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# Idiopathic Generalized Epilepsy

## Misunderstandings, Challenges, and Opportunities

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## Abstract

The idiopathic generalized epilepsies (IGE) make up a fifth of all epilepsies, but <1% of epilepsy research. This skew reflects misperceptions: diagnosis is straightforward, pathophysiology is understood, seizures are easily controlled, epilepsy is outgrown, morbidity and mortality are low, and surgical interventions are impossible. Emerging evidence reveals that patients with IGE may go undiagnosed or misdiagnosed with focal epilepsy if EEG or semiology have asymmetric or focal features. Genetic, electrophysiologic, and neuroimaging studies provide insights into pathophysiology, including overlaps and differences from focal epilepsies. IGE can begin in adulthood and patients have chronic and drug-resistant seizures. Neuromodulatory interventions for drug-resistant IGE are emerging. Rates of psychiatric and other comorbidities, including sudden unexpected death in epilepsy, parallel those in focal epilepsy. IGE is an understudied spectrum for which our diagnostic sensitivity and specificity, scientific understanding, and therapies remain inadequate.

## History and Background

Mid-to-late 19th-century neurologists distinguished patients with idiopathic epilepsy from those with symptomatic epilepsies due to structural brain lesion and sympathetic epilepsies due to systemic disorders (e.g., nephritis).<sup>1</sup> Idiopathic epilepsies were considered genetic disorders provoked by emotional stress, pain, hormonal factors, and alcohol. Myoclonic seizures and juvenile myoclonic epilepsy were recognized in late 19th-century patients with upper body jerks on awakening that progressed to convulsions. In the 1930s, the EEG hallmark of idiopathic generalized epilepsies (IGE) was identified: bilateral, symmetrical 2.5–6 Hz generalized spike-wave discharges (GSWD), which also differentiated absence from focal unaware seizures. The 1989 International League Against Epilepsy (ILAE) classification posited a genetic etiology for focal-onset and generalized-onset idiopathic epilepsies. In 2010, the ILAE replaced idiopathic with genetic.

Clinically, only absence, myoclonic, and tonic-clonic seizures occur in patients with IGE. Generalized-onset atypical absence seizures, absence with eyelid myoclonia, myoclonic absence, and tonic and atonic seizures occur in patients with epileptic encephalopathies.

The IGE comprise approximately 20% of all epilepsies, but account for less than 1% of scientific literature on epilepsy. This difference reflects prevailing perceptions that antiseizure medications (ASMs) control seizures in patients with IGE, comorbidities are infrequent and minor, and surgical procedures are ineffective for seizure control. These misconceptions limit understanding and therapies and highlight the need for research. The IGE are better controlled

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## Glossary

**ASMs** = antiseizure medications; **GGEs** = genetic generalized epilepsies; **GSWD** = generalized spike-wave discharges; **IGE** = idiopathic generalized epilepsies; **ILAE** = International League Against Epilepsy; **JME** = juvenile myoclonic epilepsy; **SUDEP** = sudden unexpected death in epilepsy.

and have more favorable long-term outcomes than focal epilepsies and developmental and epileptic encephalopathies. However, breakthrough seizures in patients with IGE are often GTCS. A missed medication dose, sleep deprivation, excess alcohol intake, or over-the-counter (e.g., diphenhydramine, pseudoephedrine)<sup>2,3</sup> or prescribed (e.g., bupropion and tramadol) medications can cause greater morbidity and mortality than in focal epilepsy, where breakthrough seizures are often non-convulsive. Counseling should emphasize medication adherence and lifestyle factors, especially challenging in adolescents and young adults.

## Classification of Generalized Epilepsies

Epilepsies are classified as generalized, focal, generalized and focal, and unknown.<sup>4</sup> The next classification level was epilepsy syndrome, which cannot always be diagnosed, but informs management, prognosis, and genetic counseling. Among the genetic generalized epilepsies (GGEs) (Figure 1), there are the IGE and epileptic encephalopathies.<sup>5</sup> The major IGE are childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy (JME), and epilepsy with GTCS alone, with overlap between syndromes.<sup>4,5</sup>

### GGE Syndromes Beyond IGE

GGEs include distinct seizure types.<sup>5</sup> Epilepsy with myoclonic-atic seizures is an epileptic encephalopathy characterized by seizures causing falls. Two other syndromes with signature seizures can manifest as developmental and epileptic encephalopathies (abundant epileptiform activity associated with developmental slowing or regression), as a static intellectual disability (no clear association between interictal activity and cognitive function), or as normal intellect. Epilepsy with eyelid myoclonia is characterized by rapid eyelid fluttering and photosensitivity, often associated with very brief absence seizures. Epilepsy with myoclonic absences presents as absence seizures with tonic upper limb abduction and superimposed 3-Hz myoclonus. Myoclonic epilepsy in infancy may be associated with intellectual disability or normal cognition.

Classifications are vital for clinicians and researchers but may artificially simplify and divide a complex spectrum and advance an illusion of understanding.

Furthermore, serial terminologies create inconsistent nosologies across physician groups. Evolving and overlapping terms and diagnoses may foster misdiagnoses. For example, epilepsy with myoclonic-atic seizures may be misdiagnosed as Lennox-Gastaut syndrome. Asymmetric or focal EEG or clinical features can cause misdiagnosis of focal epilepsy and

mistreatment (Figure 2). The overlap of focal and generalized epilepsies warrants greater study.

