Epilepsy with myoclonic-atonic seizures: an update on genetic causes, nosological limits, and treatment strategies

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Epilepsy with myoclonic-atonic seizures is a childhood-onset epilepsy syndrome characterised by a range of seizure types, including myoclonic-atonic, atonic, myoclonic, absence, and generalised tonic-clonic seizures. The causes and outcomes of this syndrome are highly variable, with many uncertainties surrounding its classification and prognosis. Traditional antiseizure medications and the ketogenic diet remain the main treatment options. Although two-thirds of children attain remission from seizures without cognitive or behavioural sequelae, some continue to have drug-resistant seizures, intellectual disability, and behavioural problems. The identification of single-gene causes in a substantial subset of patients highlights the importance of genetic testing for development of personalised treatment strategies. However, diagnostic complexities have hindered the development of trials for new therapies. Better recognition of the distinct features of epilepsy with myoclonic-atonic seizures, combined with advances in molecular genetic testing, will pave the way for more focused clinical research and drug development. Future studies should aim to identify genetic causes and tailor treatment options, offering hope for improved long-term outcomes.

Introduction

Epilepsy with myoclonic-atonic seizures, formerly called myoclonic-astatic epilepsy, causes about 2% of childhood epilepsies.[1] A population-based study in New Zealand (2000–16) reported a cumulative incidence of 16·4 (95% CI 9·69–27·7) per 100 000 children.[2]

Epilepsy with myoclonic-atonic seizures begins in early childhood, with developmental delay in a third of the affected children. Its hallmark clinical features include myoclonic-atonic seizures and typical EEG patterns, which can be absent at clinical onset. Developmental stagnation or regression often occurs during seizure exacerbations, improving once seizures are controlled.

The disease is characterised by its marked prognostic variability and genetic heterogeneity. Challenges for clinicians include access to tailored and repeated neurophysiological examinations and to rapid genetic diagnostics, due to heterogeneous practices and resource availability among clinical epilepsy centres. A scarcity of dedicated trials contributes to uncertainties about therapeutic choices. Improved knowledge of the genetic causes, alongside emerging therapeutic approaches, should allow innovative targeted management.

In this Review, we describe the clinical and neurophysiological features of epilepsy with myoclonic-atonic seizures. We also provide an update on the key elements for differential diagnosis, discuss genetic investigations, and explain outcome variability, treatment choices, prognostic indicators, and comorbidities.

Diagnosis

Clinical and neurophysiological characteristics

Seizures typically begin at the age of 2–5 years (range 6 months to 8 years).[3,4] In a third of patients, developmental or speech delay precedes seizure onset.[5–7] However, the proportion of children with early delay could be underestimated because mild impairment might not be apparent when seizure onset occurs before the age of 3 years.

Myoclonic-atonic seizures, mandatory for diagnosis, consist of brief, single or repeated myoclonic jerks affecting the proximal muscles, at times associated with a slight vocalisation, followed by a brief atonic component, leading to subtle (ie, head nod) or more prominent (ie, abrupt fall) clinical manifestations (figure 1A). Pure atonic seizures, present in some children, do not have the initial myoclonic component and lead to abrupt but brief loss of axial tone, resulting in head nods or sudden falls (figure 1C). Clinical distinction between the more frequent myoclonic-atonic falls and the rarer atonic falls, which might coexist in the same child, can be difficult. At times, the myoclonic seizure might be less pronounced, without visible post-myoclonic inhibition, not resulting in a fall (figure 1B). Other seizure types include absence and generalised tonic-clonic seizures. The latter, which often have a vibratory appearance (figure 1E) without reaching the interferential muscle contraction seen in older patients, can occur with or without fever and present as the initial seizure type in two-thirds of children. Tonic seizures can appear later during the syndrome for some patients. Non-convulsive status epilepticus occurs in 17–40% of patients[8] and can be the initial manifestation, presenting as episodes of stupor with impaired awareness, lasting from hours to days, accompanied by absence, myoclonic, and atonic features, along with somnolence, unsteadiness, drooling, speech disorders, and erratic myoclonus (figure 1D). These episodes fluctuate in intensity, often beginning insidiously and progressing over time.[3]

About a third of patients experience a so-called stormy phase, characterised by numerous seizures and seizure types, often generalised tonic-clonic and myoclonic seizures, culminating in non-convulsive status epilepticus.[3,9] The stormy phase can be observed as early as 1 month after seizure onset but more typically occurs 3 months or more after seizure onset (mean 17·5 months, range 2–60).[10,11]

Seizures are often drug resistant, particularly during the stormy phase, during which developmental plateauing or even regression is often evident. Cognitive and behavioural disorders such as attention deficit hyperactivity disorder (ADHD), as well as sleep disturbances, are common during seizure exacerbation phases but typically lessen or remit after seizure control is achieved. Although seizures are initially drug resistant, two-thirds of children attain remission, usually within 3 years of seizure onset (but often earlier) and can be weaned off antiseizure medication. In the remaining third, persistent seizures, cognitive impairment, and ADHD often persist. Once seizures are controlled and the EEG improves, developmental progress might return to premorbid levels or the child might be left with a variable degree of intellectual disability and behavioural problems.

Interictal (ie, between seizures) EEG shows typical, age-appropriate background activity and posterior dominant rhythm at seizure onset. Monomorphic biparietal theta rhythms and an occipital 4 Hz rhythm, which is consistently blocked by eye opening, are characteristic of epilepsy with myoclonic-atonic seizures but not observed in all patients. With increased seizure frequency, higher amplitude background slowing might occur. Generalised bursts of 2–6 Hz spike waves or polyspike waves, which can be activated by sleep, are mandatory for diagnosis but might not have clinical manifestations. Generalised discharges can be fragmented, and there is no consistent spike focus. Hyperventilation might elicit generalised spike-wave discharges and absence seizures. Photosensitivity is rare.[1,4]

During ictal recordings of myoclonic-atonic seizures, the myoclonic component is associated with a generalised spike or polyspike discharge, followed by a high-voltage slow wave accompanying the atonic component. The myoclonic potential is usually followed by electromyography silence lasting up to 500 ms (figure 1A). This silent period might also occur without a clear preceding jerk, leading to an atonic fall (figure 1C), although the possibility of a contraction in non-sampled muscles cannot necessarily be excluded.

