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SPECIAL REPORT

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

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Abstract

In 2017, the International League Against Epilepsy (ILAE) Classification of Epilepsies described the "genetic generalized epilepsies" (GGEs), which contained the "idiopathic generalized epilepsies" (IGEs). The goal of this paper is to delineate the four syndromes comprising the IGEs, namely childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic–clonic seizures alone. We provide updated diagnostic criteria for these IGE syndromes determined by the expert consensus opinion of the ILAE's Task Force on Nosology and Definitions (2017–2021) and international external experts outside our Task Force. We incorporate current knowledge from recent advances in genetic, imaging, and electroencephalographic studies, together with current terminology and classification of seizures and epilepsies. 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 these four IGE syndromes as a special grouping among the GGEs is helpful, as they carry prognostic and therapeutic implications.

KEYWORDS

absence seizures, childhood absence epilepsy, generalized tonic–clonic seizures, generalized tonic–clonic seizures alone, genetic generalized epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, myoclonic seizures

1 | INTRODUCTION

The idiopathic generalized epilepsies (IGEs) have historically included the syndromes childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic–clonic seizures alone (GTCA).

The 2017 International League Against Epilepsy (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 Task Force on Nosology and Definitions acknowledges that the group of GGEs is broad and includes a variety of common and rare genetic generalized epilepsy syndromes. We propose that the term IGE should pertain to a distinct subgroup of the GGEs, for the following reasons:

- They are the most common syndromes within the GGEs.
- They generally have a good prognosis for seizure control.
- They do not evolve to an epileptic encephalopathy.
- There is clinical overlap between CAE, JAE, and JME. They may evolve with age to another IGE syndrome (e.g., CAE evolving to JME).
- They have similar electroencephalographic (EEG) findings, including a normal background activity with

Key Points

- The IGEs include four syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic–clonic seizures alone
- The IGEs have polygenic inheritance, with or without environmental factors
- Development is typically normal; however, mood disorders, ADHD, and learning disabilities are common comorbidities
- Seizure types include one or a combination of the following: absence, myoclonic, tonic–clonic, and myoclonic–tonic–clonic seizures
- The EEG shows generalized 2.5–5.5-Hz spike-wave, which may be activated by hyperventilation or photic stimulation

2.5–6-Hz generalized spike-wave and/or polyspike-wave discharges that may activate with hyperventilation and photic stimulation.

The term IGE invokes the historical context from which these syndromes 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 these specific entities. Furthermore, there is overlap between IGE and non-IGE GGEs, as illustrated by higher rates of IGE syndromes in relatives of individuals with epilepsy with eyelid myoclonia, epilepsy with myoclonic absences, myoclonic epilepsy in infancy, epilepsy with myoclonic atonic seizures, and genetic epilepsy with febrile seizures plus.[1–6]

We provide updated diagnostic criteria for the IGEs determined by a rigorous process to obtain the expert consensus opinion of the ILAE's Task Force on Nosology and Definitions (2017–2021). Details regarding methodology are found in a paper by Wirrell et al.[7] Criteria for each syndrome were determined using a Delphi process, surveying all Task Force members and external recognized epilepsy syndromology experts. We incorporate current knowledge from rapid advances in genetic, imaging, and EEG studies, together with current terminology and classification of seizures and epilepsies.[8–10] 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.

1.1 | Clinical description

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.

1.2 | Epidemiology

IGE is a common group of epilepsies, accounting for approximately 15%–20% of persons with epilepsy.[11] Reliable data on the exact incidence of each syndrome are limited, as epilepsy syndromes may not be clearly defined, and the EEG may not be available.[11] Furthermore, as syndromes are age-dependent, reported incidence varies based on the age of the population studied. Population-based studies of new onset epilepsy in children and adolescents have found that 23%–43% have generalized epilepsy,[12] and of these, 53%–58% have one of the four IGE syndromes.[13,14] IGE syndromes differ in their age of onset, which typically ranges from 3 to 25 years (see below for each syndrome). Rarely, onset can occur as late as 40 years[15,16]; onset after this age is exceptional. Although response to antiseizure medications (ASMs) and need for long-term therapy vary within individual syndromes, the IGE syndromes are usually drug responsive, with about 80% responding to appropriate ASMs (appropriate refers to the use of "broad spectrum" ASMs that target generalized seizure types, or ethosuximide in the case of CAE, but specific drug therapy is beyond the scope of this article). For generalized tonic–clonic seizures, valproate may be particularly efficacious but should be used with caution in women of childbearing age.[17,18] Importantly, certain ASMs, particularly sodium channel blockers, including carbamazepine, oxcarbazepine, eslicarbazepine, and phenytoin (but not necessarily lamotrigine), and γ-aminobutyric acidergic (GABAergic) agents, such as tiagabine and vigabatrin, often exacerbate absence and myoclonic seizures in IGE (and may even provoke absence or myoclonic status epilepticus); this history may provide a clue to diagnosis.[19–23] 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.

1.3 | 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 as early manifestations focal or asymmetric features such as head and eye deviation or version, and myoclonic seizures may be

