ILAE Definition of the Idiopathic Generalized Epilepsy Syndromes: Position Statement by the ILAE Task Force on Nosology and Definitions

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Summary

In 2017, the ILAE Classification of Epilepsies described the “Genetic Generalized Epilepsies” (GGE), which contained the “Idiopathic Generalized Epilepsies” (IGEs). The goal of this paper is to delineate the syndromes that comprise the IGEs in 2021. We provide updated diagnostic criteria for the 4 syndromes comprising the IGEs determined by experts’ consensus opinion of the ILAE’s Nosology and Definitions Taskforce (2017-2021). We incorporate current knowledge from recent advances in genetics, imaging and EEG studies, together with current terminology and classification of seizures and epilepsies. The IGEs are comprised of 4 syndromes, Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy and Epilepsy with Generalized Tonic-Clonic Seizures Alone. Patients that do not fulfill criteria for one of these syndromes, but that have one, or a combination, of the following generalized seizure types: absence, myoclonic, tonic-clonic and myoclonic-tonic-clonic seizures, with 2.5-5.5 Hz generalized spike wave should be classified as having GGE. Recognizing the IGEs as a special grouping amongst the GGEs, encompassing the 4 entities (CAE, JAE, JME and GTCA), is helpful as they carry prognostic and therapeutic implications.

Introduction

The IGEs have historically included the syndromes Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME) and Generalized Tonic-Clonic Seizures Alone (GTCA).

The 2017 ILAE classification suggested that the term Genetic Generalized Epilepsies (GGEs) be used for the broad group of epilepsies with generalized seizure types and generalized spike-wave, based on a presumed genetic etiology arising from twin and family research study data. It suggested that the term IGE could be reserved for the above four syndromes. Our Nosology Task Force acknowledges that, the group of GGEs is broad, and includes a variety of common and rare genetic generalized epilepsy syndromes, that GGEs and IGEs are overlapping but not synonymous, and recognition of the IGEs as a distinct subgroup of the GGEs remains helpful as they carry prognostic and therapeutic implications. Thus, these four syndromes (CAE, JAE, JME and GTCA) continue to be regarded as a special group under the umbrella term IGEs, This term invokes the historical context from which they have emerged and the presumed genetic basis drawn from decades of clinical genetic research. Figure 1 illustrates how the IGEs fall within the larger group of GGEs. We acknowledge that distinction between
the four IGE syndromes is not always straightforward, as there is clinical overlap between them and, to some extent, a small degree of overlap between some of the other GGE syndromes (Figure 1).

We provide updated diagnostic criteria for the IGEs determined by a rigorous process to obtain expert consensus opinion of the ILAE’s Nosology and Definitions Taskforce (2017-2021). Details regarding methodology are found in the paper by Wirrell et al.¹. Criteria for each syndrome were achieved using a Delphi methodology, surveying all Task Force members and external recognized epilepsy “syndromology” experts. We incorporate current knowledge from rapid advances in genetics, imaging and EEG studies, together with current terminology and classification of seizures and epilepsies²⁴. As the term GGEs includes other syndromes beyond the IGEs, such as Epilepsy with Myoclonic Absences and Epilepsy with Eyelid Myoclonia, this paper focuses only on the four IGE syndromes.

Clinical description

Information on each of the specific IGE syndromes can be found below. Tables 1 and 2 compare and contrast CAE and JAE, and JME and GTCA, respectively. The section below focuses on clinical characteristics common to all IGEs.

Epidemiology

The estimated proportion of IGE amongst persons with epilepsy is 15-20%⁵. Population-based studies of new-onset epilepsy in children and adolescents have found that 23-43% have generalized epilepsy⁶, and of these, 53-58% have one of the IGE syndromes⁷⁸. IGE syndromes differ in their age of onset, which typically ranges from 3-25 years (see below for each syndrome). Rarely, onset can occur as late as 40 years⁹¹⁰; onset after this age is exceptional. Although response to antiseizure medications (ASMs) and need for long-term therapy varies within individual syndromes, the IGE syndromes are usually drug-responsive, with about 80% of the IGEs responding to appropriate ASMs (appropriate refers to the use of “broad spectrum” ASMs that target generalized seizure types, but specific drug therapy is beyond the scope of this article). For generalized tonic-clonic seizures, valproate may be particularly useful but should be used in caution in women of childbearing age¹¹¹². Importantly, certain ASMs, particularly sodium channel blockers and GABAergic agents, including carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, tiagabine and vigabatrin typically exacerbate
seizures in IGE, and may even provoke absence or myoclonic status epilepticus and this history may provide a clue to diagnosis. However, the IGE syndromes differ in their likelihood to remit, and the age of remission. Patients may sometimes evolve from one IGE syndrome to another.

Seizure types

Patients with IGE will experience one, or a combination, of the following generalized seizure types: absence, myoclonic, tonic-clonic and myoclonic-tonic-clonic seizures. Generalized tonic-clonic seizures may have focal or asymmetric features such as head and eye deviation or version (only if it occurs after loss of awareness) and myoclonic seizures may be focal or asymmetric. Photosensitivity occurs in a subset of patients with IGE.

Generalized tonic, atonic, myoclonic-atonic, focal seizures and epileptic spasms exclude a diagnosis of IGE.

EEG

The EEG shows the classical finding of generalized spike-wave discharges, typically 2.5-5.5 Hz, which is often brought out during drowsiness, sleep, and on awakening. Discharges often appear fragmented during sleep and can have focal features. However, consistent focal spikes or focal slowing should not occur.

A photoparoxysmal response may occur with intermittent photic stimulation in a minority of patients with IGE, although photosensitivity is also seen in specific genetic developmental and epileptic encephalopathies (DEEs) and occipital epilepsies. Hyperventilation often triggers generalized spike-wave discharges. Appropriate ASMs may abolish generalized spike-wave discharges at appropriate doses.

A normal routine EEG does not exclude a diagnosis of IGE in the setting of convincing clinical evidence (i.e. a good description of myoclonic seizures with appropriate age of onset). In such cases, a sleep-deprived or prolonged EEG recording may elicit generalized spike-wave discharges. The EEG background is normal for age.

Comorbidities

Mood disorders, anxiety, ADHD and learning disorders are often seen. However, the IGEs are not associated with intellectual disability or DEEs.

Genetics
Clinical research studies of twins and families show that the IGEs have a genetic basis\textsuperscript{18, 19}. Monozygotic twins are highly concordant with 100% concordance for the EEG trait of generalized spike-wave activity and 70% concordance for seizures\textsuperscript{20, 21}. Despite clinical genetic evidence, the search for genes for the IGEs has been slow to yield pathogenic variants. In a small proportion of cases, monogenic causes have been identified. Examples include several GABA receptor subunit genes (eg. \textit{GABRG2}, \textit{GABRA1})\textsuperscript{22, 23} and the gene encoding glucose transporter 1 (\textit{SLC2A1})\textsuperscript{24}. Both inherited and \textit{de novo} mutations occur; in the latter, the family history is negative and in the former, the family history may show incomplete penetrance with unaffected individuals carrying the pathogenic variant. For a long time, complex inheritance has thought to underpin the IGEs, which means they are likely to have a polygenic basis, with or without a contribution from environmental factors.