Neurophysiological studies show bilateral synchronous EEG discharges and synchronous myoclonic jerks on both sides of the body, indicating primary generalised epileptic myoclonus. Absence seizures are associated with 2–6 Hz generalised spike-wave complexes. During non-convulsive status epilepticus, the EEG displays long runs of high-amplitude, 2–3 Hz, irregular, generalised spike-wave activity, with background slowing (figure 1D).[3,4]

Genetic causes

A family history of epilepsy or febrile seizures is found in about a third of patients, including patients with genetic epilepsy with febrile seizures plus.[12–14] In the original description of epilepsy with myoclonic-atonic seizures, Doose[15] pointed out the high incidence of seizures and similarity of EEG findings among family members of affected individuals. Clinical seizures occurred in up to 40% of patients' relatives, with myoclonic-atonic seizures occurring in 2%, an incidence 200 times higher than in the general population for this seizure type.[15,16]

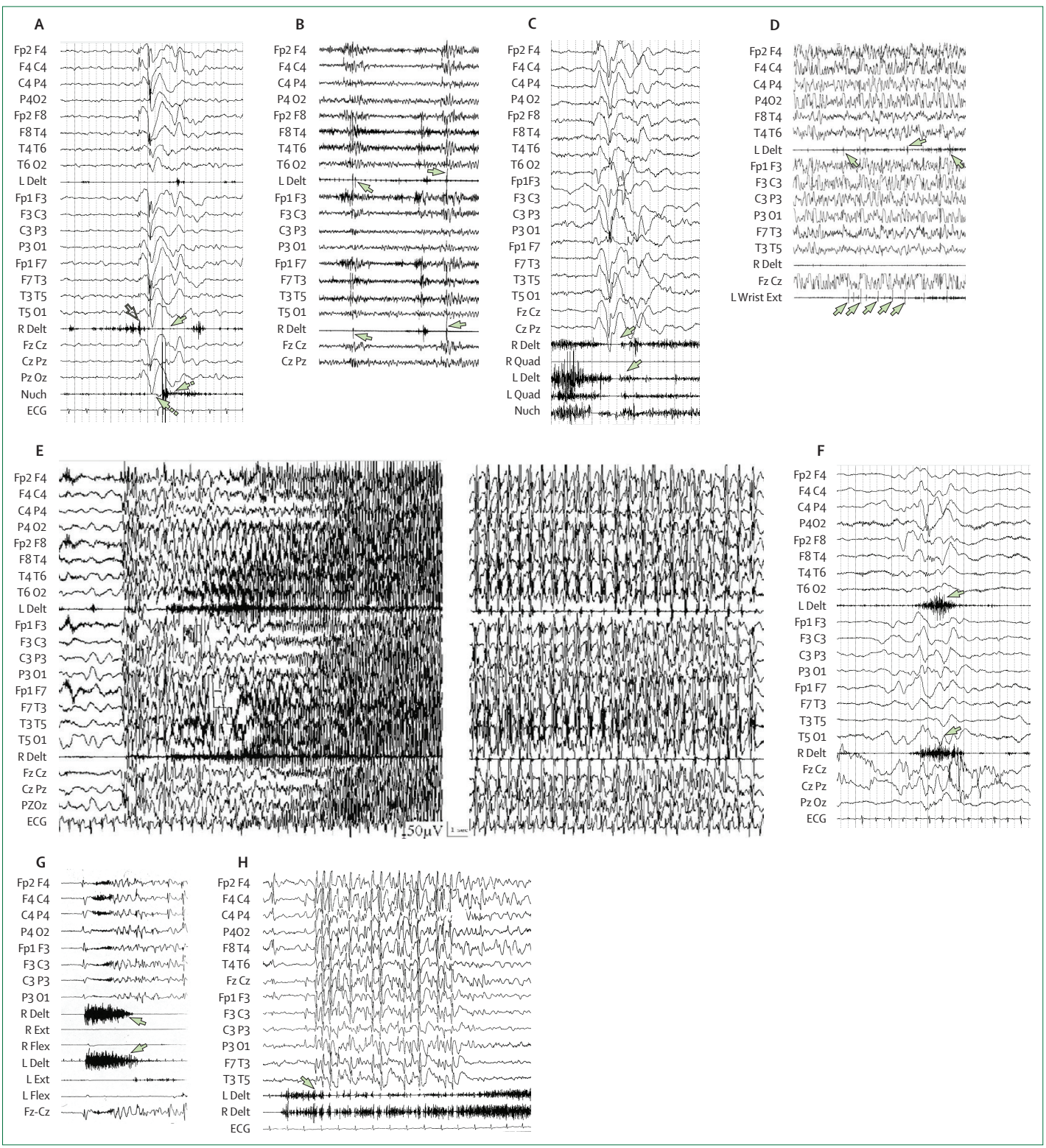
In most children, epilepsy with myoclonic-atonic seizures follows a complex inheritance pattern, suggesting a polygenic basis similar to that underlying idiopathic generalised epilepsies.[17] However, the genetic basis of non-monogenic epilepsy with myoclonic-atonic seizures remains hypothetical, as no studies have systematically investigated the contribution of common variants of minor effect, which might be combined with pathogenic alleles of major and intermediate effect. Pathogenic variants in single genes have been identified in 3–41% of patients, with high heterogeneity; the most frequent causative genes are *CACNA1H, CHD2, HNRNPU, IQSEC2, KCNT1, KCN2A, MECP2, NEXMIF, POL3B, SCN1A, SCN2A, SCN8A, SCN1B, SLC2A1, SLC6A1, STXBP1,* and *SYNGAP1* (appendix).[5,18–22]

See Online for appendix

Whole-exome sequencing (WES) is the preferred method to identify pathogenic variants in single genes for patients with epilepsy with myoclonic-atonic seizures, regardless of whether the patients have pre-existing developmental delay, drug-resistant epilepsy, or cognitive impairment. Epilepsy gene panels containing different numbers of genes are available[23] but might have insufficient coverage of the large number of known and newly identified genes associated with this syndrome. Furthermore, as new epilepsy-related genes continue to be discovered, WES allows for periodic reanalysis of negative cases,[24] enabling identification of novel genetic causes missed by targeted panels. WES also facilitates the delineation of phenotypic spectra linked to specific genes, shortening the time to establish a definitive diagnosis. For these reasons, WES provides the most comprehensive diagnostic approach for patients with epilepsy with myoclonic-atonic seizures. Studies using array-comparative genomic hybridisation or single nucleotide polymorphism arrays have shown a low yield of pathogenic copy number variants in patients with epilepsy with myoclonic-atonic seizures. Only one patient with early-onset myoclonic epilepsy among 60 with intellectual disability and genetic generalised epilepsy harboured a pathogenic copy number variant (del16p13.11).[25] However, it remains unclear whether this patient specifically presented with the phenotype of epilepsy with myoclonic-atonic seizures. In a larger cohort of 1097 patients with epilepsy, none of the 120 patients carrying a pathogenic copy number variant had epilepsy with myoclonic-atonic seizures.[26]

A study of 84 unrelated probands with epilepsy with myoclonic-atonic seizures found that four (5%) carried a pathogenic variant in the *SLC2A1* gene, which encodes GLUT1, the main glucose transporter across the blood–brain barrier.[27] These individuals had some features of

GLUT1 deficiency syndrome, including intellectual disability in all probands; paroxysmal exertional dyskinesia in two; ataxia, dysarthric speech, and poor motor performance in three; and deceleration of head growth in one. In contrast with the findings of this study, genetic testing of *SL2CA* in two independent cohorts of



51[19] and 120[28] individuals with epilepsy with myoclonic-atonic seizures did not identify any pathogenic variant.