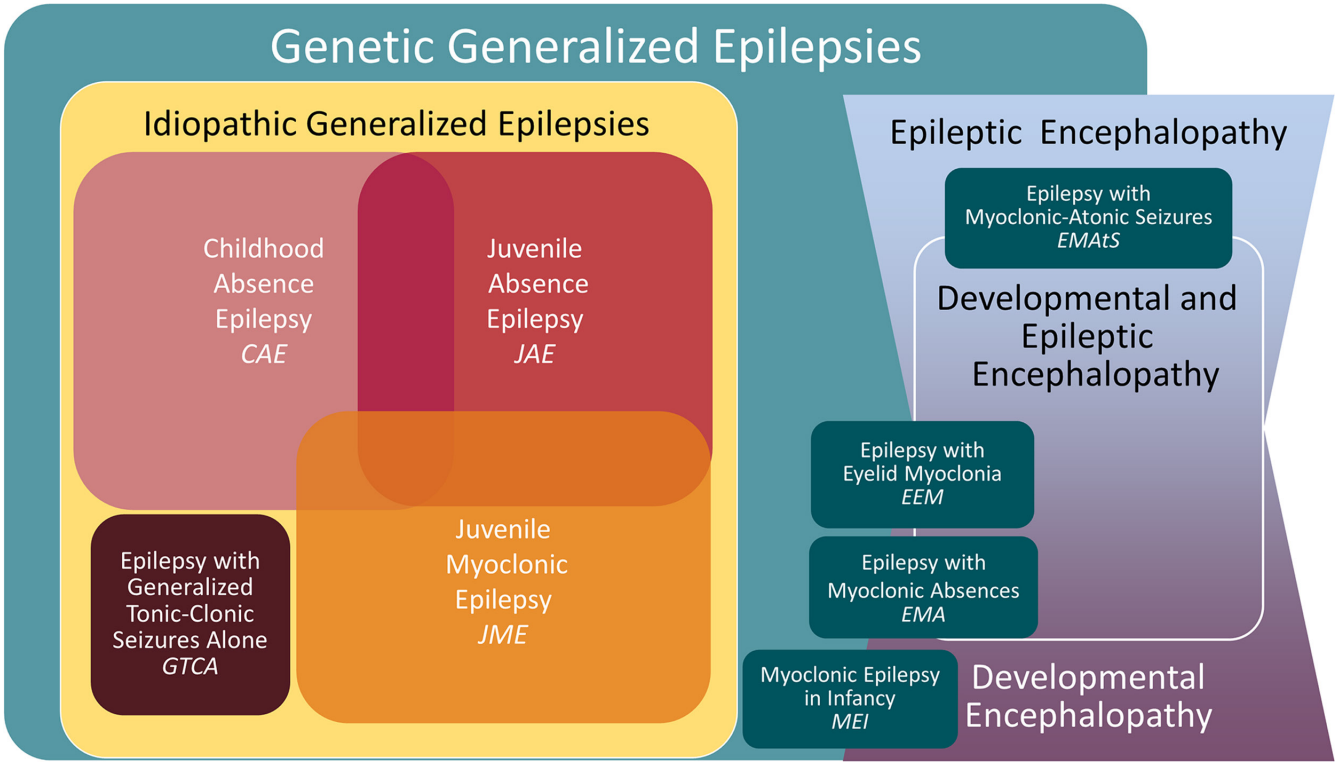

FIGURE 1 Concept of genetic generalized epilepsy versus idiopathic generalized epilepsy. The idiopathic generalized epilepsies (IGEs) are a subgroup of genetic generalized epilepsies (GGEs), comprised of the following four syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic–clonic seizures alone. These four syndromes may show some degree of overlap. In addition to the IGEs, GGEs include (1) individuals with generalized seizure types who do not meet criteria for a specific syndrome and (2) less common generalized epilepsy syndromes. These latter syndromes also have a genetic basis and may occur in the setting of normal intellect or intellectual disability. Some present with an epileptic encephalopathy such as epilepsy with myoclonic atonic seizures, whereas other syndromes, such as epilepsy with myoclonic absences and epilepsy with eyelid myoclonia, may be associated with a developmental and epileptic encephalopathy, an epileptic encephalopathy, or a developmental encephalopathy. Other syndromes such as myoclonic epilepsy in infancy may present as a generalized epilepsy in a child with a developmental encephalopathy (i.e., intellectual disability) or normal intellect

focal or asymmetric. Focal findings often shift sides from seizure to seizure. Photosensitivity occurs in a subset of patients with IGE.

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

1.4 | Electroencephalogram

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

A photoparoxysmal response occurs with intermittent photic stimulation in most untreated patients with JME and a minority of patients with CAE and JAE; however, this may depend on the methodology of intermittent photic stimulation applied.[24,25] Photosensitivity is also seen in specific genetic developmental and/or epileptic encephalopathies (DEEs) and occipital epilepsies. Hyperventilation often triggers generalized spike-wave discharges. Appropriate ASMs may abolish generalized spike-wave discharges at therapeutic 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 at onset). In such cases, a sleep-deprived or prolonged EEG recording may elicit generalized spike-wave discharges. The EEG background is normal for age.

1.5 | Comorbidities

Mood disorders, anxiety, attention-deficit/hyperactivity disorder (ADHD), and learning disorders are often seen,[26] although further research in this area is needed. The causes are likely multifactorial, including underlying neurobiological mechanisms leading to seizures, genetic

TABLE 1 Features seen in CAE and JAE

Feature	CAE	JAE
Age at onset		
Usual	4–10 years	9–13 years
Range	2–13; caution if diagnosing at <4 years of age	8–20 years; exceptional cases may present in adulthood
Development	Typically normal, but may have learning difficulties or ADHD	Typically normal, but may have learning difficulties or ADHD
Absences		
Frequency	At least daily to multiple per day but may be underrecognized by family	Less than daily
Duration	Typical duration = 3–20 s	Typical duration = 5–30 s
Impaired awareness	Severe loss of awareness	Less complete impairment of awareness
Other seizure types		
Febrile	Occasional	Occasional
Generalized tonic–clonic seizure	Rarely precede or occur during period of frequent absences but may occur later with evolution to other IGE syndrome	May precede and commonly occur during the period of frequent absences
Myoclonic	Prominent myoclonus exclusionary	Prominent myoclonus exclusionary
EEG background	OIRDA in 21%	Normal
Interictal epileptiform discharge		
Awake	2.5–4-Hz generalized spike-wave	3–5.5-Hz generalized spike-wave
Asleep	Polyspike and wave may be seen in drowsiness and sleep only	Polyspike and wave may be seen in drowsiness and sleep only
Irregular generalized spike-wave	Uncommon	More common than CAE Discharges are more frequent than in CAE
Photoparoxysmal response	Rare IPS triggers generalized spike-wave in 15%–21% but does not induce seizures	Rare IPS triggers generalized spike-wave in 25% but does not induce seizures
Hyperventilation induction	87%	87%
Ictal EEG	Regular 3-Hz (range = 2.5–4 Hz) generalized spike-wave; 21% may have absences starting at 2.5-Hz spike-wave, and 43% may have absences starting at 4 Hz; if no generalized spike-wave is seen with hyperventilation for 3 min in an untreated patient, CAE can be excluded Disorganized discharges[a] less frequent	Regular 3–5.5-Hz generalized spike-wave If no generalized spike-wave is seen with hyperventilation for 3 min in an untreated patient, JAE can be excluded Disorganized discharges[a] 8 times more frequent than CAE

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CAE, childhood absence epilepsy; EEG, electroencephalogram; IGE, idiopathic generalized epilepsy; IPS, intermittent photic stimulation; JAE, juvenile absence epilepsy; OIRDA, occipital intermittent rhythmic delta activity.

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

factors, structural brain changes, ongoing seizures or frequent interictal discharges, ASM side effects, and stigma of epilepsy. However, the IGEs are not associated with intellectual disability or DEE.