Although a family history of epilepsy associated with generalized seizures is supportive, it is most common for patients with IGE not to have a family history of epilepsy. This is explicable by either a \textit{de novo} mutation or complex inheritance. Thus, the term ‘genetic’ refers to the cause and does not mean inherited, an important distinction which is often misconstrued\textsuperscript{4}.

Recurrent copy number variants, such as microdeletions and microduplications, occur in 3% of patients with IGE\textsuperscript{25, 26}. They are likely to contribute to the aetiology of these disorders, rather than be wholly causative. They can be familial or arise \textit{de novo}, and substantially increase the risk of IGE\textsuperscript{27}. Patients with mild intellectual disability may present with IGE syndromes; in this group, copy number variants occur in about 10% of patients\textsuperscript{28}.

\textbf{Other GGEs exist that may resemble, but are not part of the IGEs}

There remain many patients who do not fit into one of the IGEs yet have generalized spike-wave on EEG and generalized seizure types. These include patients with recognized syndromes such as Myoclonic Epilepsy in Infancy, Epilepsy with Eyelid Myoclonia, Epilepsy with Myoclonic Absences and Myoclonic-Atonic Epilepsy. There are also many patients who do not fit neatly into a recognized epilepsy syndrome but have GGE, such as an intellectually normal 4-year old child with afebrile generalized tonic-clonic seizures alone and generalized spike-wave on EEG. These patients should be classified as GGE without a specific epilepsy syndrome.

\textbf{Childhood Absence Epilepsy (Table 3)}
Childhood Absence Epilepsy (CAE) occurs in an otherwise normal child with daily absence seizures associated with 2.5 - 4 Hz generalized spike-wave at seizure onset. Absence seizures are provoked by hyperventilation. Neurological examination is normal. Development and cognition are typically normal. Attention deficit hyperactivity disorder (ADHD) and learning difficulties may occur. Seizures are brief but may occur in clusters. Epilepsy remits in 60% of children, often within two years of onset or by early adolescence.

**Epidemiology**

The incidence of CAE is approximately 6.3-8.0 children per 100,000 per year\(^{29-31}\). It accounts for approximately 18% of epilepsy in school-aged children\(^{32}\).

**Clinical Context**

Age at onset is typically 4-10 years (range: 2-13 years)\(^{33-35}\). In children with onset at age 10 and older, the distinction between CAE and JAE depends on the frequency of absence seizures. Where typical absence seizures occur frequently, at least daily or more in the untreated state, a diagnosis of CAE is more likely. EEG features may help in distinguishing CAE from JAE. CAE is more common in girls (60-75% cases)\(^{33}\). A history of febrile seizures is present in 10-15% of children\(^{36-38}\). Development is typically normal although children with CAE may have specific learning difficulties and ADHD; both may be subtle and easily missed. Neurological examination and head size are normal.

While CAE may occur in individuals with intellectual disability, in such cases, investigations, including genetic testing to exclude other etiologies should be considered. In cases with onset of absence seizures under 4 years, a diagnosis of glucose transporter 1 deficiency disorder (associated with \(SLC2A1\) pathogenic variants) is found in 10% of patients\(^{24, 39, 40}\).

**Natural History**

CAE is typically drug-responsive. CAE remits by early adolescence in 60% of patients\(^{33-35, 41}\). In the remainder, patients may evolve into other IGE syndromes.

**Seizure Types**

Typical absence seizures have sudden onset of impaired awareness, with staring, loss of facial expression, interruption of activity, with or without oral and manual automatisms, and immediate return to normal activity, although children may be momentarily confused as they reorient themselves. Duration is typically 3-20 seconds, but rarely they may last more than 30
seconds\textsuperscript{42-46}. Incontinence and loss of postural control can be seen. Seizures typically occur multiple times per day but are often under-recognized.

Generalized tonic-clonic seizures rarely precede or occur during the period of frequent absence seizures in childhood. More commonly, they begin in adolescence, often after resolution of absence seizures, and may herald evolution to another IGE syndrome (eg. JME, JAE, GTCA)\textsuperscript{33}.

Myoclonic seizures, other than subtle myoclonus occurring during an absence seizure are not seen in CAE. Prominent myoclonus during absence (ratcheting up of both upper limbs with tonic posturing) should suggest a rare seizure type, myoclonic absences, which are seen in the syndrome Epilepsy with Myoclonic Absences.

\textbf{EEG}

The background is normal. Occipital intermittent rhythmic delta activity (OIRDA) occurs in 21-30\% of children with childhood absence epilepsy\textsuperscript{42, 47}, at a frequency of 2.5-4 Hz and may have a notched appearance. Paroxysms of 3 Hz (range 2.5-4 Hz) generalized spike-wave are seen which may become fragmented in sleep. Fragmented generalized spike-wave can appear focal or multi-focal but is not consistently seen in one area. The morphology of the focal spike-wave is similar to the generalized spike-wave. Polyspike-wave may be seen in drowsiness and sleep only, but not during wakefulness\textsuperscript{43, 48}. Intermittent photic stimulation triggers generalized spike-wave in 21\% of individuals\textsuperscript{43}.

Ictal EEG is characterized by regular 3 Hz (range 2.5-4 Hz) generalized spike-wave in the first second of seizure onset with absence seizures (Figure 2). Disorganized discharges, defined by brief (<1 second) or transient interruptions in the ictal rhythm, or waveforms of different frequency or morphology are significantly less common than in JAE\textsuperscript{43}. Generalized spike-wave and absence seizures are both provoked by hyperventilation in most untreated patients. Slow spike-wave (< 2.5Hz) is not seen. If an untreated child performs hyperventilation well for three minutes and no generalized spike-wave is seen, childhood absence epilepsy can be excluded.

\textbf{Imaging}

Neuroimaging is normal and is not indicated in typical CAE. It should be considered if there are atypical features of CAE, if seizures are drug-resistant, or if there is persistent focal slowing on EEG.
**Genetics**

Genetic testing is not part of current routine diagnostic evaluation. Clinical genetic studies, such as twin studies, have shown that CAE has a strong genetic component\textsuperscript{18-20}. Only a few genes conferring risk for CAE are known (eg. \textit{GABRG2}, \textit{GABRA1}, \textit{SLC2A1}) and also some recurrent copy number variants (eg. 15p13.3 microdeletion)\textsuperscript{22-26, 39}. Testing should be considered if absence seizures begin under 4 years (eg. \textit{SLC2A1} testing), if there are atypical features such as intellectual disability, movement disorders, or drug resistance, or if there is a strong family history of seizures\textsuperscript{39}.

**Other Investigations**

In typical cases, no other investigations are needed. If onset is $<$4 years or there are atypical features such as intellectual disability or movement disorder, then a diagnosis of Glucose transporter 1 deficiency should be considered. This can be identified most rapidly by hypoglycorrachia (absolute low fasting CSF glucose) or by \textit{SLC2A1} mutational analysis.