Targeted resequencing of 644 individuals with epileptic encephalopathies identified six pathogenic variants in the *SLC6A1* gene in seven individuals with epilepsy with myoclonic-atonic seizures;[29] *SLC6A1* encodes GAT-1, a voltage-dependent GABA transporter responsible for the re-uptake of GABA from the synapse. The six variants included truncations and missense alterations, most likely leading to loss of function of GAT-1 and reduced GABA re-uptake from the synapse. In this study, pathogenic *SLC6A1* variants were identified in 7 (4%) of 160 probands with epilepsy with myoclonic-atonic seizures and were more likely to be found in those with pre-existing developmental delay. In a later study, among 34 individuals with *SLC6A1* pathogenic variants, 16 (47%) were classified as having epilepsy with myoclonic-atonic seizures; most individuals had language delay and mild-to-moderate intellectual disability before epilepsy onset.[30] In a further study of 116 patients with *SLC6A1* pathogenic variants, epilepsy with myoclonic-atonic seizures was confirmed as the most common epilepsy syndrome in 20 (24%) of 82 individuals with available clinical information.[31] A child with epilepsy with myoclonic-atonic seizures onset at 18 months and pre-existing mild developmental delay harboured a de novo balanced chromosomal translocation, 46,XX,t(3;11)(p25;q13.1)dn, disrupting intron 7 of the *SLC6A1* gene, identified through long-read whole-genome sequencing.[32]

Among 13 patients with de novo pathogenic variants in *POLR3B* (which encodes the second largest subunit of RNA polymerase III, an essential protein for the transcription of small non-coding RNAs), seven patients were classified as having epilepsy with myoclonic-atonic seizures and two as having probable epilepsy with myoclonic-atonic seizures; most patients had developmental delay preceding seizure onset.[22] Among 22 patients with pathogenic variants in *GABRB3* (encoding the β_3 subunit of the $GABA_A$ receptor), five (23%) were classified as having epilepsy with myoclonic-atonic seizures.[33] Among 17 patients carrying loss-of-function pathogenic variants in *SYNGAP1* (encoding a component of the post-synaptic density of glutamatergic neurons), three (18%) had an epilepsy with myoclonic-atonic seizures phenotype, with neuro-developmental delay preceding epilepsy onset.[34] A later study described 57 patients with *SYNGAP1* pathogenic variants and identified a distinctive syndrome combining epilepsy with eyelid myoclonia and features of epilepsy with myoclonic-atonic seizures, as well as seizures triggered by eating.[35] Among 42 patients with epilepsy associated with pathogenic variants in *NEXMIF*, an X-linked gene playing an important role in early brain development, seven (17%) were classified as having epilepsy with myoclonic-atonic seizures, and an additional five (12%) had overlapping features of epilepsy with myoclonic-atonic seizures and eyelid myoclonia.[36] Among six patients with de novo pathogenic loss-of-function variants in *KCNA2* (encoding the potassium channel $K_v1.2$), one was classified as having epilepsy with myoclonic-atonic seizures; this patient had shown no developmental delay before seizure onset at 11 months.[37] Among 201 patients with pathogenic variants in the *SCN2A* gene (encoding the voltage-gated sodium channel $Na_v1.2$), two (1%) were classified as having epilepsy with myoclonic-atonic seizures, with seizure onset between 15 months and 24 months; one had pre-existing developmental delay.[38]

A targeted resequencing study of 19 known genes and 46 candidate genes for epileptic encephalopathy found pathogenic or likely pathogenic variants in three (4%) of 81 patients with epilepsy with myoclonic-atonic seizures,

Figure 1: **Examples of ictal polygraphic EEG recordings in patients with epilepsy with myoclonic-atonic seizures (A–E) and key differential diagnoses with ictal manifestations clinically mimicking myoclonic-atonic seizures in other childhood epilepsy syndromes (F–H)**

(A) Myoclonic-atonic seizure in a boy aged 22 months. An initial myoclonic jerk, visible on the readout for the right deltoid (short outlined arrow) is associated with a bilateral spike and followed by a few smaller jerks, corresponding to a polyspike discharge and an atonic phenomenon, shown by the silent electromyography activity on the right deltoid (short filled arrow) and nuchal muscles (long dashed arrow), and correlating with the slow wave component of the discharge. A mechanical artefact is present on the nuchal electrode, caused by the head drop resulting from the atonia (short dashed arrow). (B) Myoclonic seizures in a boy aged 6 years. Shock-like axial muscle jerking (arrows), not resulting in falls, is associated with bilateral diffuse fast spike and sharp-wave discharges. (C) Atonic seizure in a boy aged 9 months. An irregular high-amplitude sharp-wave and slow-wave complex lasting 1 s is accompanied by a sudden fall. Interferential anti-gravity muscle activity recorded in the deltoid, left quadricep, and nuchal muscles is suddenly interrupted or fragmented during the slow polyphasic EEG complex (arrows). (D) Myoclonic (obtundation) status in a boy aged 3 years and 5 months. The child was vacant and unresponsive and presented with drooling and continuous, erratic, and arrhythmic muscle jerks involving multiple muscles. Arrows indicate myoclonic potentials recorded from the left deltoid and right wrist extensor muscles. Irregular high-amplitude EEG activity is recorded on all EEG channels. (E) Generalised (vibratory) seizure in a boy aged 4 years. Left-hand panel: a bilateral polyspike discharge on the EEG is followed by onset of a tonic-vibratory phase with bilateral and synchronous fast muscle jerking, at 7–8 Hz, which does not reach an interferential contraction of a tonic phase. Right-hand panel: at the end of the same seizure, 35 s after onset, bilateral clinic jerking is accompanied by diffuse polyspike-wave activity. (F) Epileptic spasm in a boy aged 2 years and 6 months with infantile epileptic spasms. A polyphasic slow wave with a superimposed burst of fast activity on the EEG is associated with a rhomboid-shaped muscle artefact on deltoid electromyography (arrows), causing the child to fall forward. (G) Tonic seizure in a boy aged 6 years with Lennox-Gastaut syndrome; recording of a brief tonic seizure causing a drop attack. A bilateral sharp wave is followed by diffuse, low-voltage fast activity, associated with bilateral electromyography activity, which reaches maximum immediately and progressively decreases in axial muscles (arrows). (H) Epileptic negative myoclonus with atonic falls in a boy aged 7 years with atypical Rolandic epilepsy and developmental epileptic encephalopathy with spike-and-wave activation in sleep. An interictal spike over the right frontocentral region is followed by an ictal discharge of generalised spike-wave complexes lasting 7 s, accompanied by a drop attack. During the ictal discharge, each slow wave is accompanied by cessation of ongoing muscle activity over the deltoid muscles (arrow). Electromyography silent periods are intercalated with electromyography bursts that reflect attempts to regain postural control. The resulting semiology very closely mimics a jerky myoclonic-atonic seizure. ECG=electrocardiogram. L Delt=left deltoid muscle. L Ext=left wrist extensor muscles. L Flex=left wrist flexor muscles. L Quad=left quadricep. Nuch=nuchal muscles. R Delt=right deltoid muscle. R Ext=right wrist extensor muscles. R Flex=right wrist flexor muscles. R Delt=right deltoid muscles.