Importantly, the IGEs have also been correlated with poorer long-term social outcomes, including decreased academic achievement; increased risk of unplanned pregnancy; psychiatric, emotional, and behavior problems; and decreased social interaction with friends.[27,28]

1.6 | Genetics

IGEs follow complex inheritance, where they arise due to a polygenic basis with or without an environmental

TABLE 2 Features seen in JME and GTCA

Feature	JME	GTCA
Age at onset		
Usual	10–24 years	10–25 years
Range	8–40 years	5–40 years
Development	Typically normal but may have learning disorder or ADHD	Typically normal but may have learning disorder or ADHD
Main seizure type	Myoclonic seizures, seen predominantly on awakening	Generalized tonic–clonic seizures typically within 2 h of awakening
Other seizure types		
Febrile seizures	May occur in approximately 4%–5% Generalized tonic–clonic seizures in >90%, which are often preceded by myoclonic jerks (myoclonic–tonic–clonic), and often occur on awakening Absence seizures in 33%, typically brief (3–8 s), infrequent (<daily), and with variable impairment of awareness	May occur in approximately 15% Absence or myoclonic seizures are not present
Triggers	Sleep deprivation Photic stimulation	Sleep deprivation
EEG background	Normal	Normal
Epileptiform discharges	Irregular, generalized 3–5.5-Hz spike-wave and polyspike-wave seen in all states May fragment in sleep	Generalized 3–5.5-Hz spike-wave or polyspike-wave, which may be seen only in sleep May fragment in sleep
Photoparoxsmal response	Seen in 30%–90% and may trigger myoclonic jerks or generalized myoclonic–tonic–clonic seizures	May be seen
Hypeventilation induction	33% have hyperventilation-induced generalized spike-wave discharge but rarely induces absence seizures	May be seen
Ictal EEG	Disorganized discharges significantly more common with absences in 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	Generalized spikes with tonic phase followed by spike-wave during clonic phase, but often obscured by muscle artifact

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CAE, childhood absence epilepsy; EEG, electroencephalogram; GTCA, epilepsy with generalized tonic–clonic seizures alone; JME, juvenile myoclonic epilepsy.

contribution.[29] This draws on an extensive body of twin and family clinical research.[3,30] Monozygotic twins are highly concordant for the EEG trait of generalized spike-wave activity and show 70% concordance for seizures.[31–34] Despite clinical genetic evidence, the search for genes for the IGEs has been slow to yield pathogenic variants. This is largely because of the polygenic basis of the IGE, where an individual may require many alleles, each conferring a low to moderate risk, to express the disease. To gain insights into the molecular pathology, advances have required the aggregation of large cohorts to identify relatively low-risk alleles. The ILAE Consortium on Complex Epilepsies performed a genome-wide mega-analysis involving 15 212 persons with epilepsy and 29 677 controls and identified 11 loci associated with the GGEs.[35] This work implicates a pathogenic variant in each locus in the causation of the IGEs, but does not explain the underlying mechanism. Importantly, each pathogenic variant is neither sufficient nor necessary to explain causation for an individual.

In a small proportion of IGE patients, monogenic causes have been identified. Examples include several GABA receptor subunit genes (e.g., *GABRG2*, *GABRA1*)[36,37] and the gene encoding glucose transporter 1 (*SLC2A1*).[38] Both inherited and de novo variants 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.

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 de novo mutation or complex

inheritance. Thus, the term *genetic* refers to the cause and does not mean inherited, an important distinction that is often misconstrued.[10]

Recurrent copy number variants (CNVs), such as microdeletions and microduplications, occur in 3% of patients with IGE.[39,40] They are likely to be one of the polygenic factors that contribute to the etiology of these disorders, rather than be wholly causative. They can be familial or arise de novo, and substantially increase the risk of IGE.[41] For example, the 15q13.3 microdeletion was initially discovered in 1% of individuals with IGE compared to 0.02% of controls; the IGE patients did not have the more severe phenotype previously associated with this microdeletion of severe intellectual disability and dysmorphic features, which highlights the variable expressivity of the CNV.[39] This microdeletion arose de novo in the patient or could be inherited. Although families did not show high penetrance of IGE, inherited 15q13.3 microdeletions carried a markedly increased risk of IGE in family members.[41] Further studies found that recurrent microdeletions occurred in almost 2% of IGE patients and were more frequent in epilepsy than in other disorders such as autism spectrum disorder, schizophrenia, and intellectual disability.[40] These studies highlight the continuum and overlap between epilepsy, neurodevelopmental, and psychiatric disorders in terms of pathogenic variants, with many recurrent CNVs contributing to all of these disorders. In general, patients with epilepsy and intellectual disability are not expected to have an IGE; however, rarely, they may have a classic IGE presentation, reinforcing the overlap between these disease groups. This is further reinforced by the finding that patients with mild intellectual disability who present with classic IGE syndromes have an even higher CNV burden, with CNVs found in 10% of patients.[42] Here the CNVs are likely contributing to a polygenic basis, differentiating them from monogenic CNVs, which are wholly causative for the individual's disease.

1.7 | 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 epilepsy with myoclonic atonic seizures. 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 having a GGE without a specific epilepsy syndrome.

2 | 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 (Table 3). Absence seizures are provoked by hyperventilation. Neurological examination is normal. Development and cognition are typically normal. ADHD and learning difficulties may occur. Seizures are brief but may occur in clusters. Epilepsy remits in 60% of children, often within 2 years of onset or by early adolescence.

2.1 | Epidemiology

The incidence of CAE is approximately 6.3–8.0 children per 100 000 per year.[43–45] It accounts for approximately 18% of epilepsy in school-aged children.[46]

2.2 | Clinical context

Age at onset is typically 4–10 years (range = 2–13 years).[47–51] In children with onset at age 10 years 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.[50] EEG features may help in distinguishing CAE from JAE. CAE is more common in girls (60%–75% of cases).[47,50] A history of febrile seizures is present in 10%–15% of children.[52–54] Development is typically normal, although children with CAE may have specific learning difficulties and ADHD; both may be subtle and easily missed.[27,55–59] Higher rates of depression and anxiety are also noted.[60,61] Neurological examination and head size are normal.

Although CAE may rarely 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 at younger than 4 years, a diagnosis of glucose transporter 1 deficiency disorder (associated with *SLC2A1* pathogenic variants) is found in 10% of patients.[38,62,63]

2.3 | Natural history

CAE is usually drug responsive. CAE remits by early adolescence in 60% of patients.[47–49,64,65] In the remainder, patients may evolve into other IGE syndromes. Lack of motor automatisms may correlate with a worse seizure outcome.[66]

TABLE 3 Diagnostic criteria for CAE

	Mandatory	Alerts[a]	Exclusionary
Seizures	Typical absence seizures	GTCS prior to or during the period of frequent absence seizures Staring spells with typical duration > 30 s or with postictal confusion or fatigue Absences occurring <daily in an untreated patient	Any of the following seizure types: • Prominent myoclonic seizures • Prominent eyelid myoclonia • Myoclonic–absence seizures • Atonic seizures • Tonic seizures • Atypical absence seizures • Focal impaired awareness seizures
EEG	Paroxysms of 3-Hz (range = 2.5–4 Hz) generalized spike-wave at the start of the absence (may have been obtained historically)	Consistently unilateral epileptiform discharges Lack of HV-activated 2.5–4-Hz generalized spike-wave in untreated patient who performs HV well for 3 min or longer Recording a typical staring spell without EEG correlate in a child with a history of 2.5–4-Hz generalized spike-wave Persistent slowing of the EEG background in the absence of sedating medication	Diffuse background slowing
Age at onset		2–3 or 11–13 years	<2 or >13 years
Development at onset		Mild intellectual disability	Moderate to profound intellectual disability
Neurological exam		Potentially relevant neurological examination abnormalities, excluding incidental findings (see text)	
Comorbidities			Cognitive stagnation or decline
Imaging		Potentially relevant abnormal neuroimaging, excluding incidental findings (see text)	
Other studies: genetics, etc.			Low CSF glucose and/or *SLC2A1* pathogenic variant (testing not needed in most cases but strongly recommended in children with onset at ≤3 years, microcephaly, and/or intellectual disability)
An MRI is not required for diagnosis. An ictal EEG is not required for diagnosis, provided the interictal study shows paroxysms of 2.5–4-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 HV.			

