[Original article: 1 figure, 2 online tables, 1 online figure, 5 online videos]

The expanding spectrum of movement disorders in genetic epilepsies

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PUBLICATION DATA

Accepted for publication 01st March 2019.

Published online 29th November 2019.

ABBREVIATIONS

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CSF	Cerebrospinal fluid
EIMFS	Epilepsy of infancy with migrating focal seizures
EOEE	Early-onset epileptic encephalopathy
GABA	Gamma-aminobutyric acid
GTCS	Generalized tonic-clonic seizures
IEM	Inborn errors of metabolism
LGS	Lennox-Gastaut syndrome
NMDA	N-methyl-D-aspartate

[Abstract]

An ever-increasing number of neurogenetic conditions presenting with both epilepsy and atypical movements are now recognized. These disorders within the 'genetic epilepsy-dyskinesia' spectrum are clinically and genetically heterogeneous. Increased clinical awareness is therefore necessary for a rational diagnostic approach. Furthermore, careful interpretation of genetic results is key to establishing the correct diagnosis and initiating disease-specific management strategies in a timely fashion. In this review we describe the spectrum of movement disorders associated with genetically determined epilepsies. We also propose diagnostic strategies and putative pathogenic mechanisms causing these complex syndromes associated with both seizures and atypical motor control.

DOI: **10.1111/dmcn.14407**

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Developmental Medicine & Child Neurology 2019: XX: 000–000

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Review

What this paper adds:

- Implicated genes encode proteins with very diverse functions.
- Pathophysiological mechanisms by which epilepsy and movement disorder phenotypes manifest is often not clear.
- Early diagnosis of treatable disorders may require next generation genome sequencing.

[main text]

Recent advances have led to increased availability, reduced cost, and improved efficiency of next-generation sequencing technologies, thereby not only facilitating gene discovery for childhood epilepsy, but also enhancing the ability of clinicians to make diagnoses. This genomic revolution has however also muddied the diagnostic waters, and despite the development of robust consensus guidelines to determine mutation pathogenicity[1] it can often be difficult to determine the true pathogenic relevance of identified genetic variants. Moreover, given the significant phenotypic pleiotropy and genetic heterogeneity observed in the genetic epilepsies, it is increasingly difficult to predict genotype from phenotype.[2] As a consequence interpretation of genetic findings in clinical context can often be complex.

The development of improved clinical classification systems[3,4] has aided detailed phenotypic characterization of these genetic epilepsies, and it is now clear that the majority of these disorders are commonly associated with other neurological comorbidities including motor and cognitive delay, developmental regression, intellectual disability, neuropsychiatric features, and microcephaly. Furthermore, it is increasingly recognized that non-epileptic, atypical movements manifest in several genetic and neurometabolic syndromes which also feature epilepsy.[5–12] The increasing availability of video–electroencephalogram (EEG) has facilitated differentiation of paroxysmal movements from epileptic seizures, thereby increasing clinical awareness of such epilepsy-dyskinesia phenotypes.

In this review we report the spectrum of genetic disorders associated with epilepsy-movement phenotypes, with a focus on the genetic epileptic encephalopathies where there are rarely biomarkers to aid genetic diagnosis. We describe the clinical presentation, disease course, electroclinical syndrome, and motor semiology observed. Although many patients with epilepsy-dyskinesia syndromes have complex neurodevelopmental syndromes with pyramidal signs, such as reduced axial tone and/or velocity-dependent spasticity, the focus of this review will be to better define the spectrum of extra-pyramidal movement disorders reported in epilepsy syndromes. Finally, we propose a diagnostic algorithm as a pragmatic tool to aid clinicians in the investigation of such conditions.