**Differential diagnoses**

**Other Epilepsies:**

1. Epilepsy with Eyelid Myoclonia is characterized by absence seizures with repetitive, rhythmic, fast jerks of the eyelids, upward deviation of the eyeballs and subtle head extension; seizures are often induced by eye closure, sunlight and photic stimulation.

2. Epilepsy with Myoclonic Absences has absence seizures with 3 Hz myoclonic jerks of the upper limbs with progressive elevation (ratcheting up) of the arms.

3. Other Generalized Epilepsies with Atypical absence: Atypical Absences are often associated with more prolonged loss of awareness, more subtle onset and offset, and slow generalized spike-wave. They usually occur in the context of a DEE such as Lennox-Gastaut syndrome.

4. Juvenile Absence Epilepsy typically begins after 10 years of age, with less frequent absences (less than daily), more subtle loss of awareness, higher risk of generalized tonic-clonic seizures and absence status epilepticus. The regularity and frequency of the generalized spike-wave discharges may help to distinguish CAE from JAE.
5. Focal impaired awareness seizures are often distinguished by preceding aura, more prolonged duration of unresponsive staring (often >30 seconds), hyperkinetic phenomena and postictal features including confusion, drowsiness and headache. EEG shows focal epileptiform discharge.

Non-epileptic disorders:

1. Daydreaming
2. Inattention
3. Ocular tics

Juvenile Absence Epilepsy (Table 4)

Juvenile Absence Epilepsy (JAE) is characterized by absence seizures that typically occur less than daily in the untreated state and are associated with ≥3 Hz (range 3-5.5.5 Hz) generalized spike-wave in an otherwise normal adolescent. Generalized tonic-clonic seizures are seen in more than 90% of cases, most commonly beginning shortly after onset of absence seizures. Neurological examination is normal. Development and cognition are typically normal although ADHD and learning difficulties may occur. While seizures may be controlled with antiseizure medications, lifelong treatment is typically required.

Epidemiology:

JAE is less common than CAE, accounting for 2.4-3.1% of new-onset epilepsy in children and adolescents\(^7,8\).

Clinical context:

Typical age at onset is between 9-13 years, with a range of 8-20 years. Exceptional cases may present in adult life\(^10,41\). In cases with onset below 9 years of age, the distinction between JAE and CAE can be difficult (Table 1). Distinguishing features include the older age at onset and lower frequency of absence seizures in JAE. EEG features are similar however OIRDA is not seen and generalized discharges may be of slightly higher frequency and more irregular in JAE.

Development and cognition prior to presentation are typically normal. A history of febrile seizures is seen in between 6-33% of cases\(^19,49\). Significant cognitive impairment should suggest an alternate diagnosis.
Natural History

JAE is often drug responsive but lifelong in the majority of cases. Ethosuximide as monotherapy is not recommended due to the high likelihood of generalized tonic-clonic seizures. Broad spectrum ASMs for generalized epilepsies should be used.

Persons with JAE have higher rates of ADHD and learning problems, even if seizures are well controlled.

Seizure Types

Absence seizures are mandatory. They have abrupt onset of impaired awareness, staring with loss of facial expression, interruption of activity, with/without oral automatisms, and immediate return to normal activity (Figure 3). Loss of awareness is often less complete than in childhood absence epilepsy. During absence seizures with incomplete loss of awareness, the person may be able to respond to commands but has difficulty doing complex tasks. Typical duration is 5-30 seconds, with occasional longer seizures. Frequency is typically less than daily. Subtle myoclonus may be seen during an absence seizure.

Absence status epilepticus occurs in approximately 20% of patients.

Generalized tonic-clonic seizures occur in more than 90% of cases. They usually begin after onset of absences, but in 14-27% of cases, may precede absences. The frequency of generalized tonic-clonic seizures is variable.

Myoclonic seizures are exclusionary, with the exception of subtle myoclonus occurring during an absence seizure. Independent myoclonic jerks, particularly in the morning or with sleep deprivation, should suggest Juvenile Myoclonic Epilepsy. Prominent myoclonus during an absence seizure would suggest Epilepsy with Myoclonic Absences. Prominent eyelid myoclonia during absence should suggest Epilepsy with Eyelid Myoclonia.

Other seizure types are not expected in JAE. Staring spells lasting >30 seconds or with postictal impairment should suggest focal impaired awareness seizures.

EEG

Interictal:

The background is normal. Paroxysms of generalized spike-wave at a usual frequency of 3-4 Hz (range 3-5.5 Hz) are seen which may become fragmented in sleep. Fragmented generalized spike-wave can appear focal or multi-focal but usually is not consistently seen in one area, and morphology is similar to the generalized spike-wave. Generalized discharges are
enhanced by sleep deprivation both in awake and sleep recordings. Discharges are more frequent in JAE than CAE\textsuperscript{44}. Polyspike-wave is seen predominantly in drowsiness and sleep\textsuperscript{43, 48}.

In untreated patients, hyperventilation provokes absence seizures in approximately 87\% of cases\textsuperscript{43}. Where hyperventilation is performed well for three minutes and no generalized spike-wave is seen, absence seizures are unlikely. Intermittent photic stimulation triggers generalized spike-wave in 25\% of individuals\textsuperscript{43, 44}. Slow spike-wave (<2.5 Hz) is not seen.

**Ictal:**

Generalized spike-wave at > 3-5.5 Hz occurs at onset of absence seizures\textsuperscript{43, 44} (Figure 3). Disorganized discharges are eight times more common in JAE than CAE\textsuperscript{43}. If a staring spell occurs without EEG correlate, an absence seizure can be ruled out for that event. The EEG during generalized tonic-clonic seizures is similar to that seen with GTC alone (see below).

**Neuroimaging:**

*Neuroimaging* is normal. If the clinical presentation and EEG is typical for JAE and there are no atypical features, imaging is not required. However, imaging should be considered if atypical features of JAE or drug-resistant seizures are present, or in the presence of persistent focal slowing on EEG.

**Genetic studies:**

Genetic studies are not part of the current routine diagnostic evaluation. A family history is occasionally present, with affected family members typically having IGE\textsuperscript{19}. Clinical genetic studies, such as twin studies, have shown that JAE has a strong genetic component which significantly overlaps with CAE\textsuperscript{57}.

The pattern of inheritance is “complex” which means it is usually due to “polygenic inheritance” with or without environmental factors, although rare monogenic causes exist. Genes conferring risk for this syndrome include *GABRG2, GABRA1, CACNA1A* and *SLC2A1* and others\textsuperscript{22-26, 28, 39}. Testing should be considered when atypical features such as intellectual disability or drug resistance are present. Significant cognitive impairment should suggest an alternate diagnosis.