Borderlands present additional challenges because patients may not fit syndromic categories. For example, a 4-year-old neurotypical child with 3-Hz GSW and an afebrile GTCS has IGE? Do they have epilepsy if the GTCS was associated with a low-grade fever? If not, what temperature separates these groups? And what if the child has otitis media but no fever? Non-IGE GGE syndromes overlap with IGE in EEG findings and seizure types. Clinical and EEG features can change over time. Among patients with GGE, intellectual impairment may result from abundant epileptiform activity, seizures, or a static underlying disorder—or any combination of factors. If an adolescent with GSWD on EEG had 12 lifetime GTCS on awakening and reports rare jerks consistent with daytime myoclonic seizures, is it epilepsy with generalized tonic-clonic seizures alone (most frequent and disabling seizure) or JME (infrequent suspected but unproven myoclonic seizures)? Experts disagree. Because myoclonic seizures are rarely recorded on EEG, distinguishing epileptic myoclonus from benign jerks is challenging, especially when infrequent, never cluster, mid-day, and never progress to GTCS. Classification requires definite categories, science demands doubt.

While several IGE syndromes are associated with seizures shortly after awakening, all patients with epilepsy should be queried for circadian rhythmicity, which can inform treatment. For example, JME and GTCSA and some patients with focal epilepsy (e.g., self-limited epilepsy with centrotemporal spike patients) with seizures shortly after awakening can have ASMs targeted with higher or even only nighttime doses, improving seizure control and reducing daytime adverse effects.

## Diagnosis

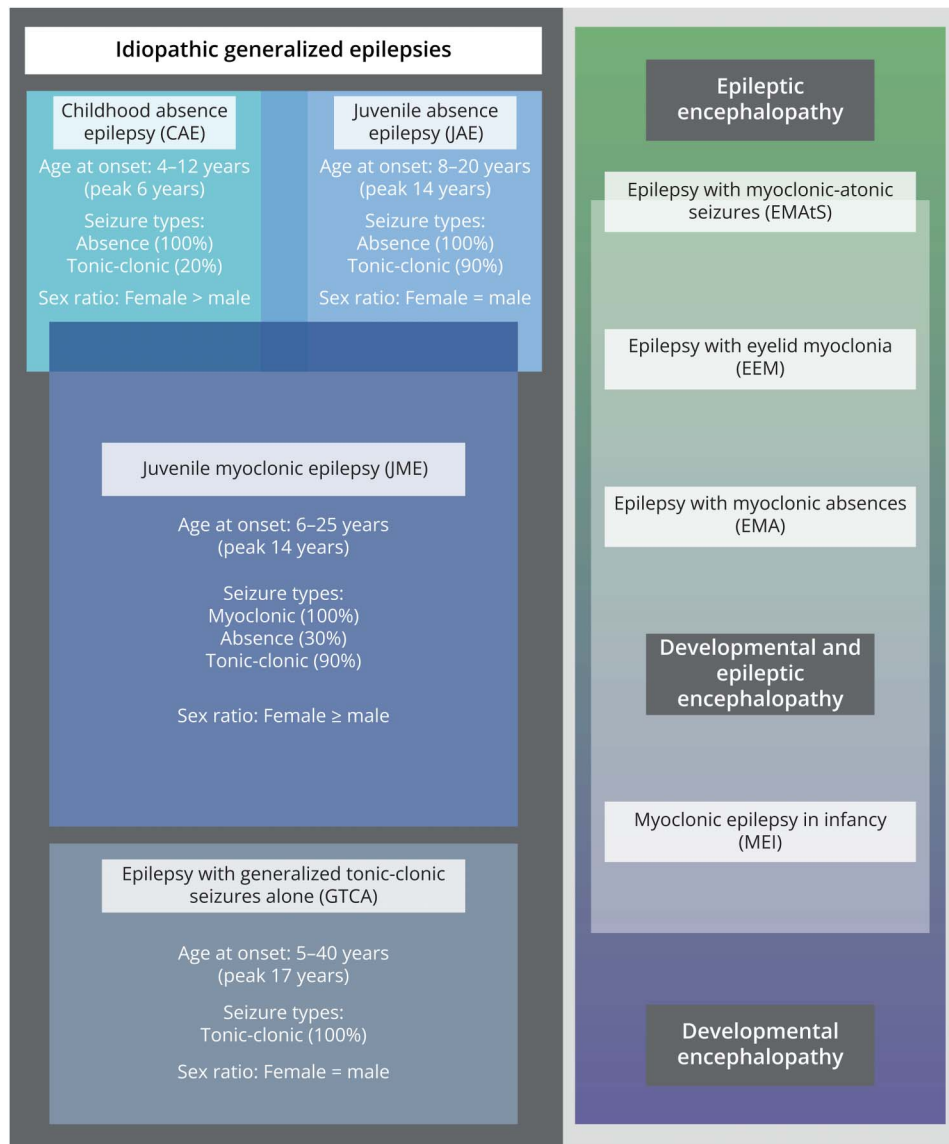
### Classic Features

IGE are characterized by GSWDs and absence, myoclonic, or GTCS. The EEG signature of IGE is GSWDs with normal background rhythms. Clinical features of the major IGE syndromes are summarized in Figure 1.<sup>4,5</sup> Seizures are often triggered by tiredness, stress, and environmental photic stimuli (e.g., driving while the sun flickers through trees).<sup>2</sup>

### Diagnostic Challenges

EEG cannot reliably differentiate IGE syndromes. For example, 3.5- to 6-Hz GSWDs alone or with polyspikes occur in juvenile myoclonic, epilepsy with GTCS alone, juvenile absence, and childhood absence epilepsies with similar frequencies. Normal EEGs may be more common in JME than other syndromes.<sup>6</sup>

**Figure 1** Classification of Genetic Generalized Epilepsies



IGE seizures often have asymmetric and focal clinical and EEG features. Versive head or eye or asymmetric limb movements can occur in GTCS. Absence seizure motor phenomena that suggest focal unaware seizures with automatisms or eyeblinks and myoclonic seizures may be asymmetric or lateralized. EEG may show unilateral lead-in to GSW in generalized-onset seizures (Figure 2). If accompanied by focal slowing on EEG, brain MRI should exclude a potential lesion and IGE-mimic (Figure 2). Asymmetric GSWDs in IGE differ from secondary bilateral synchrony: (1) lead-in of  $\leq 2$  seconds, (2) focal spike morphology similar to bisynchronous discharges, (3) no multifocal spikes, (4) no focal slowing in focal spike area temporally independent from epileptiform discharges, and (5) no focal neurologic deficits or cognitive deterioration.<sup>7,8</sup>

