JME (adapted from Kasteleijn-Nolst Trenité DG et al, Epilepsy Behav 2013 [5])	
Class I	1. Myoclonic jerks without loss of consciousness repeatedly occurring on awakening, i.e., within 2 h after awakening 2. EEG (routine, sleep, or sleep deprivation) that shows normal background and ictal generalized high amplitude polyspikes (and waves) with concomitant myoclonic jerks 3. Normal intelligence 4. Age at onset of between 10 and 25 years
Class II	1. Myoclonic jerks predominantly occurring on awakening 2. Myoclonic jerks facilitated by sleep deprivation and stress and provoked by visual stimuli and praxis or GTCSs preceded by myoclonic jerks 3. EEG shows a normal background and at least once interictal generalized spike or poly-spike and waves with some asymmetry allowed with or without myoclonic jerks 4. No mental retardation or deterioration 5. Age at onset of between 6 and 25 years

JME clinical phenotypes (adapted from Martínez-Juárez IE et al, Brain 2005 [9])	
Classic JME	Adolescence onset of myoclonic, tonic-clonic and clonic-tonic-clonic seizures with or without rare-to-infrequent absences and an EEG with 4–6 Hz polyspike-wave complexes
CAE evolving to JME	Onset with absences with 3–4 Hz spike and wave complexes before aged 12 and then developed JME
JME with adolescent absence	Onset with absences with 3–5 Hz spike and polyspike and wave complexes aged 12 or older mixed with JME
JME with astatic seizures	Astatic seizures mixed with JME

ineffective or not tolerated, lamotrigine, levetiracetam, sodium valproate, or topiramate should be offered as adjunctive treatment. If adjunctive treatment is ineffective or not tolerated, clobazam, clonazepam, or zonisamide should be considered. Lastly, the guidelines emphasize that the use of carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin should be avoided as they may aggravate seizures.

We audited a large subsample of people with epilepsy at a tertiary epilepsy center to identify those with JME with a special focus on the treatment used and to assess adherence to the NICE guidelines.

2. Material and methods

We performed a registered clinical audit to identify individuals with JME and to assess adherence to NICE guidelines regarding their treatment. We identified 1078 people with GGE from a subsample of 6600 individuals with epilepsy using an outpatient registry from the epilepsy clinic at the National Hospital for Neurology and Neurosurgery in London and the Chalfont Center in Chalfont St. Peter. We then reviewed individual records to identify those with JME according to the ILAE definition [4]. Those Those who had failled two appropriate AEDs on the grounds of efficacy were considered refractory. Clinical and demographic data collected included sex, age at seizure onset, age at diagnosis, coexisting seizure types, seizure facilitators, clinical phenotypes (according to the 2006 [9] classification), past medical history, and family history of epilepsy. Where available, EEG findings, brain imaging (magnetic resonance imaging [MRI]), and neuropsychological and psychiatric evaluations were reviewed. Only one EEG was considered per individual; whenever more than one was present, we considered the one most supportive of the diagnosis. Intermittent photostimulation was performed in all, but only few had sleep-deprived recordings. Current and past treatments were reviewed along with seizure control over the previous years, allowing for identification of people with a refractory seizures.

Data processing and statistical analysis were performed with Microsoft Excel 2013® and IBM SPSS (Statistical Package for the Social Sciences) V22.0®. Demographic and clinical characteristics were compared between the group with refractory seizures and the group with nonrefractory seizures using the 2-tailed, Wilcoxon rank-sum test for continuous variables with a non-normal distribution and the Fisher exact test for categorical variables. A p value of <0.05 was considered as statistically significant. No correction for multiple comparisons was performed as these were not considered in view of the small number of multiple comparisons.

3. Results

We identified 1078 people diagnosed with GGE, 240 of whom met the criteria for JME and were included. Demographic and clinical characteristics are summarized in Table 1. Using the ILAE definition and NICE-recommended AEDs for this syndrome, 121 individuals (50.4%) were identified as having refractory epilepsy. Table 2 characterizes and compares the group with refractory seizures and the group with nonrefractory seizures. The difference between the mean age at seizure onset and at diagnosis suggests a similar diagnostic delay of 1.4 years in both groups. Seizure types coexisting with myoclonus were convulsive seizures in 237 people (99%), absences in 98 (41%), and astatic seizures in 5 (2%).

Clinical phenotypes are described in Tables 1 and 2, with the majority (88%) having classic JME, especially in the group with nonrefractory seizures (96%). Other phenotypes were more prevalent in the group with refractory seizures. Sleep deprivation was described as a seizure precipitant by 102 people (43%), alcohol consumption by 44 (18%), photosensitivity by 33 (14%), and stress by 41 (17%). A family history of epilepsy was present in 67 people (28%), including in 38 first-degree relatives, 3 of which had JME.

Typical EEG findings were found in 192 people (80%), with photosensitivity present in 39 (20%). Normal EEG results were recorded in