**Metabolic or other laboratory studies.**

No other laboratory studies are required or suggested.
Differential diagnoses

Other Epilepsies:

1. Childhood absence epilepsy typically begins at a younger age with daily absence seizures and has a lower risk of generalized tonic-clonic seizures.
2. Juvenile Myoclonic Epilepsy is distinguished by the presence of myoclonic seizures, which are essential in JME and do not occur in JAE.
3. Epilepsy with Eyelid Myoclonia should be considered if there is repetitive, regular or irregular, fast >4 Hz jerking (fluttering) of the eyelids, with upward deviation of the eyeballs and head extension; seizures are often very frequent and induced by eye closure and photic environmental stimuli (photosensitivity is universal).
4. Epilepsy with Myoclonic Absences should be considered with 3 Hz myoclonic jerks of the upper limbs with progressive elevation (ratcheting up) of the arms during absence seizures.
5. Epilepsy with Generalized Tonic-Clonic seizures Alone lacks absence seizures.
6. Focal impaired awareness seizures are usually distinguished by preceding aura, longer duration of unresponsive staring (often >30 seconds) and postictal features including confusion, drowsiness and headache. EEG shows focal epileptiform discharge.

Nonepileptic disorders

1. Daydreaming
2. Inattention
3. Ocular tics

Juvenile Myoclonic Epilepsy (Table 5)

Juvenile myoclonic epilepsy (JME) is the most common adolescent and adult onset IGE syndrome and is characterized by myoclonic and generalized tonic-clonic seizures in an otherwise normal adolescent or adult. Myoclonic seizures typically occur shortly after waking and when tired. Sleep deprivation is an important provoking factor. The EEG shows >3-5.5 Hz generalized spike-wave and polyspike-wave. Photosensitivity is common, occurring in up to 90% of individuals with appropriate photic stimulation. Life-long treatment is usually required.
Epidemiology:

JME is common, with a prevalence ranging from 1-3 per 10,000 persons in population-based studies\(^5^8,^5^9\). It accounts for approximately 9.3% of all epilepsies\(^6^0\).

Clinical context

Typical age at onset is 10-24 years, range: 8-40 years. There is a slight female preponderance. Five to 15% of cases evolve from CAE to JME\(^3^3,^6^1\). If myoclonic seizures start before the age of 8 years, another diagnosis should be considered. A history of febrile seizures is seen in approximately 4-5% of patients\(^6^2,^6^3\).

Antenatal and birth history, and cognition are typically normal although impairments in specific cognitive domains (e.g. executive functions, attention, decision making) can be seen\(^6^4-^6^7\). Progressive decline in cognition after seizure onset should suggest a progressive myoclonic epilepsy. Rarely, JME can occur in individuals with mild intellectual disability, and in such cases, chromosomal microarray detects a recurrent microdeletion in approximately 10%\(^2^8\). There are also higher rates of anxiety and depression in patients with JME compared with the general population\(^6^6-^6^8\).

Natural History

Seizures in 67-92% of patients with JME are drug responsive when using appropriate antiseizure medications\(^6^9-^7^2\). A common seizure trigger is sleep deprivation. Myoclonic seizures may be more difficult to control than generalized tonic-clonic seizures. Sodium channel blockers such as carbamazepine, oxcarbazepine and phenytoin often aggravates myoclonic and absence seizures in JME\(^1^7,^7^3,^7^4\). Lamotrigine may aggravate myoclonic seizures in some patients\(^7^5-^7^7\).

JME is usually considered a lifelong disorder, often requiring lifelong therapy\(^1^2,^6^9,^7^0\). Occasional cases may successfully discontinue ASMs later in life\(^7^0,^7^2,^7^8,^7^9\).

Seizure Types

Myoclonic seizures are mandatory for diagnosis. They occur most commonly within the first hour after awakening and when the patient is tired. Patients may not recognize myoclonic jerks as seizures – they are frequently recognized retrospectively, after presentation with a generalized tonic-clonic seizure. Myoclonic status epilepticus can occur rarely\(^8^0,^8^1\).

Myoclonic seizures may be unilateral or bilateral. Myoclonic seizures can predominate on one side of the body, frequently involving the upper extremities. Myoclonic seizures can
also involve the lower limbs and cause falls. Myoclonic seizures can be reflex, triggered by photic stimulation or praxis. When myoclonic seizures are exclusively unilateral, consider focal epilepsy. If myoclonic seizures occur exclusively during reading, a diagnosis of Epilepsy with Reading Induced Seizures should be considered. Hypnic jerks that occur only during sleep are nonepileptic.

Generalized tonic-clonic seizures occur in >90% of individuals, these are often preceded by a series of myoclonic seizures that increase in frequency and severity resulting in a myoclonic-tonic-clonic seizure. These often occur on awakening or with sleep deprivation. The frequency of generalized tonic-clonic seizures is variable. Generalized tonic-clonic status epilepticus is uncommon. The occurrence of head deviation prior to alteration of awareness during a generalized tonic-clonic seizure should raise the possibility of focal epilepsy, however, head deviation after alteration of awareness is common in JME.

Absence seizures occur in one third of cases. These are brief (3-8 seconds), occurring less than daily, and have variable, but often subtle impairment of awareness (typically less severe than in childhood absence epilepsy). Absence status epilepticus may occur rarely. Focal seizures and generalized tonic or atonic seizures are exclusionary.

**EEG**

The background is normal. Generalized slowing is not seen, other than in the postictal period following a generalized tonic-clonic seizure.

Interictal:

Recording of generalized spike-wave activity, typically with generalized polyspike-wave, is mandatory for a definitive diagnosis, although the diagnosis can be strongly suspected on clinical grounds. Irregular, generalized polyspike-wave and spike-wave at a frequency of ≥3-5.5 Hz is seen in both wakefulness and sleep. Interictal epileptiform activity is brought out by sleep deprivation. In sleep, the discharges often fragment and can appear focal or multifocal, but usually are not consistently seen in one area. Focal or multi-focal spikes and spike-wave discharges can be observed in up to 20% of patients, mostly over the frontal regions, and may shift location from one record to the other. The morphology of the focal spike-wave appears similar to the generalized spike-wave. If focal slowing and focal spikes are consistently seen in one area, the possibility of focal epilepsy and a structural brain abnormality should be considered. Although a normal awake EEG can be seen in some untreated individuals with JME, further recording with sleep deprivation usually elicits generalized spike-wave activity.
A photo-paroxysmal response to intermittent photic stimulation is seen in over one third of cases and, with specialized testing, can be detected in up to 90% of untreated patients. Intermittent photic stimulation may induce myoclonic seizures, eyelid myoclonia and rarely, generalized tonic-clonic seizures.

Generalized spike-wave or polyspike-wave and clinical absence seizures may be provoked by hyperventilation.

**Ictal**

An ictal recording is not mandatory for diagnosis. Myoclonic seizures are associated with a generalized polyspike-wave discharge, with the spike concurrent with the actual jerk (Figure 4). Absence of a generalized spike-wave discharge associated with myoclonus is consistent with non-epileptic myoclonic jerks.

Absence seizures are associated with ≥3-5.5 Hz generalized polyspike-wave or generalized spike-wave discharge at seizure onset.