Abbreviations: CAE, childhood absence epilepsy; CSF, cerebrospinal fluid; EEG, electroencephalogram; GTCS, generalized tonic–clonic seizures; HV, hyperventilation; MRI, magnetic resonance imaging.

[a]Criteria that are absent in the vast majority of patients who have a syndrome, but rarely can be seen. Alerts alone would not exclude the syndrome but should cause the clinician to rethink the diagnosis and undertake further investigations to rule out other conditions. The more alerts that are present, the less confident one can be about diagnosis of a specific syndrome.

2.4 | Seizure types

Typical absence seizures have sudden onset of complete loss of awareness in most children, with staring, loss of facial expression, and interruption of activity. Oral and/or manual automatisms occur in 86% of patients and eye involvement with blinking, eye opening, or subtle eyelid or perioral myoclonus in 76.5% of patients. There is immediate return to normal activity, although children may be momentarily confused as they reorient themselves.[66,67] Duration is typically 3–20 s, with a median duration of 10 s, but rarely they may last >30 s.[66,68–72] Incontinence and loss of postural control can be seen. Seizures typically occur multiple times per day but are often underrecognized.

Generalized tonic–clonic seizures rarely precede or occur during the period of frequent absence seizures in

childhood.[51,67] More commonly, they begin in adolescence, often after resolution of absence seizures, and may herald evolution to another IGE syndrome (e.g., JME, JAE, GTCA).[47]

Myoclonic seizures, other than subtle myoclonus occurring during an absence seizure, are not seen in CAE. Prominent myoclonus during absence seizures (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.

2.5 | Electroencephalogram

2.5.1 | Interictal

The background is normal. Occipital intermittent rhythmic delta activity (OIRDA) occurs in 21%–30% of children with CAE,[68,73] 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.[67] Fragmented generalized spike-wave can appear focal or multifocal 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.[69,74] Intermittent photic stimulation triggers generalized spike-wave in 21% of individuals.[69]

2.5.2 | Ictal

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). Approximately 21% of patients have at least some absences starting at 2.5 Hz, and 43% have at least some absences starting at 4 Hz.[68] Disorganized discharges, defined by brief (<1 s) or transient interruptions in the ictal rhythm, or waveforms of different frequency or morphology are significantly less common than in JAE.[69] Generalized spike-wave and absence seizures are both provoked by hyperventilation in most untreated patients.[51,75,76] Slow spike-wave (<2.5 Hz) is not seen. If an untreated child performs hyperventilation well for 3 min and no generalized spike-wave is seen, childhood absence epilepsy can be excluded.

2.6 | 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.

2.7 | Genetics

Genetic testing is not part of current routine diagnostic evaluation but, as more genetic determinants are

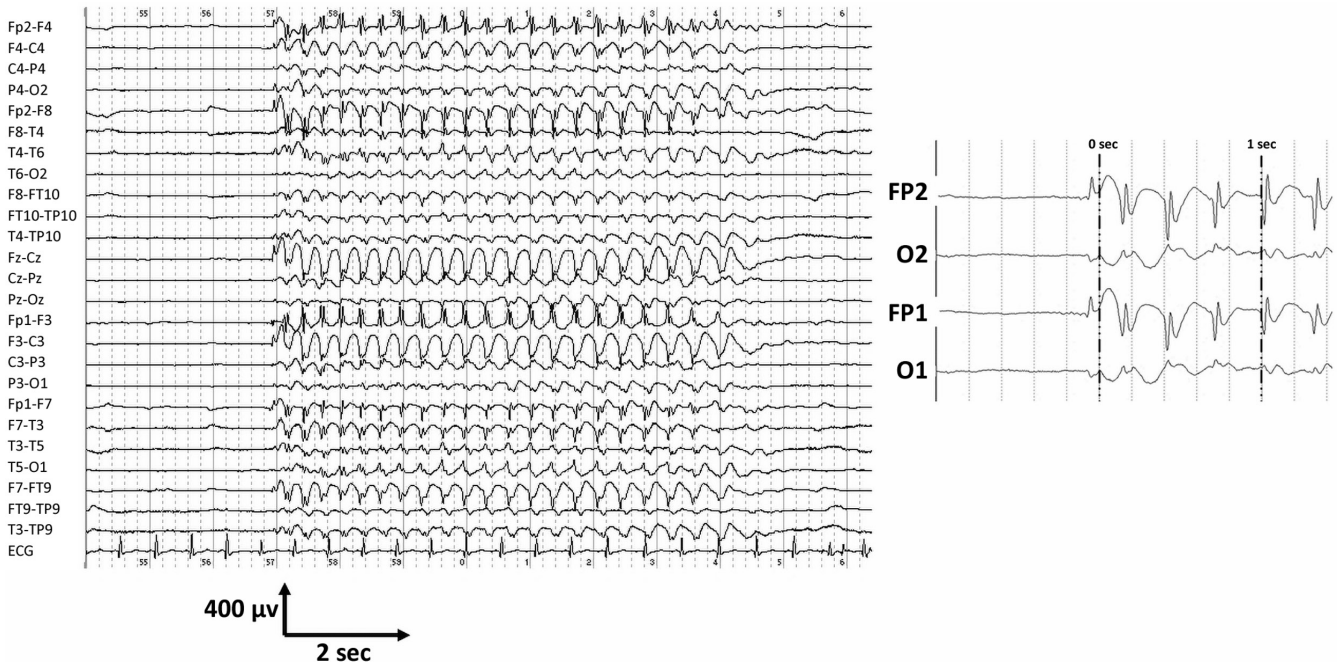

FIGURE 2 Typical absence seizure in a 7-year-old girl, with bilateral synchronous spike-wave (frontal maximal amplitude). The regularity and frequency at onset (3.5 Hz) and duration (7 s) are consistent with childhood absence epilepsy

identified, it may enter the diagnostic realm. Clinical genetic studies, such as twin studies, have shown that CAE has a strong genetic component.[3,30,31,34] Only a few genes conferring monogenic risk for CAE are known, largely identified through family studies where there are many affected individuals with IGE or large cohort studies (e.g., *GABRG2*, *GABRA1*, *SLC2A1*).[36–40,62] Testing should be considered if absence seizures begin before 4 years of age (e.g., *SLC2A1* testing), as 10% of children have glucose transporter 1 deficiency and especially if there are atypical features such as intellectual disability, movement disorders, or drug resistance, or if there is a strong family history of seizures.[62,63,77,78] There are also recurrent CNVs (e.g., 15q11.2, 15q13.3, and 16p13.11 microdeletion) that contribute to complex inheritance.[39–41] If a child has significant learning disabilities, a chromosomal microarray should be considered, as a higher frequency of pathogenic CNVs is found.[42]

2.8 | Other investigations

In typical cases, no other investigations are needed. If onset is at <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 hypoglycorrhachia (absolute low fasting cerebrospinal fluid glucose) or by *SLC2A1* mutational analysis.