Occasionally, patients with normal intellect have focal and generalized epilepsies, such as temporal lobe epilepsy and JME.<sup>1</sup> While IGE are not associated with brain lesions, subtle focal MRI structural and functional anomalies are more frequent in patients with JME and their siblings than controls (e.g., unilateral or bilateral hippocampal malrotation and anomalous cognitive activation).<sup>8</sup>

IGE occur in patients with autism spectrum disorder and other intellectual or psychiatric disabilities, although IGE cohorts may exclude such patients. This artificially “pure IGE” group denies biodiversity, curtailing the mapping of the clinical spectrum, pathophysiologic mechanism, and therapies. For example, pathogenic *SCN1a* variants exclude a focal or IGE diagnosis. This spectrum, often unrecognized without access to genetic testing, is confidently diagnosed without genetic data but falsely narrowed by a priori assumptions.

**Figure 2** EEG Findings in IGE and IGE Mimics

**A. Classic generalized epileptiform discharges**



**B. Focal findings in patients with otherwise generalized EEG activity**



**C. Activity consistent with secondary bilateral synchrony**



(A) Symmetric and synchronous generalized epileptiform discharges. (B) Asymmetric or focal EEG features in patients with IGE based on their clinical history and other EEGs with symmetrical and synchronous generalized discharges. (C) Focal slow, focal spikes, and asymmetric generalized discharges in patient with a right frontal lesion and secondary bilateral synchrony.

## Etiology

### Genetics

IGE twin and family studies strongly support genetic inheritance, with multiple genes contributing; that is, “complex genetics.” Concordance for epilepsy among twins with IGE is 76% in

monozygotes and 33% in dizygotes. If one monozygotic twin has IGE, and the other has epilepsy, IGE concordance is 94%.<sup>9</sup> Large IGE families are rare. Monogenic causes are infrequent (e.g., glucose transporter 1 deficiency and GABA-A receptor subunit gene variants; Table 1). Thus, clinical gene panels and whole-exome sequence studies are typically unrevealing in most

**Table 1** Gene Variants Associated With IGE Syndromes<sup>a</sup>

Gene	Encoded protein function	Epilepsy syndrome (s)	Seizure types	Animal/human phenotype
<b>CACNA1A</b>	P/Q-type calcium channel alpha subunit (Cav2.1 protein); primarily excitatory neurotransmission	JAE	Absence, GTC	Epilepsy, ataxia, migraine dystonia, nystagmus, hemiplegia, ID, and premature death
<b>CACNA1G</b>	T-type calcium channel alpha subunit	CAE		Epilepsy, spinocerebellar ataxia
<b>CACNA1H</b>	T-type calcium channel alpha subunit	CAE JME	Absence	Absence, GTCS, myoclonic & febrile seizures
<b>CACNB4</b>	P/Q-type calcium channel beta 4 subunit	JME	Absence and praxis-induced	Absence epilepsy, ataxia, and focal myoclonus
<b>CACNG3</b>	Calcium voltage-gated channel auxiliary subunit gamma 3	CAE	??	??
<b>CASR</b>	Calcium-sensing receptor	JME	Febrile convulsions, myoclonic, absence, generalized tonic-clonic	??
<b>EFHC1</b>	Myoclonin1	JAE, JME	Myoclonic & generalized clonic-tonic or clonic-tonic-clonic	Frequent spontaneous myoclonus
<b>GABRD</b>	Extrasynaptic GABAA receptor delta subunit	JME	Atypical absences & generalized myoclonic and/or bilateral tonic-clonic	??
<b>GABRA1</b>	GABAA receptor	CAE, JME	Tonic-clonic and myoclonic	??
<b>GABRG2</b>	GABAA receptor	CAE	Febrile	??
<b>GABRB3</b>	GABAA receptor	CAE	Absence ± eyelid myoclonus	Myoclonic and atypical absence seizures, impaired cognition, motor coordination, and somatosensory processes
<b>SLC2A1</b>	Glucose transporter 1 deficiency syndrome	JAE, CAE	Absence ± myoclonus	Aberrant gaze saccades, movement disorders, ID, dysarthria, language disorders

Abbreviation: IGE = idiopathic generalized epilepsies.

<sup>a</sup>Select refs: 11, 12.

patients with IGE, and are not clinically indicated. A large genome-wide association study identified 22 “IGE” loci.<sup>10</sup> Complex inheritance underlies many heritable human traits, such as height, but can create an illusion of understanding. Most cases with IGE have no known cause, and attribution to multiple genes is likely in many cases, but remains unproven, and can minimize consideration of other mechanisms.

### Epigenetic and Environmental Factors

Animal models support environmental and epigenetic risk factors in IGE. The approximately 25% discordance among IGE monozygotic twins sharing womb and childhood environments<sup>13</sup> supports a minimum estimate for nonheritable factors. Among 6 monozygotic twins discordant for IGE, the *OTX1* and *ARID5B* genes had different CpG methylation patterns, supporting epigenetic alterations in gene expression influence IGE risk. Gene variants influencing DNA methylation (e.g., *Mecp2*) and histone modifications (e.g., *WDR5*) cause neurodevelopmental disorders with epilepsy.

Potential environmental factors include diet, microbiome, head injuries, infections, and immune responses. While kindling is an experimental model of focal epilepsy, it may also be relevant to IGE, where recurrent exposure to

seizure-provocative factors (e.g., sleep deprivation, alcohol, or benzodiazepine withdrawal) may convert diathesis to disorder.

Diet and metabolic alterations influence epileptogenesis, seizure threshold, inflammation, and epigenomics. Microbiome disorders can cause inflammation and disrupt neuromodulation and the blood-brain barrier.<sup>14</sup> Antiseizure effects of low-carbohydrate diets may involve microbiome changes. Risk factors may interact (e.g., diet, microbiome, substance abuse, sleep deprivation<sup>15</sup>) with susceptibility genes to convert a latent to manifest disorder.