With generalized tonic-clonic seizures, the ictal EEG is often obscured by movement artifact. Generalized fast rhythmic spikes are seen in the tonic stage, which is followed by bursts of spikes and after-coming slow waves, synchronous with clonic jerks, during the clonic phase. A postictal period of irregular slow activity follows a generalized tonic-clonic seizure.

**Neuroimaging**

Neuroimaging is normal. If the clinical presentation and EEG are typical for JME and there are no atypical features, imaging is not required. However, imaging should be considered if atypical features of JME or drug-resistant seizures are present, or in the presence of persistent focal slowing on EEG.

**Genetic findings**

Genetic testing is not part of the current routine diagnostic evaluation. Clinical genetic studies, such as twin studies, have shown that JME has a strong genetic component. A family history is occasionally present - typically affected family members have an IGE syndrome, but not necessarily JME. Rare pathogenic variants have been reported in isolated patients in a range of genes including CACNB4, GABRA1, GABRD and EFHC1. The molecular findings to date have largely been for susceptibility alleles where the variant contributes to the epilepsy, but is not a
monogenic cause. Similarly, recurrent microdeletions, such as 15q13.3, 15q11.2 and 16p13.11 microdeletions, are susceptibility alleles for JME\textsuperscript{25-27}.

*Metabolic or other laboratory studies*

No other laboratory studies are indicated.

*Differential diagnoses*

*Other Epilepsies:*

1. Myoclonic Epilepsy in Infancy: onset of myoclonic seizures occurs prior to age 3 years.
2. Juvenile Absence Epilepsy: there are no myoclonic seizures.
3. Generalized tonic-clonic seizures alone: there are no other seizure types.
4. Epilepsy with Eyelid Myoclonia: consider if absence seizures with prominent eyelid myoclonia.
5. Epilepsy with Myoclonic Absences: myoclonic absences are not seen in JME.
6. Progressive Myoclonic Epilepsies: consider if there is cognitive decline, appearance of permanent, erratic, drug-resistant myoclonus, EEG background slowing and a photoparoxysmal response at low frequencies of photic stimulation (<3Hz).
7. Epilepsy with reading-induced seizures: consider if myoclonic jerks occur exclusively during reading.
8. Late-onset Lennox-Gastaut syndrome: consider if tonic seizures and/or generalized paroxysmal fast activity on EEG.
9. Focal epilepsy: consider if myoclonic or generalized tonic-clonic seizures have consistent focal features from seizure to seizure, or seizures consistently arise from sleep and not on awakening.
10. Familial Adult Myoclonic Epilepsy (FAME), also known as Adult Myoclonic Epilepsy with Cortical tremor: FAME resembles JME closely but is associated with prominent cortical tremor which is usually present, but varies in severity, often worsening with age and affects limbs, face and voice. This tremor is often misdiagnosed as iatrogenic secondary to valproate or lamotrigine. In addition to myoclonic seizures; GTCS are seen in 15% to 100% of individuals\textsuperscript{89}.

*Non-epileptic disorders* (ictal recordings lack EEG correlate):

1. Hypnic jerks commonly occur in sleep in healthy individuals.
2. Periodic limb movements during sleep (PLMs) are repetitive, highly stereotyped limb movements occurring during relaxed wakefulness (PLMW) or during sleep (PLMS).
Unlike JME, these movements are not seen during activity and are most prominent in the legs.

3. Propriospinal myoclonus is a rare condition seen in mid adulthood, with myoclonic activity arising in the relaxation period preceding sleep onset which causes severe insomnia\textsuperscript{90}. Myoclonic activity begins in spinally innervated muscles, propagating at low speed to rostral and caudal muscular segments. The jerks disappear during sleep.

4. Non epileptic jerks: Patients with psychogenic nonepileptic seizures, functional neurological disorders or movement disorders may also have jerks or twitches that are difficult to distinguish from myoclonic seizures\textsuperscript{91}.

5. Metabolic, Toxic, Neurodegenerative (Alzheimer) or Genetic (Trisomy 21) encephalopathies: These entities typically present with confusion, dementia and generalized or focal negative or positive myoclonus or a combination of these.

**Generalized Tonic-Clonic Seizures Alone (GTCA) (Table 6)**

This syndrome (originally called epilepsy with grand mal seizures on awakening) is a common IGE syndrome. Individuals have generalized tonic-clonic seizures of variable frequency which usually begin in the second or early third decade of life and are typically provoked by sleep deprivation. Other seizure types do not occur. The EEG shows $>$3-5.5 Hz generalized spike-wave or polyspike-wave discharge. Remission rate is low and life-long treatment is usually required.

**Epidemiology:**

Epidemiological data is limited, although in one study, GTCA accounted for one third of all adolescent-onset IGEs\textsuperscript{50}.

**Clinical Context:**

Typical age at onset is 10-25 years (80\% have their first tonic-clonic seizure in the second decade) with a range of 5-40 years. Seizure onset is on average about 2 years later than in JAE or JME\textsuperscript{50, 54}. There is no clear sex difference.

Birth and antecedent history are typically normal. A history of febrile seizures may be present. Cognition is typically normal however impairments in specific cognitive domains (e.g. executive function, attention, decision making) may be seen. There are also higher rates of anxiety and depression. Although GTCA can occur in individuals with intellectual disability,
in such cases, investigations, including genetic testing to exclude specific etiologies should be considered.

Course of Illness

Seizures are typically infrequent, sometimes yearly or less. Treatment is often required for life. Sleep deprivation, fatigue and alcohol lower the patient’s seizure threshold\(^2\). Seizures are usually drug-responsive\(^2\).

Seizure Types

Generalized tonic-clonic seizures are mandatory for this epilepsy syndrome. These often occur within 2 hours of awakening but can also be seen at other times in both awake and sleep states.

Other seizure types such as absence or myoclonic seizures are exclusionary and should prompt consideration of another IGE syndrome (eg JAE, JME).

EEG

The EEG background is normal. Generalized slowing is only seen in the postictal period. Focal slowing seen consistently over one area should suggest a structural brain abnormality.

Interictal:

Generalized spike-wave or polyspike-wave at \(\geq 3\)-5.5 Hz is seen, with 50% of patients only showing these abnormalities in sleep. A photo-paroxysmal response may be seen. In sleep, the discharges often fragment and can appear focal or multi-focal, but usually are not consistently seen in one region. The interictal epileptiform activity is enhanced by sleep deprivation. Fragments of focal spike-wave may rarely be seen consistently in one area, however in such cases, focal epilepsy should be considered. Slow spike-wave (<2.5 Hz) is not seen.

Ictal:

With generalized tonic-clonic seizures, the ictal EEG is often obscured by artifact. Generalized fast rhythmic spikes are seen in the tonic stage. Bursts of spikes and after-coming slow waves may occur synchronously with clonic jerks. A postictal period of irregular slowing may be seen.

Neuroimaging
Neuroimaging is normal. If the clinical presentation and EEG is typical, imaging is not required. However, imaging should be considered with atypical features, drug-resistant seizures or with persistent focal slowing on EEG.