2.9 | 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 is characterized by 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 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. JAE typically begins after 10 years of age, with less frequent absences (less than daily), more subtle loss of awareness, and 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 initial focal nonmotor features, more prolonged duration of unresponsive staring (often >30 s), and postictal features including confusion, drowsiness, and headache. EEG shows focal epileptiform discharge.

Nonepileptic disorders:

1. Daydreaming
2. Inattention
3. Ocular tics

3 | 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 Hz) generalized spike-wave in an otherwise normal adolescent.[67] Generalized tonic–clonic seizures are seen in >90% of cases, most commonly beginning shortly after onset of absence seizures (Table 4). Neurological examination is normal. Development and cognition are typically normal, although ADHD and learning difficulties may occur. Although seizures may be controlled with ASMs, lifelong treatment may be required.

3.1 | Epidemiology

JAE is less common than CAE, accounting for 2.4%–3.1% of new onset epilepsy in children and adolescents.[13,14] However, it may be underdiagnosed, as absences can be subtle and overlooked.[11]

3.2 | Clinical context

Typical age at onset is between 9 and 13 years, with a range of 8–20 years. Exceptional cases may present in adult life.[16,64] In cases with onset at <10 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

TABLE 4 Diagnostic criteria for JAE

	Mandatory	Alerts[a]	Exclusionary
Seizures	Typical absence seizures	Staring spells with typical duration > 30 s or with postictal confusion or fatigue Absence seizure frequency of >10 per day	Any of the following seizure types: • Prominent myoclonic seizures • Prominent eyelid myoclonia • Myoclonic–absence seizures • Atonic seizures • Tonic seizures • Atypical absence seizures • Focal impaired awareness seizures
EEG	Paroxysms of 3–5.5-Hz generalized spike-wave (may have been obtained historically)	Lack of HV-activated 3–5.5-Hz generalized spike-wave in an untreated patient who performs HV well for 3 min or longer Persistent EEG background slowing in the absence of a sedating medication	Consistently unilateral focal epileptiform discharges Diffuse background slowing Recorded typical staring spell without EEG correlate
Age at onset			<8 or >20 years
Development at onset		Mild intellectual disability	Moderate to profound intellectual disability
Neurological exam		Potentially relevant neurological examination abnormalities, excluding incidental findings (see text)	
Comorbidities			Cognitive stagnation or decline
Imaging		Potentially relevant abnormal neuroimaging, excluding incidental findings (see text)	
Other studies: genetics, etc.			Low CSF glucose and/or *SLC2A1* pathogenic variant (testing not needed in most cases but strongly recommended in those with microcephaly and/or mild intellectual disability)
Course of illness		Lack of GTCS over course of the epilepsy, in the absence of treatment with ASMs that are effective for GTCS	
An MRI is not required for diagnosis. An ictal EEG is not required for diagnosis, provided the interictal study shows paroxysms of 3–5.5-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 HV.			

Abbreviations: ASM, antiseizure medication; CSF, cerebrospinal fluid; EEG, electroencephalogram; GTCS, generalized tonic–clonic seizures; HV, hyperventilation; JAE, juvenile absence epilepsy; MRI, magnetic resonance imaging.

[a]Criteria that are absent in the vast majority of patients who have a syndrome, but rarely can be seen. Alerts alone would not exclude the syndrome but should cause the clinician to rethink the diagnosis and undertake further investigations to rule out other conditions. The more alerts that are present, the less confident one can be about diagnosis of a specific syndrome.

between 6% and 33% of cases.[3,79,80] Significant cognitive impairment should suggest an alternate diagnosis.

3.3 | Natural history

JAE is often drug responsive, but lifelong therapy may be required.[64,81,82] Ethosuximide as initial monotherapy is not recommended due to the high likelihood of generalized tonic–clonic seizures.[83] 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.[59,84,85] Higher rates of depression and anxiety are also noted.[61]

3.4 | 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 CAE.[67,86] 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 s, with occasional longer seizures. Frequency is typically less than daily.[64,86] Subtle myoclonus may be seen during an absence seizure.

Absence status epilepticus occurs in approximately 20% of patients.[87]

Generalized tonic–clonic seizures occur in >90% of cases.[64] They usually begin after onset of absences, but in 14%–27% of cases, may precede absences.[64,88] The frequency of generalized tonic–clonic seizures is variable.

Myoclonic seizures are exclusionary except for subtle myoclonus occurring during an absence seizure.

Other seizure types are not expected in JAE.

3.5 | Electroencephalogram

3.5.1 | 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.[69] Fragmented generalized spike-wave can appear focal or multifocal 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 in both awake and sleep recordings. Discharges are more frequent in JAE than CAE.[70] Polyspike-wave is seen predominantly in drowsiness and sleep.[69,74]

In untreated patients, hyperventilation provokes absence seizures in approximately 87% of cases.[69] Where hyperventilation is performed well for 3 min and no generalized spike-wave is seen, absence seizures are unlikely. Intermittent photic stimulation triggers generalized spike-wave in 25% of individuals.[69,70] Slow spike-wave (<2.5 Hz) is not seen.

3.5.2 | Ictal

Generalized spike-wave at 3–5.5 Hz occurs at onset of absence seizures (Figure 3).[69,70] Disorganized discharges are eight times more common in JAE than CAE.[69] 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 GTCA (see below).