including variants in *CHD2* (n=2) and *GABRG2* (n=1); only one patient with *CHD2*-related epilepsy with myoclonic-atonic seizures had mild developmental delay before seizure onset.[18] Another study conducted array-comparative genomic hybridisation and WES in 27 patients with epilepsy with myoclonic-atonic seizures, all of whom showed typical developmental progress before seizure onset, and found candidate disease-causing variants in 11 (41%); variants were found in known epilepsy genes in five (19%) patients, namely *CACNA1H, CHD2, KCNA2, KCNT1,* and *STXBP1,* but no variants were identified in *SLC2A1* or *SLC6A1*.[20] A WES study of 29 individuals with epilepsy with myoclonic-atonic seizures identified four likely pathogenic variants in four (14%) of 29 individuals, namely missense variants in *SLC6A1* and *HNRNPU*, a microdeletion at 2q24.2 involving *SCN1A,* and a microdeletion at Xp22.31 involving *STS*. *HNRNPU* and *STS* remain possible novel candidates for causative genes for epilepsy with myoclonic-atonic seizures, requiring further confirmation.[21] A further WES study found pathogenic variants in 12 (14%) of 101 patients with epilepsy with myoclonic-atonic seizures, including variants in *KCNA2, KCNB1, NEXMIF, MECP2, SCN2A, SLC6A1, STX1B,* and *SYNGAP1*;[5] three new potential candidate genes were also identified—*ASH1L, CHD4*, and *SMARCA2*. In the same study, patients with epilepsy with myoclonic-atonic seizures and a coexistent neurodevelopmental disorder were more likely to have an underlying genetic cause. Additional reports have confirmed the genetic heterogeneity of epilepsy with myoclonic-atonic seizures, describing pathogenic variants in *ANKRD11,*[39] *CSNK2B,*[40] *SCN1A* (in patients with genetic epilepsy with febrile seizures plus),[41] *SCN1B* (also in a patient with genetic epilepsy with febrile seizures plus),[42] *SCN8A,*[43] SEMA6B,[44] *STX1B,*[45] *CHD2,*[46] and *MBD5*.[47]

Differential diagnosis

Distinguishing epilepsy with myoclonic-atonic seizures from other childhood-onset epilepsy syndromes or diseases with generalised seizures can be challenging. A key differential diagnosis is late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, which presents in children with typical development or isolated speech delay. Although these children might have prominent myoclonic and generalised convulsive seizures, unlike children with epilepsy with myoclonic-atonic seizures they show rapid motor and cognitive decline and ataxia, ultimately evolving to progressive myoclonus epilepsy a few years after clinical onset.[48] EEG hallmarks include progressive background slowing, high-voltage focal slow waves, often over temporal and occipital regions, and a photoparoxysmal response at low frequencies. The latter feature is rare in epilepsy with myoclonic-atonic seizures, making photosensitivity testing at very low frequencies (eg, 1 Hz) crucial for differential diagnosis. Genetic testing has identified biallelic pathogenic variants in *TPP1* in patients with CLN2.[49] Cerliponase alfa, an enzyme replacement therapy, prolongs life and slows disease progression in patients with classic CLN2 disease.[50]

Seizures causing sudden falls, such as brief tonic, myoclonic, myoclonic-atonic, and atonic seizures are also seen in Lennox-Gastaut syndrome (figure 1G). Lennox-Gastaut syndrome can be distinguished from epilepsy with myoclonic-atonic seizures by the early occurrence of tonic seizures, absence of episodes of myoclonic status epilepticus, and EEG showing slow (<2·5 Hz) generalised spike-wave complexes and generalised ictal and interictal paroxysmal fast activity during sleep. Children with Lennox-Gastaut syndrome often have moderate-to-severe developmental delay before seizure onset and might have a history of infantile epileptic spasms syndrome.[51] Epileptic spasms, another cause of sudden loss of posture (figure 1F), typically cluster and show interictal and ictal EEG features absent in epilepsy with myoclonic-atonic seizures.[52]

Other differential diagnoses include myoclonic epilepsy of infancy and Dravet syndrome. Myoclonic epilepsy of infancy is not associated with abrupt myoclonic-atonic seizures and typically presents earlier in life than epilepsy with myoclonic-atonic seizures.[53] Dravet syndrome is characterised by prolonged generalised clonic or hemiclonic seizures precipitated by fever, illness, or vaccination in the first year, with myoclonic seizures emerging from the second to third year of life but rarely causing falls.[54] Developmental epileptic encepalopathy with spike-and-wave activation in sleep (also known as continuous spike wave in sleep) is an age-related syndrome marked by developmental regression and continuous diffuse spike-wave complexes during sleep, usually appearing between 4 years and 6 years of age.[1] Spike-wave complexes might also appear during wakefulness and cause atonic absences or loss of postural control due to negative myoclonus, the appearance of which, without ictal polygraphic EEG recordings, can be indistinguishable from myoclonic-atonic seizures (figure 1H). Subacute sclerosing panencephalitis, a rare, rapidly progressive condition, causes spasm-like or myoclonic seizures with falls and a diagnostic EEG pattern.[55] Focal structural abnormalities on neuroimaging, along with focal seizures and focal abnormalities on neurological examination or EEG, exclude a diagnosis of epilepsy with myoclonic-atonic seizures.[7] Additionally, developmental epileptic encepalopathies caused by known mutations might include myoclonic-atonic seizures among the various generalised seizures observed either at onset or during the disease course and, thus, show overlapping symptoms with epilepsy with myoclonic-atonic seizures (table 1).[35,36,56]

Epilepsy with myoclonic-atonic seizures is diagnosed when a patient develops epilepsy with myoclonic-atonic seizures in early childhood associated with generalised

	Key differentiating features
CHD2-related developmental epileptic encephalopathy	Developmental delay before seizure onset; photosensitivity common; myoclonic-atonic seizures uncommon; remission uncommon
Developmental epileptic encephalopathy with spike-and-wave activation in sleep*	Developmental regression; near-continuous diffuse spike-and-wave EEG complexes during sleep; atonic absences and negative myoclonus with falls possible and very difficult to differentiate from myoclonic-atonic seizures based on clinical observation alone; EEG-electromyography recordings show that myoclonic-atonic seizures do not occur
Dravet Syndrome	Typically presents in infancy, earlier than epilepsy with myoclonic-atonic seizures, with hyperthermia-induced generalised clonic or hemiclonic seizures that are prolonged and often repeated; myoclonic seizures or subtle myoclonic jerking frequently seen, but myoclonic-atonic seizures do not occur
Focal epilepsy syndromes	Focal structural abnormalities on neuroimaging; focal seizures; focal EEG abnormalities; possible diffuse bilateral synchronous spike-wave EEG activity
Lennox-Gastaut syndrome	Tonic seizures while awake and asleep; slow generalised spike-wave <2·5 Hz; ictal or subclinical low-voltage fast activity in sleep
Myoclonic epilepsy of infancy	Typically presents earlier than epilepsy with myoclonic-atonic seizures, between the ages of 4 months and 3 years; myoclonic seizures do not show the myoclonic-atonic sequence; atypical absence seizures and generalised convulsive seizures might appear after the age of 5 years in some patients, and usually after a seizure-free interval following remission of myoclonic seizures
Neuronal ceroid lipofuscinosis	Progressive motor and cognitive decline; increasingly frequent multifocal myoclonus and generalised myoclonic seizures; photoparoxysmal EEG response at low stimulus frequencies; high-voltage slow waves over the temporo-occipital regions; progressive EEG background slowing
NEXMIF-related developmental epileptic encephalopathy	Frequent developmental delay before seizure onset; photosensitivity and eye closure sensitivity on EEG can be present; most patients have cognitive impairment
Subacute sclerosing panencephalitis	Fulminant or rapid disease progression; diagnostic EEG pattern
SYNGAP1-related developmental epileptic encephalopathy	More severe developmental delay before seizure onset than in children with epilepsy with myoclonic-atonic seizures; focal or multifocal and generalised EEG abnormalities; most patients have cognitive impairment

*Formerly known as continuous spike wave in sleep.