Genetic studies

Genetic testing is not part of the current routine diagnostic evaluation. A first degree family history of epilepsy is present in approximately 12% of cases in one study. As with all the IGEs, family members with epilepsy typically have an IGE or GGE syndrome. If seizures are drug-resistant, a chromosomal microarray should be performed to look for recurrent copy number variants.

Metabolic or other lab studies

No other lab studies are required or suggested.

Differential diagnoses

Other Epilepsies:

1. Juvenile Myoclonic Epilepsy is distinguished by a history of myoclonic seizures.
2. Juvenile Absence Epilepsy is differentiated by a history of absence seizures.
3. Febrile Seizures Plus: should be considered when there is a past history of febrile seizures that continue past the age of 6 years, with or without afebrile tonic-clonic seizures.

Non-epileptic disorders (ictal EEG recordings lack epileptiform activity)

1. Psychogenic non-epileptic seizures are one of the most common mimickers of generalized convulsive seizures. Clues that suggest PNES include preserved consciousness, out-of-phase limb movements, absence of whole body rigidity throughout the episode, pelvic thrusting, side-to-side head and body turning and a fluctuating course.
2. Syncope with motor phenomena: brief tonic and clonic activity can be mistaken for a tonic-clonic seizure, but can be differentiated based on context, and brevity with rapid resolution. Tongue biting is rare in syncope but urinary incontinence occasionally occurs.

Discussion
The word “idiopathic” derives from the Greek term “idios” and refers to self, own, and personal and is meant to infer a genetic etiology. In the 1989 Proposal for Revised Classification of the Epilepsies, the term *idiopathic* was used to describe disorders “not preceded or occasioned by another”, and where there was no underlying cause other than a possible hereditary predisposition. The 1989 Proposal however included several more syndromes, which are no longer considered to be part of the IGEs. The 2017 Classification Commission suggested that the term “genetic” was more precise than “idiopathic”. However they acknowledged that the term IGE continued to have clinical utility. Our Nosology Task Force confirms that the IGEs should be exclusively limited to group the four common syndromes CAE, JAE, JME and GTCA, and that this is a special subgroup of the Genetic Generalized Epilepsies (Figure 1).

These four syndromes differ from each other by age at onset and predominant seizure type. There is however overlap with indistinct boundaries between the IGE syndromes, with respect to age of onset and seizure types. Patients may evolve from one of the IGE syndromes to another, such as CAE evolving to JME.

We recognize that, at times, other GGE syndromes and GEFS+ may resemble the IGEs. Epilepsy syndromes such as Epilepsy with Myoclonic Absences and Epilepsy with Eyelid Myoclonia also have generalized spike-wave activity, but have specific seizure types which are not part of the four IGEs, and while they may occur in the setting of normal intellect, have higher association with intellectual disability.

**Conclusion**

Recognition of the IGEs is important for clinical care as it informs diagnosis, prevents unnecessary investigations, allows optimal selection of antiseizure medications and provides prognostic guidance. It also enables identification of a relatively homogeneous group of patients for clinical research and antiseizure therapy trials. There has been some debate regarding how the terms IGE and GGE should be used. Here we clearly define that the IGEs are a distinctive subgroup within the GGEs, and the term IGE should be explicitly confined to the four syndromes, CAE, JAE, JME and GTCA.
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We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.
Figure 1: Concept of Genetic Generalized Epilepsy versus Idiopathic Generalized Epilepsy

The IGEs are a specific subgroup of Genetic Generalized Epilepsies, comprised solely of CAE, JAE, JME and GTCA. In addition to the IGEs, Genetic Generalized Epilepsies include (1) individuals with generalized seizure types and generalized 2.5-5.5 spike-wave discharge on EEG who do not meet criteria for a specific syndrome, and (2) syndromes which have genetic overlap with the IGE syndromes but may also, at times, be associated with DEEs, such as Myoclonic-Atonic Epilepsy, Epilepsy with Myoclonic Absences and Epilepsy with Eyelid Myoclonia; other syndromes such as Myoclonic Epilepsy in Infancy are more consistent with a generalized epilepsy which may have a developmental encephalopathy (ie. intellectual disability). Additionally, certain cases of GEFS+, with only generalized seizure types could be classified as GGEs, but individuals with GEFS+ and focal seizures would not be included. The triangles denote individuals with generalized epilepsies and developmental delay/intellectual disability (dark blue) and those with DEEs (light blue). The distinction between these two groups is that patients with DEEs have developmental slowing or regression with frequent epileptiform activity on EEG and/or frequent seizures.
**Figure 2:** Typical absence seizure in a 7-year-old girl, with bilateral synchronous spike-wave (frontal maximal amplitude). The regularity and frequency at onset (3.5 Hz) and duration (7 seconds) is consistent with CAE.
Figure 3: Typical absence seizure in a 12-year-old boy. The irregularity and frequency at onset (4 Hz) and duration (10-11 seconds) of discharge is most consistent with JAE.
Figure 4A and B: Interictal discharge in an 18-year-old girl with a history of a single generalized tonic-clonic seizure and myoclonic seizures showing generalized polyspike and wave (Figure 4A). The ictal EEG demonstrating generalized poly-spike-wave discharge, with bilateral symmetric limb jerks (Figure 4B). This clinical history and EEG are most suggestive of JME.
Table 1: Features seen in Childhood and Juvenile Absence Epilepsy