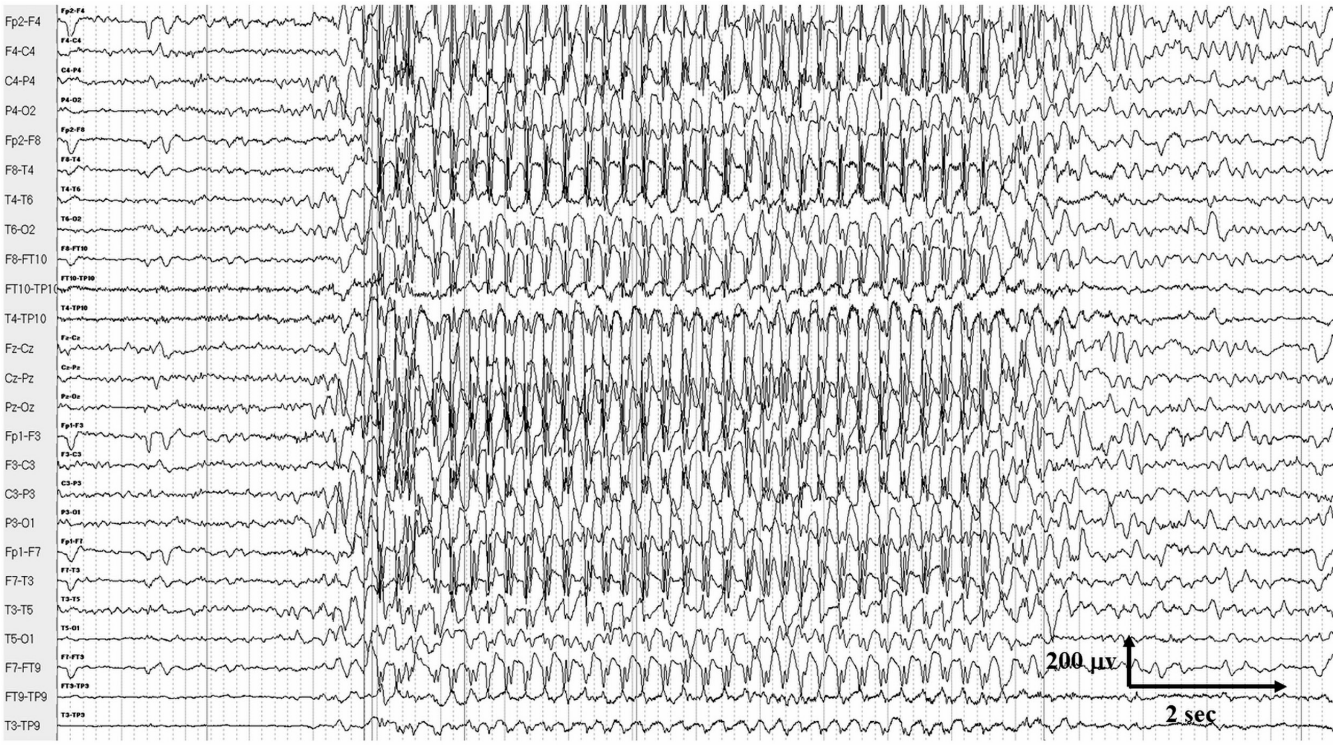

FIGURE 3 Typical absence seizure in a 12-year-old boy. The irregularity and frequency at onset (4 Hz) and duration (10–11 s) of discharge are most consistent with juvenile absence epilepsy

3.6 | Neuroimaging

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

3.7 | 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.[3] Clinical genetic studies, such as twin studies, have shown that JAE has a strong genetic component, which significantly overlaps with CAE.[89]

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*, *SLC2A1*, and others.[36–40,42,62] Testing should be considered when atypical features such as intellectual disability or drug resistance are present. Significant cognitive impairment should suggest an alternate diagnosis.

3.8 | Metabolic or other laboratory studies

No other laboratory studies are required or suggested.

3.9 | Differential diagnoses

Other epilepsies:

1. CAE typically begins at a younger age with daily absence seizures and has a lower risk of generalized tonic–clonic seizures.
2. JME is distinguished by the presence of myoclonic seizures, particularly in the morning or with sleep deprivation, 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. GTCA lacks absence seizures.
6. Focal impaired awareness seizures are usually distinguished by initial nonmotor features, longer duration of unresponsive staring (often >30 s), and postictal features including confusion, drowsiness, and headache. EEG shows focal epileptiform discharge.

Nonepileptic disorders:

1. Daydreaming
2. Inattention
3. Ocular tics

4 | 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 (Table 5). 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 when appropriate photic stimulation testing methodology is used. Life-long treatment is often required.

4.1 | Epidemiology

JME is common, with a prevalence ranging from one to three per 10 000 persons in population-based studies.[90,91] It accounts for approximately 9.3% of all epilepsies.[92]

4.2 | 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.[47,93] 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.[94,95]

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.[59,96–100] Progressive decline in cognition after seizure onset should suggest a progressive

TABLE 5 Diagnostic criteria for JME

	Mandatory	Alerts[a]	Exclusionary
Seizures	Myoclonic seizures (see text)	Generalized tonic–clonic status epilepticus Consistent unifocal semiology (i.e., always affecting the same body part on the same side) at onset of generalized tonic–clonic seizures Consistent unifocal myoclonus	• Myoclonic–absence seizures • Atonic seizures • Tonic seizures • Atypical absence seizures • Focal impaired awareness seizures • Myoclonus predominantly or exclusively during sleep • Myoclonic seizures that occur exclusively with reading • Cortical tremor with myoclonus (see text)
EEG	3–5.5-Hz generalized spike-wave or generalized polyspike-wave on EEG (may be obtained historically; see text)		Habitual myoclonic event captured on EEG in the absence of polyspike and spike-wave discharge Focal slowing Consistently unilateral focal epileptiform abnormalities Generalized slow spike-wave at frequency < 2.5 Hz (unless it is at the end of a higher frequency burst) Diffuse background slowing that is not limited to the postictal period
Age at onset		8–9 years or 25–40 years	<8 years or >40 years (CAE may occasionally evolve to JME; in such cases, persons may have onset of absence seizures, but not GTCS or myoclonic seizures prior to age 8 years)
Development at onset		Mild intellectual disability	Moderate to profound intellectual disability
Neurological exam		Potentially relevant neurological examination abnormalities, excluding incidental findings (see text)	
Imaging		Potentially relevant abnormal neuroimaging, excluding incidental findings (see text)	
Course of illness			Progressive cognitive decline Progressive myoclonus with impaired fine motor function
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.			

Abbreviations: CAE, childhood absence epilepsy; EEG, electroencephalogram; GTCS, generalized tonic–clonic seizures; JME, juvenile myoclonic epilepsy; MRI, magnetic resonance imaging.