## Pathophysiology

### Neurophysiology

In animal models of IGE and in patients with IGE, hyper-synchronization of thalamocortical networks generate generalized SWDs and seizures and can result from variants in calcium channel and  $\gamma$ -aminobutyric acid (GABA) receptor genes (Table 1).<sup>16,17</sup> Other mechanisms are also implicated, including increased thalamic glutamate and decreased N-acetyl aspartate.<sup>18</sup> Thalamic reticular neurons, interconnected in functional excitatory-inhibitory loop, are pacemakers in

physiologic (e.g., sleep spindles) and pathologic (GSWDs, generalized seizures) states. Robust reciprocal thalamocortical connections generate and maintain synchronized neuronal activity in cortical and subcortical regions.

The term generalized suggests that all brain neurons are affected synchronously and homogeneously in IGE, but electrical, neuroimaging, and molecular studies support involvement of specific thalamocortical networks with sparing of others.<sup>18,19</sup> In patients with IGE, structural imaging studies reveal atrophy and functional imaging studies reveal abnormal nodes in frontocentral cortical areas<sup>19-21</sup> (Figure 3). The basal ganglia and cerebellar regions may also be functionally impaired in IGE.<sup>20</sup> Focal epilepsies produce localized spike-wave discharges and with focal lesions near parasagittal frontoparietal regions with callosal connections, they can rapidly generalize (Figure 2).

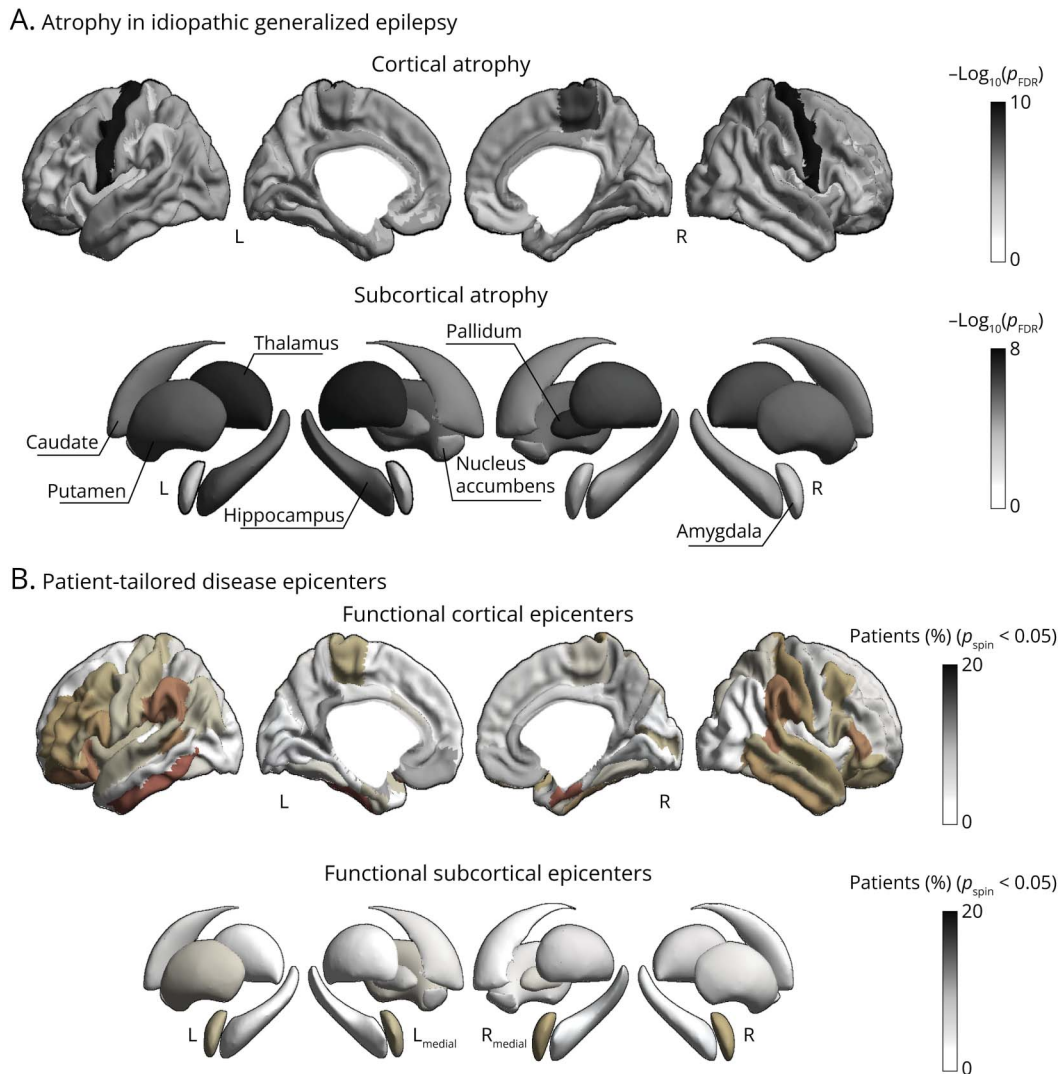
Shared thalamocortical networks in IGE and sleep-wake states may explain why epileptiform activity and seizures have circadian rhythmicities.<sup>13</sup> Generalized polyspike train and GSWDs in sleep may mark drug resistance in IGE,<sup>22,23</sup> sharing abnormal thalamocortical hypersynchrony with generalized paroxysmal fast activity in Lennox-Gastaut syndrome.<sup>24</sup>

## Therapies

### Antiseizure Medication

ASMs reduce neuronal hyperexcitability and are the primary IGE therapy. First-line and second-line treatments of specific IGE epilepsy syndromes are summarized in Table 2. Decisions regarding ASM initiation and choice, dosing, and discontinuation depend on seizure type and epilepsy syndrome

**Figure 3** Structural and Functional Changes in IGE Cohorts



(A) Cortical thickness and subcortical volume reductions in IGE ( $n = 289$ ), relative to controls ( $n = 1,075$ ), affected predominantly bilateral precentral cortical regions ( $P_{FDR} < 9 \times 10^{-10}$ ) and the thalamus ( $P_{FDR} < 3 \times 10^{-6}$ ). Negative  $\log_{10}$ -transformed FDR-corrected  $p$  values are shown. (B) Patient-specific functional disease epicenters identified by keeping brain regions whose connectivity profiles significantly correlated with the patient's atrophy map ( $P_{spin} < 0.05$ ). In IGE, bilateral frontocentral areas (including sensorimotor cortices) and amygdala were disease epicenters (modified from reference 19).