Table 1: **Main differential diagnoses of epilepsy with myoclonic-atonic seizures**

spike-wave complexes on EEG. Nonetheless, as we have noted, although myoclonic-atonic seizures are a distinct seizure type, they can occur in other epilepsy syndromes. Additionally, single-gene disorders might initially present with partial features, with the full phenotype emerging only with long-term follow-up. For example, a patient with generalised spike-wave complexes and myoclonic-atonic seizures in the setting of a single-gene disorder might initially fulfil criteria for epilepsy with myoclonic-atonic seizures. However, long-term follow-up might enable the distinct trajectory related to the specific genetic cause to be delineated more clearly.

Nosological limits

Unlike epilepsy syndromes for which clinical manifestations are closely tied to a specific genetic cause, such as Dravet syndrome or *CDKL5*-related developmental epileptic encepalopathy, epilepsy with myoclonic-atonic seizures encompasses a phenotypic pattern that is common to various genetic causes. The onset of coherent clinical and EEG findings with a variety of causes within particular age limits is also seen in children with Lennox-Gastaut syndrome or developmental epileptic encepalopathy with spike-and-wave activation in sleep, both of which include seizures with falling. Epilepsy with myoclonic-atonic seizures and Lennox-Gastaut syndrome share a similar age of onset, and both are associated with multiple types of generalised seizures. Developmental epileptic encepalopathy with spike-and-wave activation in sleep also has a similar age of onset but is associated with focal seizures, absence seizures, and atonic falls. Brief tonic seizures in Lennox-Gastaut syndrome and negative myoclonus in developmental epileptic encepalopathy with spike-and-wave activation in sleep might mimic the myoclonic-atonic seizures of epilepsy with myoclonic-atonic seizures. Unlike these diseases, however, epilepsy with myoclonic-atonic seizures never appears in individuals with macroscopic structural brain lesions,[7] suggesting that to generate the typical generalised electroclinical pattern of epilepsy with myoclonic-atonic seizures, brain anatomy and function must be spared within particular limits.

Both epilepsy with myoclonic-atonic seizures and Lennox-Gaustaut syndrome might manifest incompletely in some individuals. Incomplete presentations of Lennox-Gastaut syndrome are not uncommon and are now categorised as developmental epileptic encepalopathies. Although incomplete presentations of epilepsy with myoclonic-atonic seizures are not rare, no studies have analysed whether, for example, children who only manifest myoclonic-atonic seizures might be a distinct subgroup associated with different outcomes. Large-scale, systematically designed studies that incorporate both detailed polygraphic EEG and genetic data are necessary to clarify the extent to which idiopathic forms of epilepsy with myoclonic-atonic seizures and those related to specific genetic causes might differ. Because of the gap in knowledge in these areas, the nosological boundaries of epilepsy with myoclonic-atonic seizures are uncertain. Further uncertainty derives from the historical context of

epilepsy with myoclonic-atonic seizures. In the original description of this condition, myoclonic-atonic seizures were highlighted as the central expression of a syndromic picture, despite being one clinical element among several others. Thus, epilepsy with myoclonic-atonic seizures could, in part, represent a construct shaped by the context of its original definition and characterisation in terms of phenotypic traits.

Treatment approach

Table 2 summarises treatment strategies and their rationale. According to the Paediatric Epilepsy Research Consortium survey, valproate is the only recommended first-line therapy for epilepsy with myoclonic-atonic seizures.[52] An international Delphi consensus[6] endorsed valproate and clobazam as first-line treatments, with the ketogenic diet identified as the optimal second-line treatment.[7,53] Clonazepam was also considered a first-line option, whereas ethosuximide was strongly recommended as second-line therapy.[6] A combination of valproate and ethosuximide might be effective, even if either drug fails individually.

During the stormy phase, low-dose phenobarbital might help control generalised convulsive seizures resistant to other medications, as supported by our clinical experience (panel). A case report also showed that a patient with a different syndrome—epilepsy with myoclonic absences—who was resistant to multiple antiseizure medications achieved complete epilepsy remission on low-dose phenobarbital.[69] The Delphi consensus recommended valproate and benzodiazepines (either alone or in combination) and the ketogenic diet for treatment during the stormy phase;[6] steroids can also be considered. Carbamazepine, phenytoin, and vigabatrin are contraindicated in epilepsy with myoclonic-atonic seizures[6] as they might increase seizure frequency and precipitate myoclonic status. Invasive treatment such as vagus nerve stimulation or corpus callosotomy are strongly discouraged early in the disease course unless four or five treatments, including the ketogenic diet, have failed.[6]

The combination of lamotrigine with valproate and benzodiazepine might reduce generalised seizures; however, lamotrigine can worsen myoclonus and carries

	Rationale and source of evidence
First-line	
Valproate	Recommended as the primary first-line therapy by the Paediatric Epilepsy Research Consortium[57] and a Delphi consensus based on expert opinion[6]
Clobazam	Included as first-line treatment by Delphi consensus[6]
Clonazepam	Considered useful as first-line treatment in some patients[6]
Second-line	
Ethosuximide	Strongly recommended by Delphi consensus as a second-line therapy; particularly effective against spike-wave-related interictal and electroclinical phenomena[6]
Combination of valproate and ethosuximide	Recommended by Delphi consensus when either drug alone fails[6]
Ketogenic diet	Recommended as an optimal second-line therapy and occasionally first-line in severe cases, particularly during the stormy phase (based on retrospective studies)[6,7,58,59–61]; especially effective in *SLC2A1*-related epilepsies[27]
Phenobarbital (1–3 mg/kg per day)	Effective in the stormy phase to control generalised convulsive seizures (authors' clinical experience)
Third-line	
Benzodiazepines	Used as part of combination therapy for stormy phase or generalised seizures (retrospective studies)[6]
Steroids	Sometimes used in combination therapy during the stormy phase (retrospective studies)[6]
Other lines	
Lamotrigine (with valproate and benzodiazepines)	Can reduce generalised seizures but may worsen myoclonus (retrospective studies)[62,63]
Cannabidiol	Shown to reduce seizures by >50% in retrospective studies; used as an add-on treatment in patients resistant to other antiseizure medications (retrospective study)[64]
Sulthiame	A retrospective study showed >50% seizure reduction in patients unresponsive to other treatments[65]
Felbamate	High response rate for patients with intractable drug-resistant seizures (retrospective study); not available in many countries; serious adverse effects[6,66,67]
Topiramate, zonisamide, and perampanel	Potential efficacy suggested in anecdotal reports[6]
4-phenylbutyrate	Shown to improve seizure control in epilepsies caused by *STXBP1* and *SLC6A1* variants (single-treatment group, multiple-dose, open-label study)[68]
Not recommended	
Carbamazepine, phenytoin, and vigabatrin	Shown to increase seizure frequency and precipitate myoclonic status (retrospective studies)[6]
Invasive treatments (vagus nerve stimulation and corpus callosotomy)	Consensus against use unless multiple treatments have failed (including ketogenic diet)[6]

Within each category, treatments are listed based on the available literature and the authors' own expertise.