[a]Criteria that are absent in the vast majority of patients who have a syndrome, but rarely can be seen. Alerts alone would not exclude the syndrome but should cause the clinician to rethink the diagnosis and undertake further investigations to rule out other conditions. The more alerts that are present, the less confident one can be about diagnosis of a specific syndrome.

myoclonus epilepsy. Rarely, JME can occur in individuals with mild intellectual disability, and in such cases, chromosomal microarray detects a recurrent microdeletion in approximately 10%.[42] There are also higher rates of anxiety and depression in patients with JME compared with the general population.[98,99,101] Additionally, several studies have documented higher rates of impulsivity, which may lead to social or psychiatric problems.[102–104]

4.3 | Natural history

Seizures in 65%–92% of patients with JME are drug responsive when using appropriate ASMs.[105–111] 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 aggravate myoclonic and absence seizures in JME.[23,112,113] Lamotrigine may aggravate myoclonic seizures in some patients.[114–116]

JME is usually considered a lifelong disorder, often requiring lifelong therapy.[18,105,106] Although occasional cases may successfully discontinue ASMs later in life,[106,108,117,118] a recent meta-analysis documented that seizures recurred in 78% (95% confidence interval = 58%–94%) of cases after medication withdrawal.[109] Risk factors for drug-resistant seizures include absence seizures, psychiatric comorbidities, history of CAE, praxis-induced seizures, and younger age at epilepsy onset.[109]

4.4 | Seizure types

Myoclonic seizures are mandatory for diagnosis.[67] They occur most commonly within the first hour after awakening and are facilitated by sleep deprivation.[67] Patients may not recognize myoclonic jerks as seizures[67]; they are frequently recognized retrospectively, after presentation with a generalized tonic–clonic seizure. Myoclonic status epilepticus can occur rarely.[119,120]

Myoclonic seizures may be unilateral or bilateral. Myoclonic seizures can predominate on one side of the body, frequently involving the upper extremities.[121] Myoclonic seizures can also involve the lower limbs and cause falls. Myoclonic seizures can be reflex, triggered by photic stimulation or praxis.[67]

Generalized tonic–clonic seizures occur in >90% of individuals[67]; these are often preceded by a series of myoclonic seizures that increase in frequency and severity, resulting in a myoclonic–tonic–clonic seizure.[67] 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.[106,119] 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.[122–124]

Absence seizures occur in one third of cases.[105,125] These are brief (3–8 s), occurring less than daily, and have variable but often subtle impairment of awareness (typically less severe than in CAE).[24,67,126] Absence status epilepticus may occur rarely.[119]

Focal seizures and generalized tonic or atonic seizures are exclusionary.

4.5 | Electroencephalogram

The background is normal.[67] Generalized slowing is not seen, other than in the postictal period following a generalized tonic–clonic seizure.

4.5.1 | Interictal

Recording generalized spike-wave activity, typically with generalized polyspike-wave, is mandatory for a definitive diagnosis of JME, 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.[69] 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 multifocal 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 EEG recording to another. The morphology of the focal spike-wave appears similar to the generalized spike-wave. If focal slowing and focal discharges 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 photoparoxysmal response to intermittent photic stimulation is seen in more than one third of cases[69,70,127] and, with specialized testing, can be detected in up to 90% of untreated patients.[128] Intermittent photic stimulation may induce myoclonic seizures, eyelid myoclonia, and rarely, generalized tonic–clonic seizures.

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

4.5.2 | 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 generalized spike-wave discharge associated with myoclonus is consistent with nonepileptic myoclonic jerks.

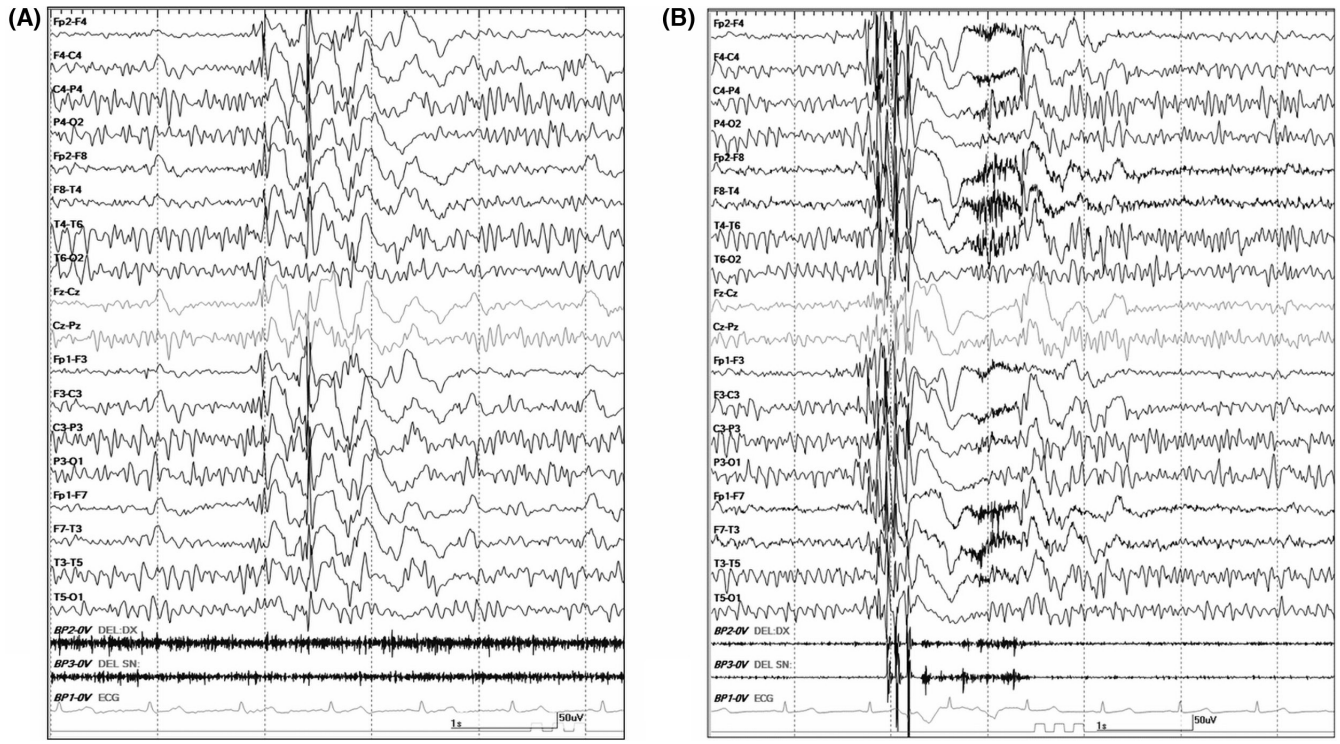

FIGURE 4 Interictal discharge in an 18-year-old girl with a history of a single generalized tonic–clonic seizure and myoclonic seizures showing generalized polyspike and wave (A). The ictal electroencephalogram (EEG) demonstrating generalized polyspike-wave discharge, with bilateral symmetric limb jerks (B). This clinical history and EEG are most suggestive of juvenile myoclonic epilepsy

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.[129,130] A postictal period of irregular slow activity follows a generalized tonic–clonic seizure.

4.6 | Neuroimaging

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

4.7 | 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.[3]

Rare pathogenic variants have been reported in individual patients in a range of genes including *CACNB4*, *GABRA1*, *GABRD*, and *EFHC1*,[29,131]; however, with larger cohort studies, many of these genes have been discredited.[132] 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.[39–41]

4.8 | Metabolic or other laboratory studies

No other laboratory studies are indicated.