**Table 2** Common IGE Antiseizure Medications: Mechanisms and Indications<sup>25-32</sup>

Antiseizure medication	Mechanism of action	Effective for seizure types	Indications	ILAE Recommendations
<b>First generation</b>				
<b>Ethosuximide</b>	T-type calcium blockade	Absence seizures Myoclonic seizures	First-line monotherapy for CAE	Level A for initial monotherapy in children with CAE
<b>Valproate</b>	Sodium channel blockade, GABA potentiation	GTCS Absence seizures Myoclonic seizures	First-line monotherapy except in women of childbearing ages	Level A for initial monotherapy in children with CAE Level C for adults with GTCS Level C for children with GTCS Level D for JME
<b>Second generation</b>				
<b>Lamotrigine</b>	Sodium channel blockade Some effect on GABA potentiation	GTCS Absence seizures May worsen myoclonic seizures	First-line monotherapy for women of childbearing ages	Level C for initial monotherapy in children with CAE Level C for adults with GTCS
<b>Levetiracetam</b>	Binding to SV2a protein	GTCS Myoclonic seizures	First-line monotherapy for women of childbearing potential	Level D for adults with GTCS
<b>Topiramate</b>	Sodium channel blockade, some effect on GABA potentiation	GTCS	Adjunctive therapy	Level C for adults with GTCS Level C for children with GTCS Level D for JME
<b>Zonisamide</b>	Sodium and calcium channel blockade	GTCS Myoclonic seizures	Adjunctive therapy	
<b>Third generation</b>				
<b>Lacosamide</b>	Slow sodium channel inactivation	GTCS	Adjunctive therapy	

Abbreviation: IGE = idiopathic generalized epilepsies.

and patient demographics, lifestyle and comorbidities, drug interactions, and side effects. Treatment outcomes are good for most childhood-onset IGE; many patients with childhood absence epilepsy transition off ASMs. Patients with IGE with seizures beginning or persisting in adolescence and young adulthood (e.g., JME) often require lifelong treatment. However, many can reduce or eliminate medication with improved lifestyle factors, including sleep, adherence, and limited alcohol intake (Figure 4).

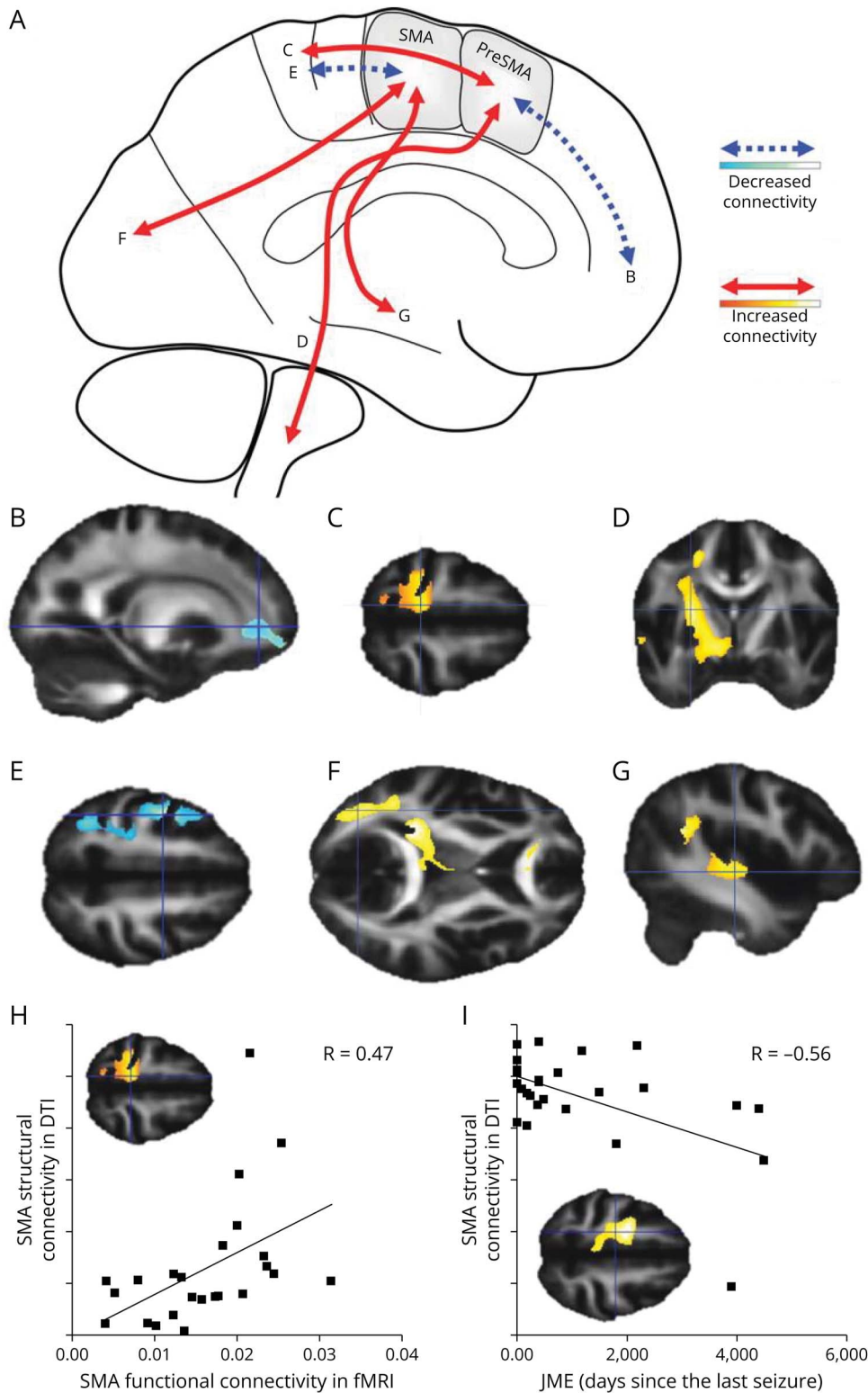
Studies evaluating ASMs for IGE are limited with level A evidence for typical absence seizures, level C for GTCS, and level D evidence for JME.<sup>25</sup> One trial compared valproate, lamotrigine, and topiramate in 450 patients with IGE.<sup>26</sup> Valproate was superior to lamotrigine and topiramate in time-to-treatment failure; valproate was superior to lamotrigine and similar to topiramate in time to 12-month remission.<sup>26</sup> Ethosuximide and valproate had superior efficacy over lamotrigine for childhood absence epilepsy, with ethosuximide the treatment of choice with fewer adverse effects. Lamotrigine failure usually reflected poor seizure control. Valproate failure usually reflected adverse effects. In JME, seizure freedom rates are better for valproate, but lamotrigine is better tolerated.<sup>27</sup> Lamotrigine may exacerbate myoclonic seizures. Levetiracetam is FDA approved to treat JME and generalized tonic-clonic seizures. Zonisamide, benzodiazepines, and felbamate are