Table 2: **Treatment options for children with epilepsy with myoclonic-atonic seizures**

the risk of Stevens-Johnson syndrome.[62,63] Other treatments, such as cannabidiol, topiramate, zonisamide, felbamate, and sulthiame are based on anecdotal evidence and can be considered at later stages of treatment. In a retrospective open-label study involving 35 children with epilepsy with myoclonic-atonic seizures who were unresponsive to at least five antiseizure medications and non-pharmacological treatments, add-on sulthiame led to a greater than 50% seizure reduction in most patients after a mean follow-up of 30 months.[65] Another retrospective open-label study of 22 patients with epilepsy with myoclonic-atonic seizures who were resistant to most antiseizure medications and non-pharmacological treatments found that add-on purified cannabidiol led to a 50% or greater reduction in seizures in most patients, improving myoclonic-atonic, generalised tonic-clonic, and atypical absence seizures and non-convulsive status epilepticus.[64] A small case series reported that four of six patients with intractable epilepsy with myoclonic-atonic seizures became seizure free on felbamate.[66] In a retrospective analysis of felbamate usage for treating epilepsy with myoclonic-atonic seizures, of 37 patients treated with felbamate, 23 (62%) were responders, a higher rate than those treated with valproate (32%) or levetiracetam (15%) and similar to the response rate in patients treated with the ketogenic diet (69%).[67] However, felbamate is unavailable in many countries and requires close monitoring due to its side-effect profile.[6]

A retrospective analysis of 166 children with epilepsy with myoclonic-atonic seizures found that only 26% responded to the first three antiseizure medications, defined as a greater than 50% seizure reduction.[7] Response rates were 31% for valproate, 17% for levetiracetam, and 26% for other antiseizure medications combined. Drug resistance occurred within 3 months of initiating medications in 90% of patients. Levetiracetam was one of the first three medications prescribed in 81% of cases, and valproate was one of the first three medications in 61%. Despite valproate's recommendation as a first-line treatment for generalised epilepsy, a prospective study of 495 children in 17 paediatric epilepsy centres found that it was prescribed in only 61% of patients, with levetiracetam being the most prescribed first-line monotherapy (81% of patients), regardless of the type of epilepsy or existing evidence.[70] This finding aligns with current empirical prescribing practices for young children with new-onset epilepsy, but the use of levetiracetam as first-line monotherapy does not have a rationale and does not follow any specific guideline—rather, it reflects ease of use of levetiracetam, regardless of whether it is proven to be efficacious.

For patients who have difficulty complying with the ketogenic diet, the less restrictive modified Atkins (ketogenic) diet is also beneficial for treating epilepsy with myoclonic-atonic seizures.[71,72] Studies reported seizure freedom with the ketogenic diet in 18–58% of patients with epilepsy with myoclonic-atonic seizures and a greater than 50% seizure reduction in 35–55%.[59–61] A 2017 study reported a greater than 50% seizure reduction in 25 (83%) of 30 patients with drug-resistant epilepsy with myoclonic-atonic seizures, including 47% who became seizure free with the modified Atkins diet.[72] In a large retrospective study by Nickels and colleagues, 75 (79%) of 95 patients responded to dietary therapies (either ketogenic or modified Atkins), a significantly greater percentage than that responding to the first three antiseizure medications.[7]

Panel: **A child with epilepsy with myoclonic-atonic seizures**

A boy aged 2 years presented to our emergency department after experiencing tonic-vibratory seizures, following isolated myoclonic-atonic seizures a few weeks previouly. Before seizure onset, his developmental milestones, including early language acquisition, were typical for his age. Treatment with valproate and clonazepam failed to fully control the seizures. Initial interictal EEG recordings showed isolated spike-wave discharges with normal background activity. Brain MRI was normal.

At the age of 3 years, the patient had language regression and ataxia. EEG showed long runs of high-amplitude, 2–3 Hz irregular, generalised spike-wave activity, with background slowing and prolonged runs of slow spike-wave complexes, consistent with non-convulsive status epilepticus. Array-based comparative genomic hybridisation found no pathogenic copy number variants. A low dose of phenobarbital was added to valproate and clonazepam, leading to rapid improvement of the patient's clinical and EEG features. Clonazepam was then withdrawn, and ethosuximide was introduced.

While on phenobarbital, valproate, and ethosuximide, he remained seizure free for about 6 months, but clusters of myoclonic-atonic, myoclonic, and tonic-vibratory seizures reappeared, accompanied by ataxia and further language regression. He was then started on a ketogenic diet, which led to a new sustained period of seizure freedom, along with gradual improvement in gait and language. He was completely seizure free by the age of 6 years, and all drugs were gradually discontinued by the age of 8 years. He continued the ketogenic diet until the age of 10 years. Whole-exome sequencing did not identify any possible causative variants. Longitudinal psychometric follow-up showed no cognitive impairment. This individual is now aged 23 years, is seizure free and treatment free, and has no neurological deficits.

Treatments based on genetic cause

When specific genetic causes are identified, targeted treatment should be considered. Knowledge of the genetic cause can inform treatment strategies and improve outcomes (figure 2). An example is epilepsy with myoclonic-atonic seizures with underlying GLUT1

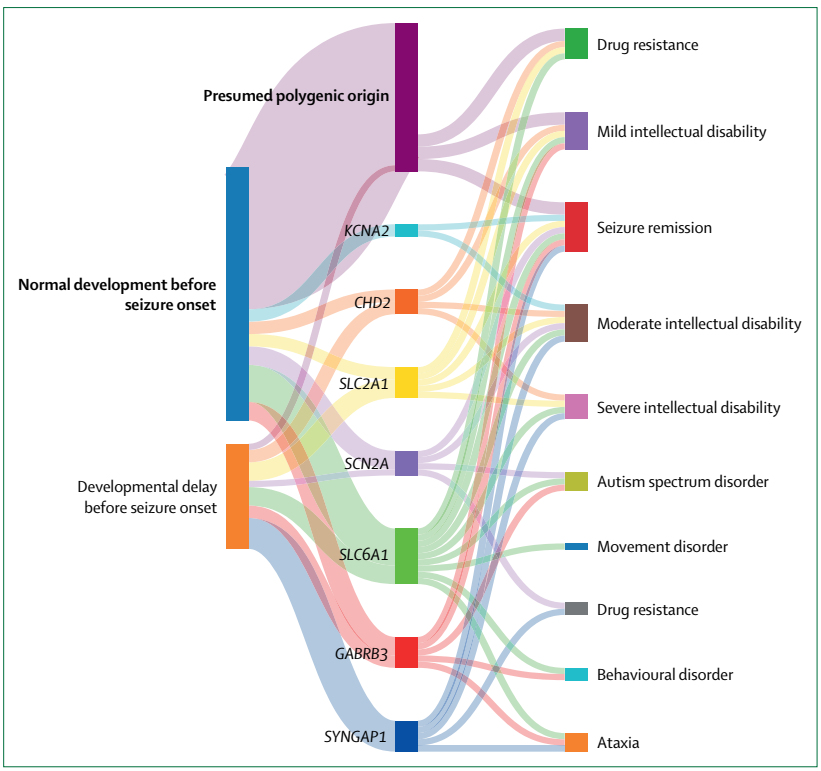


Figure 2: **Genetic and clinical heterogeneity in epilepsy with myoclonic-atonic seizures**
Some of the established single-gene causes of epilepsy with myoclonic-atonic seizures are shown; most patients do not have an identified pathogenic variant and a polygenic origin is assumed. There is a variable association with developmental delay before seizure onset, interpretation of which should consider that the earlier the onset of seizures, the lower the chance of detecting a pre-existing deficit unless it is already severe; seizure and developmental outcomes also differ in epilepsy with myoclonic-atonic seizures. There is no clear genotype–phenotype correlation. Relative frequency (estimated) of developmental delay before seizure onset, single-gene versus polygenic origin, and disease outcomes are indicated by the height of the bars. Stream colours correspond to developmental status before seizure onset (left) and seizure or other clinical outcomes (right) associated with each gene.