<table>
<thead>
<tr>
<th>Feature</th>
<th>Childhood Absence Epilepsy (CAE)</th>
<th>Juvenile Absence Epilepsy (JAE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Usual</td>
<td>4-10 years</td>
<td>9-13 years</td>
</tr>
<tr>
<td>-Range</td>
<td>2-13 (caution if diagnosing &lt;4 years of age)</td>
<td>8-20 years – exceptional cases may present in adulthood</td>
</tr>
<tr>
<td>Development</td>
<td>Typically normal, but may have learning difficulties or ADHD</td>
<td>Typically normal, but may have learning difficulties or ADHD</td>
</tr>
<tr>
<td>Absences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Frequency</td>
<td>At least daily to multiple per day but may be under-recognized by family</td>
<td>Less than daily</td>
</tr>
<tr>
<td>-Duration</td>
<td>Typical duration 3-20 seconds</td>
<td>Typical duration 5-30 seconds</td>
</tr>
<tr>
<td>-Impaired awareness</td>
<td>Severe loss of awareness</td>
<td>Less complete impairment of awareness</td>
</tr>
<tr>
<td>Other seizure types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Febrile</td>
<td>Occasional</td>
<td>Occasional</td>
</tr>
<tr>
<td>-Generalized tonic clonic seizure</td>
<td>Rarely precede or occur during period of frequent absences but may occur later with evolution to other IGE syndrome</td>
<td>May precede and commonly occur during the period of frequent absences</td>
</tr>
<tr>
<td>-Myoclonic</td>
<td>Prominent myoclonus exclusionary</td>
<td>Prominent myoclonus exclusionary</td>
</tr>
<tr>
<td>EEG Background</td>
<td>OIRDA in 21%</td>
<td>Normal</td>
</tr>
<tr>
<td>Epileptiform discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Awake</td>
<td>2.5-4 Hz generalized spike-wave</td>
<td>3-5.5 Hz generalized spike-wave</td>
</tr>
<tr>
<td>-Asleep</td>
<td>Polyspike and wave may be seen in drowsiness and sleep only</td>
<td>Polyspike and wave may be seen in drowsiness and sleep only</td>
</tr>
<tr>
<td>-Irregular generalized spike-wave</td>
<td>Uncommon</td>
<td>More common than CAE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discharges are more frequent than in CAE</td>
</tr>
<tr>
<td>Photoparoxysmal response</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>IPS triggers generalized spike-wave in 15% but does not induce seizures</td>
<td>IPS triggers generalized spike-wave in 25% but does not induce seizures</td>
</tr>
<tr>
<td>Hyperventilation induction</td>
<td>87%</td>
<td>87%</td>
</tr>
<tr>
<td>Ictal EEG</td>
<td>Regular 2.5-4 Hz generalized spike-wave</td>
<td>Regular 3-5.5 Hz generalized spike-wave</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td></td>
<td>If no generalized spike-wave is seen with hyperventilation x 3 minutes in an untreated patient, CAE can be excluded</td>
<td>If no generalized spike-wave is seen with hyperventilation x 3 minutes in an untreated patient, JAE can be excluded</td>
</tr>
<tr>
<td></td>
<td>Disorganized discharges less frequent</td>
<td>Disorganized discharges 8x more frequent than CAE</td>
</tr>
</tbody>
</table>

Disorganized discharges are defined as either brief (<1 second) and transient interruptions in ictal rhythm or waveforms of different frequency or morphology during the ictal rhythm.

ADHD: Attention deficit hyperactivity disorder

OIRDA: Occipital intermittent rhythmic delta activity

IPS: Intermittent photic stimulation
Table 2: Features seen in Juvenile Myoclonic Epilepsy and Epilepsy with Generalized Tonic Clonic Seizures Alone

<table>
<thead>
<tr>
<th></th>
<th>Juvenile Myoclonic Epilepsy (JME)</th>
<th>Generalized Tonic-Clonic Seizures Alone (GTCA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>10-24 years</td>
<td>10-25 years</td>
</tr>
<tr>
<td>-Usual</td>
<td>8-40 years</td>
<td>5-40 years</td>
</tr>
<tr>
<td>Development</td>
<td>Typically normal but may have learning disorder or ADHD</td>
<td>Typically normal but may have learning disorder or ADHD</td>
</tr>
<tr>
<td>Main seizure type</td>
<td>Myoclonic seizures, seen predominantly on awakening</td>
<td>Generalized tonic-clonic seizures typically within 2 hours of awakening</td>
</tr>
<tr>
<td>Other seizure types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Febrile seizures</td>
<td>May occur in approximately 15%</td>
<td>May occur in approximately 15%</td>
</tr>
<tr>
<td></td>
<td>Generalized tonic-clonic seizures in &gt;90% which are often preceded by myoclonic jerks (myoclonic-tonic-clonic), and often occur on awakening</td>
<td>Absence or myoclonic seizures are not present</td>
</tr>
<tr>
<td></td>
<td>Absence seizures in 33% - typically brief (3-8 seconds), infrequent (&lt;daily) and with variable impairment of awareness</td>
<td></td>
</tr>
<tr>
<td>Triggers</td>
<td>Sleep deprivation</td>
<td>Sleep deprivation</td>
</tr>
<tr>
<td></td>
<td>Photic stimulation</td>
<td></td>
</tr>
<tr>
<td>EEG Background</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Epileptiform Discharges</td>
<td>Irregular, generalized 3-5.5 Hz spike-wave and polyspike-wave seen in all states May fragment in sleep</td>
<td>Generalized 3-5.5 Hz spike-wave or polyspike-wave, which may be seen only in sleep May fragment in sleep</td>
</tr>
<tr>
<td>Photoparoxsomal response</td>
<td>Seen in 33% and may trigger myoclonic jerks or generalized myoclonic-tonic-clonic seizures</td>
<td>May be seen</td>
</tr>
<tr>
<td>Hypeventilation induction</td>
<td>33% have hyperventilation-induced generalized spike-wave discharge but rarely induces absence seizures</td>
<td>May be seen</td>
</tr>
<tr>
<td>Ictal EEG</td>
<td>Disorganized discharges 110 fold more common in absences with JME than CAE Generalized polyspike-wave with myoclonic jerks 3.5-6 Hz generalized spike-wave or polyspike-wave with absences Generalized spikes with tonic phase of generalized tonic-clonic seizure followed by spike-wave during clonic phase – but often obscured by muscle artifact</td>
<td>Generalized spikes with tonic phase followed by spike-wave during clonic phase – but often obscured by muscle artifact</td>
</tr>
</tbody>
</table>

ADHD: Attention deficit hyperactivity disorder
Table 3: Diagnostic Criteria for Childhood Absence Epilepsy

<table>
<thead>
<tr>
<th></th>
<th>Mandatory</th>
<th>Alerts</th>
<th>Exclusionary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seizures</strong></td>
<td>Typical absence seizures</td>
<td>GTCS prior to or during the period of frequent absence seizures</td>
<td>Any of the following seizure types:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Staring spells with typical duration &gt;30 seconds or with postictal confusion or fatigue</td>
<td>• Prominent myoclonic seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absences occurring &lt;daily in an untreated patient</td>
<td>• Prominent eyelid myoclonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Myoclonic-absence seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Atonic seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Tonic Seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Atypical absence seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Focal impaired awareness seizures</td>
</tr>
<tr>
<td><strong>EEG</strong></td>
<td>Paroxysms of 2.5-4 Hz GSW (may have been obtained historically)</td>
<td>Consistently unilateral focal spikes</td>
<td>Diffuse background slowing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of HV activated 2.5-4 Hz GSW in untreated patient who performs HV well for 3 minutes or longer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recording a typical staring spell without EEG correlate in a child with a history of 2.5-4 Hz generalized spike-wave</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persistent slowing of the EEG background in the absence of sedating medication</td>
<td></td>
</tr>
<tr>
<td><strong>Age at onset</strong></td>
<td>2-3 or 11-13 years at onset</td>
<td>&lt;2 or ≥13 years</td>
<td></td>
</tr>
<tr>
<td><strong>Development at onset</strong></td>
<td>Mild intellectual disability</td>
<td>Moderate to profound intellectual disability</td>
<td></td>
</tr>
<tr>
<td><strong>Neurological exam</strong></td>
<td>Potentially relevant neurological examination abnormalities, excluding incidental findings (see text)</td>
<td>Potentialy relevant neurological examination abnormalities, excluding incidental findings (see text)</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td>Cognitive stagnation or decline</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>Potentially relevant abnormal neuroimaging, excluding incidental findings (see text)</td>
<td>Low CSF glucose and/or SLC2A1 pathogenic variant (testing not needed in most cases but strongly recommended in children with onset &lt;3 years, with microcephaly and/or intellectual disability)</td>
<td></td>
</tr>
</tbody>
</table>

**Are MRI or ictal EEG required for diagnosis?**

An MRI is not required for diagnosis.