effective in some patients with IGE.<sup>28</sup> Sodium channel blockers (e.g., phenytoin, carbamazepine, and oxcarbazepine) can be beneficial for some patients with IGE but exacerbate seizures in some, especially those with generalized polyspike-wave discharges. Lacosamide<sup>29</sup> and perampanel<sup>30</sup> reduced GTCS, but perampanel did not reduce myoclonic or absence seizures.<sup>31</sup> Anecdotal evidence supports efficacy for many ASMs in generalized-onset seizures (e.g., brivaracetam, zonisamide, clobazam, and clonazepam).

For adolescent and young adult patients with IGE, seizure recurrence is often related to ASM nonadherence, sleep deprivation, alcohol withdrawal, or stress.<sup>2</sup> These factors often concur. For example, after examinations, a sleep-deprived college student may consume excess alcohol; intoxication promotes nonadherence; and alcohol withdrawal impairs sleep quality and lowers the seizure threshold.

Women of reproductive age pose therapeutic challenges because ASMs can interact with hormonal contraceptives, are potentially teratogenic, and excreted in breast milk. Enzyme-inducing ASMs (e.g., phenobarbital, phenytoin, carbamazepine, perampanel, cenobamate >> topiramate, lamotrigine, felbamate, clobazam) increase hepatic metabolism of oral contraceptives, increasing the risk of an unplanned pregnancy risk.

**Figure 4** Altered Structural Connectivity in Juvenile Myoclonic Epilepsy (JME)



(A) The anterior presupplementary motor area (SMA) cluster showed reduced connectivity to frontopolar region (B) and increased connectivity to medial central region (C) and descending motor pathways (D). The posterior SMA cluster showed reduced connectivity to the central region (E) but increased connectivity to the temporal (F) and occipital (G) cortices. (H) Functional connectivity (fMRI) between prefrontal cortex and SMA correlated with the structural connectivity on diffusion tensor imaging (DTI). (I) SMA connectivity correlated with disease activity. From Vollmar et al.<sup>23</sup> with permission.

Before conception, women should be counseled to allow for patient-provider shared decision-making regarding key aspects of care. Preconception counseling should include ASM and strategies to reduce risks: folate supplementation (1–4 mg daily),

reducing ASM number and dose if possible, and interactions between ASMs and contraceptives. Among children whose mothers took high-dose folate (mean, 4.3 mg) during pregnancy, one study found a >2.5-fold risk of cancer.<sup>33</sup>

All ASMs have potential teratogenic risk: lowest for levetiracetam, lamotrigine, and oxcarbazepine (approximately 1%–3% risk of major congenital malformations; ~0%–1% higher than the general population). Topiramate, carbamazepine, and phenytoin have higher risk (~3%–5%) while phenobarbital (~6%) and valproate (~7%–10%) are those with highest risk.<sup>27–29</sup> The low teratogenicity of lamotrigine and levetiracetam make them first-line ASMs for women with IGE of reproductive age. At low-to-modest doses, their risk is similar to controls for major congenital malformations: lamotrigine (2.3%), levetiracetam (1.8%) vs women without epilepsy (1.5%–2.5%).<sup>34</sup>

Teratogenic ASM risks correlate with number and dose of medications. Four ASMs with dose-dependent risks for major congenital malformations are valproate (>1,450 mg/d: 25.2%; 650–1,449 mg/d: 11.3%; ≤650 mg/d: 6.3%), phenobarbital (>130 mg/d: 11.7%; 80–129 mg/d: 6.2%; ≤80 mg/d: 2.7%), carbamazepine (>700 mg/d: 7.2%; ≤700 mg/d: 4.5%), and lamotrigine (>325 mg/d: 4.3%; ≤325 mg/d: 2.5%).<sup>34–36</sup>