deficiency caused by pathogenic variants of *SLC2A1*, whereby early diagnosis and early initiation of a ketogenic diet can result in an excellent response in seizure control and development.[27] Valproate has been reported as the most effective drug for *SLC6A1*-related epilepsies, with lamotrigine and ethosuximide also showing efficacy.[30,31] However, it is unclear whether these responses are based on the underlying pathophysiology of the genetic disorder or the specific electroclinical features of the epilepsy syndrome. Patients with epilepsy with myoclonic-atonic seizures caused by loss-of-function *SCN2A* variants should not be treated with sodium channel blockers, as these drugs could substantially worsen their condition.[38] Based on evidence from a preprint paper, treatment of children with pathogenic *STXBP1* or *SLC6A1* variants with 4-phenylbutyrate resulted in improved seizure control in a single-treatment, multiple-dose, open-label study.[68] Additionally, recent preclinical and clinical evidence supports acetazolamide for treating epilepsies caused by *CHD2* variants.[73]

Prognosis

The prognosis for children with epilepsy with myoclonic-atonic seizures ranges from spontaneous remission with no effects on development to intractable seizures with moderate-to-severe intellectual disability. Approximately two-thirds of patients have complete seizure remission (defined as no seizures and not on antiseizure medication).[74] Although more than half of the patients who attain complete remission show typical developmental progress, approximately a quarter of these children are expected to have learning disorders without intellectual disability. Patients who continue to have seizures after 5 years, along with persistent EEG abnormalities, are unlikely to attain long-term remission.[6] This outcome underscores the importance of accurate syndrome diagnosis and prompt initiation of effective treatment, which could have a positive effect on long-term outcomes.[16]

Retrospective studies have identified several negative prognostic factors for seizure remission and cognitive function, including tonic seizures, absence seizures, prolonged or frequent non-convulsive status epilepticus, generalised tonic-clonic seizures in the first 2 years of life, sleep-onset seizures, early seizure onset (before 1 year of age), and drug resistance. EEG features associated with poor prognosis include frequent generalised abnormalities, focal spikes, paroxysmal fast activity, and abnormal background activity.[6,8,9,16,58,75] However, these reports are based on disparate observations and probably include patients with tonic seizures (typical of Lennox-Gastaut syndrome) and focal abnormalities (typical of Rolandic epilepsy with spike-and-wave activation in sleep), limiting their reliability. Nonetheless, a retrospective study showed that early introduction of the ketogenic diet after failure of three or fewer antiseizure medications significantly improved seizure remission and correlated with better developmental and cognitive outcomes compared with later introduction of the ketogenic diet.[58]

To date, no studies have specifically investigated an association between genetic cause and risk of drug-resistant disease and developmental outcomes in people with epilepsy with myoclonic-atonic seizures. However, epilepsy with myoclonic-atonic seizures caused by pathogenic variants in specific genes, such as *SLC6A1*, is associated with more severe phenotypes and a higher likelihood of drug resistance than disease without an identified genetic cause.[29,30] In *SLC6A1*-related epilepsy with myoclonic-atonic seizures, seizures can persist into adulthood, with no clear-cut correlation between seizure control and cognitive outcome; all individuals have intellectual disability, ranging from mild to severe, and might develop autistic features, behavioural problems, movement disorders, and ataxia. In *GABRB3*-related epilepsy with myoclonic-atonic seizures, freedom from seizures has been reported soon after epilepsy onset, with most patients having mild intellectual disability, variably

associated with ataxia, autism spectrum disorder, and behavioural disturbance.[33] In *SYNGAP1*-related epilepsy with myoclonic-atonic seizures, seizure outcomes are variable, but all patients have moderate-to-severe intellectual disability and ataxia.[34,35] In *POLR3B*-related epilepsy with myoclonic-atonic seizures, epilepsy is often drug resistant and associated with mild-to-moderate intellectual disability, autism spectrum disorder, microcephaly, ataxia, and spasticity.[22] One patient with *KCNA2*-related epilepsy with myoclonic-atonic seizures showed no signs of developmental delay before seizure onset at 11 months, became seizure free by the age of 4 years, and had mild-to-moderate intellectual disability by the age of 7 years.[37] Two patients with *SCN2A*-related epilepsy with myoclonic-atonic seizures showed contrasting seizure outcomes—one was having intractable seizures at follow-up at 3 years, and the other had become seizure free by 18 months; however, both had moderate intellectual disability and autism spectrum disorder (appendix).[38] There is some evidence that epilepsy with myoclonic-atonic seizures caused by single-gene variants is associated with a higher incidence of intellectual disability and autism spectrum disorder.[5,19–21]

Impairments in daily life executive function have been observed in children with epilepsy with myoclonic-atonic seizures, as measured with the Behavioral Rating Inventory of Executive Functions (BRIEF) for school-aged children and BRIEF-P, the version for preschool-aged children, via parental questionnaires.[76] Compared with typically developing children, patients with epilepsy with myoclonic-atonic seizures had greater executive function deficits, which were linked to earlier seizure onset, longer epilepsy duration, and poorer seizure control.[76] A retrospective analysis of 166 patients with epilepsy with myoclonic-atonic seizures found a bidirectional relationship between cognitive and seizure outcomes.[7] Patients with persistent global developmental delay were unlikely to attain seizure freedom, and those who did not become seizure free were likely to continue to have global developmental delay.