4.9 | Differential diagnoses

Other epilepsies:

1. Myoclonic epilepsy in infancy: Onset of myoclonic seizures occurs prior to age 3 years.
2. JAE: There are no myoclonic seizures.

3. GTCA: There are no seizure types except generalized tonic–clonic seizures.
4. Epilepsy with eyelid myoclonia: Consider if there are absence seizures with prominent eyelid myoclonia.
5. Epilepsy with myoclonic absences: Myoclonic absences are not seen in JME.
6. Progressive myoclonus epilepsies: Consider if there is cognitive decline, appearance of permanent, erratic, drug-resistant myoclonus, EEG background slowing, or a photoparoxysmal response at low frequencies of photic stimulation (<3 Hz).
7. Epilepsy with reading-induced seizures: Consider if myoclonic jerks occur exclusively during reading.
8. Late onset Lennox–Gastaut syndrome: Consider if there are 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 affecting 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%–100% of individuals.[133]

Nonepileptic disorders (ictal recordings lack EEG correlate):

1. Psychogenic nonepileptic seizures are common mimickers of generalized tonic–clonic seizures.
2. Hypnic jerks commonly occur in sleep in healthy individuals.
3. Periodic limb movements during sleep are repetitive, highly stereotyped limb movements occurring during relaxed wakefulness or during sleep. Unlike JME, these movements are not seen during activity and are most prominent in the legs.
4. Propriospinal myoclonus is a rare condition seen in middadulthood, with myoclonic activity arising in the relaxation period preceding sleep onset that causes severe insomnia.[134] Myoclonic activity begins in spinally innervated muscles, propagating at low speed to rostral and caudal muscular segments. The jerks disappear during sleep.
5. Nonepileptic 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.[135]
6. 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.

5 | EPILEPSY WITH GENERALIZED TONIC–CLONIC SEIZURES ALONE

This syndrome (originally called epilepsy with grand mal seizures on awakening) is a common IGE syndrome (Table 6). Individuals have generalized tonic–clonic seizures of variable frequency that 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 may be required.

5.1 | Epidemiology

Epidemiological data are limited, although in one study, GTCA accounted for one third of all adolescent onset IGEs.[81]

5.2 | 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.[81,86] 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.[59] 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.

5.3 | Course of illness

Seizures are typically infrequent, sometimes yearly or less. Treatment may be required for life. Sleep deprivation,

TABLE 6 Diagnostic criteria for GTCA

	Mandatory	Alerts[a]	Exclusionary
Seizures	Generalized tonic–clonic seizures (see text)	Consistent unifocal semiology (i.e., always affecting the same body part on the same side) at seizure onset	Generalized myoclonic–tonic–clonic seizures (suggest JME) Any other seizure type
EEG	3–5.5-Hz generalized spike-wave or polyspike-wave on EEG (may be obtained historically)		Focal slowing Consistently unilateral focal epileptiform discharges Generalized slow spike-wave at frequency < 2.5 Hz (unless it is at the end of a higher frequency burst) Diffuse background slowing that is not limited to the postictal period
Age at onset		5–9 or 26–40 years	<5 or >40 years
Development at onset		Mild intellectual disability	Moderate to profound intellectual disability
Neurological exam		Potentially relevant neurological examination abnormalities, excluding incidental findings (see text)	
Comorbidities			
Imaging		Potentially relevant abnormal neuroimaging, excluding incidental findings (see text)	Abnormal neuroimaging with causative lesion
Course of illness			Progressive cognitive decline
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.			

Abbreviations: EEG, electroencephalogram; GTCA, epilepsy with generalized tonic–clonic seizures alone; JME, juvenile myoclonic epilepsy; MRI, magnetic resonance imaging.

[a]Criteria that are absent in the vast majority of patients who have a syndrome, but rarely can be seen. Alerts alone would not exclude the syndrome but should cause the clinician to rethink the diagnosis and undertake further investigations to rule out other conditions. The more alerts that are present, the less confident one can be about diagnosis of a specific syndrome.

fatigue, and alcohol lower the patient's seizure threshold.[136] Seizures are usually drug responsive.[136]

5.4 | Seizure types

Generalized tonic–clonic seizures are mandatory for this epilepsy syndrome. These often occur within 2 h 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 (e.g., JAE, JME).

5.5 | Electroencephalogram

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.

5.5.1 | Interictal

Generalized spike-wave or polyspike-wave at 3–5.5 Hz is mandatory for diagnosis (but may be obtained historically). However, a sleep recording may be needed to detect this mandatory finding. A photoparoxysmal response may be seen. In sleep, the discharges often fragment and can appear focal or multifocal, 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.

5.5.2 | 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.

5.6 | Neuroimaging

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

5.7 | Genetic studies

Genetic testing is not part of the current routine diagnostic evaluation. A first-degree family history of epilepsy was present in approximately 12% of cases in one study.[81] As with all the IGEs, family members with epilepsy typically have an IGE or GGE syndrome.[3] If seizures are drug resistant, a chromosomal microarray should be performed to look for recurrent CNVs.

5.8 | Metabolic or other laboratory studies

No other laboratory studies are required or suggested.

5.9 | Differential diagnoses

Other epilepsies:

1. JME is distinguished by a history of myoclonic seizures.
2. JAE is distinguished 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.[6]

Nonepileptic disorders (ictal EEG recordings lack epileptiform activity):

1. Psychogenic nonepileptic seizures: Clues that suggest this diagnosis 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.[137,138]
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.[139] Tongue biting is rare in syncope but urinary incontinence occasionally occurs. In persons whose events occur most prominently during physical exercise, cardiac diagnoses such as prolonged Q-T syndrome leading to convulsive syncope should be excluded.

6 | 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.[10] 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.[50] 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.[10] Our Task Force on Nosology and Definitions elected to continue the convention that the IGEs should be exclusively limited to the four common syndromes CAE, JAE, JME, and GTCA, and that this is a special subgroup of the GGEs (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 at onset and seizure types. Patients may evolve from one of the IGE syndromes to another, such as CAE evolving to JME.[47]

We recognize that, at times, other GGE syndromes and genetic epilepsy with febrile seizures plus 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 that are not part of the four IGEs, and although they might occur in the setting of normal intellect, they have higher association with intellectual disability. Given the overlap between various IGE syndromes and between IGEs and other GGE syndromes, longitudinal natural history studies will allow further refinement of these proposed criteria over time.

7 | CONCLUSIONS

Recognition of the IGEs is important for clinical care, as it informs diagnosis, prevents unnecessary investigation,

allows optimal selection of ASMs, 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 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. The definitions for epilepsy syndromes provided in this paper will require validation in longitudinal studies and may be further refined as new data are published over time.

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CONFLICT OF INTEREST

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