Valproate is highly efficacious in controlling seizures yet highly teratogenic and associated with intellectual delay, autism, and intellectual disability in children exposed *in utero*.<sup>37,38</sup> Such children had reduced intelligence quotient (7–10 points) and impaired verbal and memory functions compared with children exposed prenatally to phenytoin, lamotrigine, or carbamazepine.<sup>38</sup> Neither levetiracetam nor lamotrigine monotherapy increases autism or intellectual disability risk. In addition to maternal risk of accidents due to GTCS in pregnancy and death during labor and delivery, children of women with epilepsy had higher rates of low birth weight, small-for-gestational age, and preterm delivery, while children of mothers with ≥5 GTCS during pregnancy had higher rates of neurodevelopmental delays.<sup>39</sup>

Men with epilepsy face few reproductive risks from ASMs or epilepsy itself. Enzyme-inducing ASMs can reduce testosterone levels. Valproate may also be associated with reversible male infertility.<sup>40</sup>

### ASM Withdrawal

While most patients with childhood absence epilepsy successfully come off ASMs, ASM withdrawal outcomes in other well-controlled IGE is less predictable. Patients with juvenile absence epilepsy often remain seizure-free after ASM withdrawal, while higher recurrence rates occur in those with JME (>75% recur) and in those with epilepsy with GTCS alone (approximately 60% recur). For patients with JME, seizures are more likely to recur after ASM withdrawal for patients of earlier age at start of withdrawal, shorter seizure-free interval, and polytherapy.<sup>41</sup>

### Lifestyle/Hygiene

In patients with IGE, seizures are provoked or precipitated by strong negative emotions (e.g., work or relationship stress), sleep deprivation (see further), circadian rhythms, alcohol

withdrawal, and external or internal stimuli (for example, flashing lights (photosensitivity), hyperventilation, hot water, writing, and arithmetic).<sup>2,15</sup> Seizure control may improve with stress-reducing interventions (e.g., mindfulness, progressive muscle relaxation, yoga, biofeedback, and cognitive behavioral therapy), which can also improve quality of life and psychiatric comorbidities. Seizures may be triggered by internal or external factors. Female patients and patients with JME are most frequently photosensitive.

Alcohol consumption increases seizure risk in patients with IGE, especially >2 drinks per occasion. Alcohol use disorder is approximately 4-fold increased in people with epilepsy compared with that in controls.<sup>42</sup> Patients should be counseled to avoid excess alcohol intake and be referred for treatment if alcohol use disorder is diagnosed.

## Drug Resistance in IGE

Many patients with IGE are drug resistant. Despite adequate ASM trials, nearly one-third of patients with JME have ongoing seizures. ASM resistance can affect all IGE seizure types and is associated with psychiatric comorbidities, catamenial epilepsy, epileptiform focality, history of CAE, family history of epilepsy, status epilepticus, and history of febrile seizures.<sup>41</sup> Drug-resistant patients with IGE should consider alternative ASMs (e.g., perampanel<sup>30,31</sup> and felbamate) and neuromodulation (see further).

Treatment responsiveness, a core IGE characteristic, was dropped from the ILAE 2022 classification to include patients with drug resistance and “less benign” syndromes as IGE.<sup>43</sup> Up to 30% of patients with JME have persistent seizures despite multiple ASM trials,<sup>41</sup> often presenting at younger ages and more often having psychiatric and neurocognitive comorbidities.

By definition, imaging is “normal” in IGE. Neither imaging nor genetic studies support a disease phenotype associated with ASM-resistant IGE, but were limited by drug-sensitive controls at specialized centres.<sup>44</sup> Abnormalities in cortical thickness and misfolding may mark neurodegeneration and psychiatric and neurodevelopmental disorders.<sup>45</sup> In patients with JME and their siblings, abnormalities in hippocampal volume, shape, and position are associated with functional reorganization and may reflect genetically influenced variation in the development of brain anatomy, connectivity, and function.<sup>45</sup>

Reduced connectivity in the default mode network (brain regions active when one is not focused on the outside world) may mark or contribute to drug resistance in IGE. In patients with JME, resting-state default mode network connectivity was lower than in healthy controls, and drug-resistant patients had lower connectivity than drug-sensitive patients.<sup>46</sup> Default mode network connectivity negatively correlates with disease duration.<sup>47</sup> Epilepsy-related factors may negatively affect the brain over time, supporting therapies beyond seizure control to prevent cognitive and behavioral changes.

An EEG-fMRI study found greater spike-related activation of paracingulate cortex in valproate-unresponsive vs valproate-responsive patients with IGE.<sup>48</sup> Patients with frequent GSWDs and drug-resistant IGE may have excess motor default mode executive network cross talk.<sup>49</sup> Patients with JME often have executive and attentional dysfunction. Impaired functional and structural connectivity between basal ganglia and superior frontal and supplementary motor areas in patients with JME may underlie myoclonus and executive impairments.

## Neuromodulation

No randomized controlled trials establish the efficacy of neuromodulatory therapy in IGE (Level D evidence), although open-label series suggest potential benefit. Vagus nerve stimulation, deep brain stimulation, and responsive neurostimulation may reduce seizures in drug-resistant IGE, although we cannot predict which patients will benefit. As with focal epilepsies, neuromodulatory efficacy often correlates with treatment duration, which may reflect regression to the mean progressive therapeutic benefits, changes in other therapies, and bias.

Vagus nerve stimulation activates the medullary solitary tract nucleus, which projects to hypothalamic, thalamic, and limbic areas. Thalamic activation is associated with improved seizure control.<sup>50</sup> In drug-resistant IGE, vagus nerve stimulation reduced seizures by >50% in most patients after 16 months, with some reducing ASMs.<sup>51</sup> Vagus nerve stimulation side effects include hoarseness, cough, and throat pain.

Deep brain and responsive neurostimulation target the centromedian (CMT) and anterior (ANT) thalamic nuclei in patients with IGE. fMRI-EEG studies suggest that CMT-DBS reduces GSWD initiation while ANT-deep brain stimulation reduces GSWD maintenance.<sup>52</sup> Among small IGE cohorts treated with deep brain stimulation—CMT or responsive neurostimulation CMT—several became seizure-free, and many had a >50% seizure reduction.<sup>53,54</sup> Deep brain and responsive neurostimulation side effects include implant site pain, headaches, and dysesthesia.