Associated comorbidities

Epilepsy with myoclonic-atonic seizures is frequently associated with a spectrum of neurodevelopmental comorbidities. Intellectual disability is reported in 34–63% of patients, depending on the psychometric tools and cognitive definitions used, ranging from mild to profound impairment. Behavioural disorders, such as hyperactivity and aggression, occur in up to 25% of patients.[6] Other manifestations include deficits in adaptive behaviour, with low functioning in conceptual, social, and practical skills in up to 69% of patients,[5] as well as impaired daily life executive function in up to 53%.[76] Behavioural and sleep disturbances typically improve or remit once seizures are controlled.[6]

Symptoms of autism spectrum disorder and ADHD have been identified in 5–45% of patients with epilepsy with myoclonic-atonic seizures across various studies; ataxia and other motor impairments are also common and might occur independently of a stormy phase.[6] These impairments might be linked to antiseizure medication or the underlying genetic cause (figure 2). Comorbid cognitive and behavioural conditions might also result from the sum of the effects of epileptic activity and heavy treatment; nonetheless, patients with neurodevelopmental symptoms or neurological signs are more likely to have an identified genetic cause than those without such symptoms.[5,21] Screening for neurodevelopmental comorbidities at a child's diagnosis and monitoring throughout follow-up are crucial. Early identification helps to prevent difficulties in school, work, and home life, as cognitive and behavioural issues can hinder academic success and are associated with adverse psychosocial outcomes.[77] Medications such as risperidone for behavioural disturbances or methylphenidate for ADHD should be considered when appropriate,[78] along with behavioural therapy, speech therapy, psychological counselling, and optimised environmental and academic interventions, as indicated in all children with developmental epileptic encepalopathies.[79]

Systematic data on morbidity and mortality specific to epilepsy with myoclonic-atonic seizures are scarce, but an analysis of genetic developmental epileptic encepalopathies, including epilepsy with myoclonic-atonic seizures, suggested that patients' prognoses can vary widely, depending on the underlying genetic variant.[80]

Conclusions and future directions

Epilepsy with myoclonic-atonic seizures is a complex, paediatric generalised epilepsy syndrome with heterogeneous causes and variable severity and outcomes. Genetic causes are increasingly recognised, with both polygenic inheritance and single-gene variants implicated in the pathogenesis. Interictal generalised spike-wave EEG discharges and ictal recording of myoclonic-atonic seizures are important for diagnosis because other epilepsy syndromes with onset in childhood, especially Lennox-Gastaut syndrome and developmental epileptic encepalopathy with spike-and-wave activation in sleep, can be accompanied by seizures that are difficult to distinguish from the myoclonic-atonic falls. Current treatment approaches are based largely on traditional antiseizure medications, with valproate, ethosuximide, and clobazam forming the backbone of therapy. The ketogenic diet is also frequently used. Despite early drug resistance, remission is attainable in a substantial proportion of patients. However, developmental outcomes remain variable, with cognitive and behavioural impairments often persisting even after seizure control.

Genetic testing of patients with epilepsy with myoclonic-atonic seizures should be prioritised to

Search strategy and selection criteria

We searched PubMed, Embase, and Cochrane library for high-quality peer-reviewed articles, systematic reviews, and clinical trials using MeSH terms such as "Epilepsies, Myoclonic" and subheadings such as "atonic," "astatic," "Doose syndrome," alongside free text terms, including "Epilepsy with myoclonic-atonic seizures", "EMAtS", "aetiology," "EEG," "genetics," "treatment," "prognosis," and "comorbidities", from Jan 1, 2010, to Nov 30, 2024. Non-English publications were also considered, to avoid language bias. We also screened the reference lists from the selected publications. Articles were evaluated for relevance, quality, and scope, excluding irrelevant or poor-quality research and duplicates. The final reference list was generated on the basis of relevance to the topics covered in this Review.

identify single-gene causes, which can inform both prognosis and treatment. For example, the ketogenic diet should be considered early in patients with GLUT1 deficiency, whereas sodium channel blockers are contraindicated in *SCN2A*-related epilepsy with myoclonic-atonic seizures. The syndrome necessitates a multidisciplinary approach, integrating care teams of neurologists, geneticists, psychologists, and educators. Early identification of neurodevelopmental and cognitive issues can enable timely interventions, potentially improving long-term outcomes. If first-line antiseizure medications fail, clinicians should be prepared to consider less frequently used treatments such as phenobarbital or the ketogenic diet. The temptation to use new-generation antiseizure medications should be resisted because they have not been proven to be helpful in this syndrome. Treatments such as carbamazepine and phenytoin, which can exacerbate myoclonic and absence seizures, should be avoided

Future research should focus on better understanding the genetic underpinnings of epilepsy with myoclonic-atonic seizures, particularly in terms of how specific variants influence disease progression and response to treatment. This research will require larger, well-characterised patient cohorts and a more systematic use of WES or whole-genome sequencing. Furthermore, there is a pressing need for dedicated clinical trials to assess the efficacy of antiseizure medications. Because of its relative rarity, epilepsy with myoclonic-atonic seizures has never been the subject of dedicated trials—unlike Dravet syndrome and Lennox-Gastaut syndrome. However, epilepsy with myoclonic-atonic seizures is considerably more common than Dravet syndrome,[2] and consideration of personalised medicine approaches tailored to specific genetic causes is warranted. Additionally, exploring the role of gene variants or molecular interventions for specific single-gene causes could revolutionise treatment options and outcomes in the future.

Contributors
RG and SB contributed to conceptualisation and literature search and drafted the manuscript. IS critically revised and synthesised the evidence.

Declaration of interests
RG has served on scientific advisory boards for Zogenix, Biocodex, GW-Jazz, Angelini, Takeda, Rapport Therapeutics, SK Life Science, Stoke Therapeutics, UCB, and Ethypharm; has received speaker honoraria and funding for travel from Zogenix, Biocodex, GW-Jazz, Angelini, Takeda, Rapport Therapeutics, Novartis, SK Life Science, Stoke Therapeutics, UCB, Marinus, and GRIN Therapeutics; and has served as an investigator for Zogenix, Biocodex, UCB, GRIN Therapeutics, SK Life Science, TEVA, Marinus, Lundbeck, and The Loulou Foundation. IS has served on scientific advisory boards for BioMarin, Chiesi, Eisai, Encoded Therapeutics, GSK, Knopp Biosciences, Nutricia, Takeda Pharmaceuticals, UCB, Xenon Pharmaceuticals, and Longboard Pharmaceuticals; has received speaker honoraria from GSK, UCB, BioMarin, Biocodex, Chiesi, Liva Nova, Nutricia, Zuellig Pharma, Stoke Therapeutics, Eisai, Akumentis, and Praxis; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin, Encoded Therapeutics, Stoke Therapeutics, Eisai, Longboard Pharmaceuticals; has served as an investigator for Anavex Life Sciences, Cerevel Therapeutics, Eisai, Encoded Therapeutics, EpiMinder Inc, Epygenyx, ES-Therapeutics, GW Pharma, Longboard Pharmaceuticals, Marinus, Neurocrine BioSciences, Ovid Therapeutics, SK Life Science, Takeda Pharmaceuticals, UCB, Ultragenyx, Xenon Pharmaceuticals, Zogenix, and Zynerba; and has consulted for Care Beyond Diagnosis, Epilepsy Consortium, Atheneum Partners, Ovid Therapeutics, UCB, Zynerba Pharmaceuticals, BioMarin, Encoded Therapeutics, Biohaven Pharmaceuticals, Stoke Therapeutics, and Praxis; and is a Non-Executive Director of Bellberry Ltd and a Director of the Australian Academy of Health and Medical Sciences. She might accrue future revenue on pending patent WO61/010176 (filed in 2008): Therapeutic Compound; has a patent for SCN1A testing held by Bionomics and licensed to various diagnostic companies; and has a patent molecular diagnostic/theranostic target for benign familial infantile epilepsy [PRRT2] 2011904493 and 2012900190 and PCT/AU2012/001321 (TECH ID: 2012-009). SB has served on scientific advisory boards for Biocodex and Longboard Pharmaceuticals and has received speaker honoraria from Angelini, Biocodex, Eisai, Lusofarmaco, and Jazz Pharma.

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