An ictal EEG is not required for diagnosis, provided the interictal study shows paroxysms of 2.5-3.5 Hz generalized spike wave discharge during wakefulness. However, most untreated patients will have a recorded absence seizure on routine EEG.

**Syndrome without laboratory confirmation:** In resource limited regions, CAE can be diagnosed in children without Alerts, who meet all other mandatory and exclusionary criteria if they have a witnessed typical absence seizure with hyperventilation.
Table 4: Diagnostic Criteria for Juvenile Absence Epilepsy

<table>
<thead>
<tr>
<th>Mandatory</th>
<th>Alerts</th>
<th>Exclusionary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>Typical absence seizures</td>
<td>Any of the following seizure types:</td>
</tr>
<tr>
<td></td>
<td>Staring spells with typical duration &gt;30 seconds</td>
<td>• Prominent myoclonic seizures</td>
</tr>
<tr>
<td></td>
<td>or with postictal confusion or fatigue</td>
<td>• Prominent eyelid myoclonia</td>
</tr>
<tr>
<td></td>
<td>Absence seizure frequency of greater</td>
<td>• Myoclonic-absence seizures</td>
</tr>
<tr>
<td></td>
<td>than 10 per day.</td>
<td>• Atonic seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tonic Seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Atypical absence seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Focal impaired awareness seizures</td>
</tr>
<tr>
<td>EEG</td>
<td>Paroxysms of 3-5.5 Hz GSW</td>
<td>Consistently unilateral focal spikes</td>
</tr>
<tr>
<td></td>
<td>(may have been obtained historically)</td>
<td>Diffuse background slowing</td>
</tr>
<tr>
<td></td>
<td>Lack of HV activated 3-5.5 Hz GSW in an untreated</td>
<td>Recorded typical staring spell without EEG correlate</td>
</tr>
<tr>
<td></td>
<td>patient who performs HV well for 3 minutes or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>longer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persistent EEG background slowing in the</td>
<td></td>
</tr>
<tr>
<td></td>
<td>absence of a sedating medication</td>
<td></td>
</tr>
<tr>
<td>Age at onset</td>
<td>&lt;8 or &gt;20 years</td>
<td></td>
</tr>
<tr>
<td>Development at onset</td>
<td>Mild intellectual disability</td>
<td>Moderate to profound intellectual disability</td>
</tr>
<tr>
<td>Neurological exam</td>
<td>Potentially relevant neurological examination</td>
<td>Cognitive stagnation or decline</td>
</tr>
<tr>
<td></td>
<td>abnormalities, excluding incidental findings</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Potentially relevant abnormal neuroimaging,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>excluding incidental findings (see text)</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>Low CSF glucose and/or SLC2A1 pathogenic variant</td>
<td></td>
</tr>
<tr>
<td>Other studies – genetics, etc</td>
<td>Lack of GTCS over course of the epilepsy, in the</td>
<td>(testing not needed in most cases but strongly recommended in those with microcephaly and/or mild</td>
</tr>
<tr>
<td></td>
<td>absence of treatment with antiseizure medications</td>
<td>intellectual disability)</td>
</tr>
<tr>
<td></td>
<td>which are effective for GTCS</td>
<td></td>
</tr>
</tbody>
</table>

Are MRI or ictal EEG required for diagnosis?

An MRI is not required for diagnosis.

An ictal EEG is not required for diagnosis, provided the interictal study shows paroxysms of 2.5-3.5 Hz generalized spike wave discharge during wakefulness. However, most untreated patients will have a recorded absence seizure on routine EEG.

Syndrome without laboratory confirmation: In resource limited regions, JAE can be diagnosed in persons without Alerts, who meet all other mandatory and exclusionary criteria if they have a witnessed typical absence seizure with hyperventilation.
<table>
<thead>
<tr>
<th><strong>Table 5: Diagnostic Criteria for Juvenile Myoclonic Epilepsy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mandatory</strong></td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
</tr>
<tr>
<td><strong>EEG</strong></td>
</tr>
<tr>
<td><strong>Age at onset</strong></td>
</tr>
<tr>
<td><strong>Development at onset</strong></td>
</tr>
<tr>
<td><strong>Neurological exam</strong></td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
</tr>
<tr>
<td><strong>Course of illness</strong></td>
</tr>
</tbody>
</table>

**Are MRI or ictal EEG required for diagnosis?**

- An MRI is not required for diagnosis.
- An ictal EEG is not required for diagnosis.

**Syndrome without laboratory confirmation:** In resource limited regions, JME can be diagnosed in persons without Alerts, who meet all other mandatory and exclusionary clinical criteria.
<table>
<thead>
<tr>
<th></th>
<th>Mandatory</th>
<th>Alerts</th>
<th>Exclusionary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seizures</strong></td>
<td>Generalized Tonic Clonic seizures (see text)</td>
<td></td>
<td>Generalized Myoclonic-Tonic-Clonic Seizure (suggests JME)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any other seizure type</td>
</tr>
<tr>
<td><strong>EEG</strong></td>
<td>≥3-5.5 Hz generalized spike-wave or polyspike-wave on EEG (may be obtained historically)</td>
<td></td>
<td>Focal slowing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consistently unilateral focal spikes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Generalized slow spike-wave at frequency &lt;2.5 Hz (unless it is at the end of a higher frequency burst)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diffuse background slowing that is not limited to the postictal period</td>
</tr>
<tr>
<td><strong>Age at onset</strong></td>
<td>Age at onset 5-9 years or 26-40 years</td>
<td>Age at onset &lt;5 years or &gt;40 years</td>
<td></td>
</tr>
<tr>
<td><strong>Development at onset</strong></td>
<td>Mild intellectual disability</td>
<td>Moderate to profound intellectual disability</td>
<td></td>
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<td><strong>Comorbidities</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>Potentially relevant abnormal neuroimaging, excluding incidental findings (see text)</td>
<td>Abnormal neuroimaging with causative lesion</td>
<td></td>
</tr>
<tr>
<td><strong>Course of illness</strong></td>
<td></td>
<td>Progressive cognitive decline</td>
<td></td>
</tr>
</tbody>
</table>

**Are MRI or ictal EEG required for diagnosis?**

An MRI is not required in every case but should be considered with Alerts or if clinical concern for a possible structural lesion exists.

An ictal EEG is not required for diagnosis.

**Syndrome without laboratory confirmation:** In resource limited regions, GTCA cannot be diagnosed without interictal EEG showing generalized spike wave, as one cannot exclude focal onset without EEG.
References


Cavazzuti GB. Epidemiology of different types of epilepsy in school age children of Modena, Italy. Epilepsia 1980 Feb;21:57-62.