Noninvasive transcranial magnetic stimulation alters cortical excitability and can reduce seizures. Intermittent transcranial magnetic stimulation over 3 years altered cortical excitability and seizure control in patients with IGE and focal epilepsy: those with reduced seizures had reduced cortical excitability; nonresponders had increased cortical excitability.<sup>55</sup>

## Dietary Therapy

High fat/low carbohydrate ketogenic and modified Atkins diets are effective for diverse drug-resistant epilepsies, including the non-IGE myoclonic-atonic epilepsy. Among 86 adults with IGE treated for 1–24 months, 41 (48%) had a >50% reduction in seizures.<sup>56</sup> Long-term compliance is challenging due to dietary restrictions and side effects and can be improved with close monitoring by a dietician.

## Comorbidities

Patients with IGE typically have normal intelligence, but many have executive impairments and personality, anxiety, mood, and autism spectrum disorders.<sup>57</sup> Childhood absence epilepsy, a “benign” disorder usually outgrown epilepsy by adolescence, is associated with unfavorable psychosocial outcomes compared with those in controls with another chronic medical illness (e.g., rates of high school dropout, unplanned pregnancy, psychiatric disorder, unskilled work, or unemployed).<sup>58</sup>

GGE networks involve cortical and subcortical regions. Abnormal frontal connectivity may relate to cognitive dysfunction in IGE, with hyperconnectivity between prefrontal cognitive and motor networks implicated (see above). Supplementary motor area-motor cortex hyperconnectivity during a working memory task paralleled abnormal structural connections.<sup>59</sup> Cognitive tasks may induce myoclonic jerks (i.e., praxis induction),<sup>60</sup> possibly reflecting prefrontal cognitive-supplementary motor area hyperconnectivity. Similarly, frontotemporal limbic-sensorimotor hyperconnectivity may underlie emotion-triggered seizures. An individual’s pattern of excitability, and its overlap with areas physiologically activated during cognitive, motor, or emotional activities, may reveal triggers to lower or raise seizure threshold. Complex tasks, tapping multiple cortical systems, may activate a critical cortical mass to precipitate seizures.

In IGE, frontal hypoconnectivity and hyperconnectivity can affect other brain areas. Frontal involvement predominates in JME and may contribute to impairments in judgment and impulsivity,<sup>58-62</sup> although temporal involvement (e.g., reduced hippocampal volumes, abnormal lateral temporal areas, and altered frontotemporoparietal development) may contribute to epileptogenesis and comorbidities.<sup>61,63</sup> Fiber tracts in IGE cohorts have aberrant connections.<sup>61,63</sup>

## Sleep and Sleep Disorders

Sleep and IGE are reciprocally related. Patients with IGE have altered sleep architecture, and brain rhythms are disrupted by epileptiform activity. Sleep deprivation and arousal from sleep may provoke seizures. Patients with IGE, especially patients with JME, experience decreased sleep quality, sleep efficiency, total N2 sleep, and a delay to the onset of rapid eye movement sleep—all unrelated to ASMs.<sup>15</sup> Clinicians should regularly ask about patients’ sleep habits and counsel on the importance of sleep hygiene and refer to sleep specialists when indicated.

Children with IGE have more sleep respiratory disorders than controls; findings are inconsistent in adults.<sup>13,64</sup> Patients with IGE with ongoing seizures have less REM sleep and longer REM onset latency than patients with controlled seizures.<sup>65</sup> Sleep alterations, including non-REM interictal epileptiform discharges, can impair memory consolidation, cognition, and behavior.

Sleep deprivation lowers the seizure threshold for most epilepsies, but IGE are especially sensitive. Sleep deprivation triggers interictal epileptiform activity and seizures during the transition into and out of sleep and during sleep. Epileptiform activity is greatest in N1 and N2 non-REM sleep stages.

Myoclonic and tonic-clonic seizures are more frequent during the first 2 hours of wakefulness—the matutinal period. Seizures on arousal or after awakening are more common after sleep deprivation, alcohol withdrawal, or being awakened suddenly or rushing out of bed. Self-reported seizure-provocative factors include sleep deprivation, alcohol, stress, photic stimulation, and menstruation.

### Sudden Unexpected Death in Epilepsy

Sudden unexpected death in epilepsy (SUDEP) rates are similar among focal epilepsy and IGE cohorts,<sup>66</sup> although focal epilepsy is more often drug resistant. Uncontrolled GTCS is the leading SUDEP risk factor, yet most SUDEPs affect patients with infrequent GTCS.<sup>66</sup> Drug-responsive patients may be at greater SUDEP risk after a breakthrough convulsion because sustained seizure freedom may reduce adaptive responses. Furthermore, in contrast to breakthrough nonconvulsive focal seizures, breakthrough IGE seizures are often GTCS.

## Concluding Remarks and Future Directions

The science of IGE holds more questions than answers. Why do some patients outgrow epilepsy while others do not? Why are some patients with CAE or JME drug resistant while others are not? What drives cognitive, psychiatric, sleep, and other comorbidities? How do comorbidities such as impulsivity and anxiety disorder influence medication adherence and seizure control? Can we identify and modify epigenetic and environmental risk factors of IGE and comorbidities? As we decipher genomic elements underlying complex inheritance, the more tangled interactions of genomic and environmental factors remain unexplored. We need a fuller understanding of factors that provoke or prevent breakthrough seizures, and how these factors interact.

Despite our limitations, effective diagnostic tools and therapies are available. Outcomes can be greatly improved by promoting healthful behaviors and tailoring medications and dosing schedules to minimize adverse events, seizures, morbidity, and mortality.

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<b>Shobi Sivathamboo, PhD</b>	Department of Neuroscience, Central Clinical School, Monash University; Department of Neurology, Alfred Health; Departments of Medicine and Neurology, The Royal Melbourne Hospital, The University of Melbourne, Victoria, Australia	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data
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