EPILEPSY AND MOVEMENT DISORDERS IN INBORN ERRORS OF METABOLISM

Many inborn errors of metabolism (IEM) can manifest with both epilepsy and atypical involuntary movements.[13,14] A detailed description of such conditions is beyond the scope of this review; however, consideration in the differential diagnosis is crucial since targeted, disease-specific treatments are available for many of these disorders. An IEM may be suspected in patients with epilepsy born to consanguineous parents or with a family history of unexplained infantile deaths. IEM may be heralded by a number of suggestive clinical features including neonatal encephalopathy, neurological regression after a period of typical development, or clinical deterioration after intercurrent illness or starvation.[15] In contrast to the genetic epilepsies, where there is a significant lack of reliable diagnostic biomarkers, biochemical and radiological features can often provide useful aids towards diagnosis of an IEM. For example, blood and urine testing can aid the diagnosis of specific lysosomal storage disorders,[16] while serum transferrin isoelectric focusing is often atypical in congenital disorders of glycosylation. Congenital disorder of glycosylation type Is, caused by *ALG13* mutations, has been recently linked with West syndrome,[17] choreoathetosis, and dyskinesia.[18,19] Mitochondrial disorders, such as *POLG*-related disease, can also often present with a combination of epilepsy and atypical movements.[8,20] Here, diagnosis is often aided by characteristic brain magnetic resonance imaging (MRI) appearances as well as high

plasma and cerebrospinal fluid (CSF) lactate levels.[21] CSF studies are indeed key to diagnosing a number of IEM. A low fasting CSF to plasma glucose ratio is commonly detected in glucose transporter type 1 protein deficiency, due to mutations in *SLC2A1*. Patients with glucose transporter type 1 protein deficiency present with a broad range of epileptic seizures including atonic, myoclonic, and generalized tonic-clonic seizures (GTCS); Reported movement disorders include ataxia, dystonia, chorea, and paroxysmal kinesigenic dyskinesia, paroxysmal non-kinesigenic dyskinesia, and paroxysmal exercise-induced dyskinesia.[22,23] Severe depletion of CSF 5-methyltetrahydrofolate is a classical feature of *FOLR1*-related disorders,[24] where affected patients present with neurological regression and seizures (tonic, myoclonic, and myoclonic-astatic events), as well as ataxia, tremor, chorea, dystonia, and non-epileptic myoclonus. Primary neurotransmitter defects, which often lead to a combination of dyskinesias and epilepsy, can also be diagnosed by detection of specific CSF pterin and monoamine metabolite patterns.[12]

EARLY ONSET EPILEPTIC ENCEPHALOPATHIES ASSOCIATED WITH MOVEMENT DISORDERS

The early-onset epileptic encephalopathies (EOEEs) encompass a broad range of neurological disorders typically characterized by pharmacoresistant seizures and neurodevelopmental delay presenting in the neonatal period or infancy. EOEEs are clinically and genetically heterogeneous, which is attributed to a broad range of underlying aetiologies, including structural brain malformations, IEM, and single gene defects.[4,25,26] Since the advent of next generation sequencing over 100 monogenic causes of EOEE have been reported,[27] of which an increasing number are reported to result in epilepsy-dyskinesia phenotypes (Fig. 1, Table S1, online supporting information).

Sodium channel genes

Mutations in *SCN2A***,** encoding the alpha-2 subunit of the voltage-gated sodium channel, are reported in EOEE syndromes such as Dravet syndrome, Ohtahara syndrome, West syndrome, and Lennox-Gastaut syndrome (LGS), epilepsy of infancy with migrating focal seizures (EIMFS), as

well as in benign familial neonatal-infantile seizures and genetic epilepsy with febrile seizures plus.[28,29] Severe hyperkinetic movement disorders, including dystonia and chorea, are often reported especially in neonatal-onset disease. Patients occasionally also manifest oculogyric crises, episodic ataxia, and prominent stereotypies in childhood.[29,30]

SCN8A, encoding another sodium channel subunit, has recently emerged as an important cause of EOEE, implicated in West syndrome, LGS, and Dravet syndrome, as well as benign familial neonatal-infantile seizures. Multiple seizure types are described including GTCS, tonic, focal (with or without impaired awareness), absence, and myoclonic seizures.[31] Axial hypotonia is often present. Extrapyramidal features include dystonia, choreoathetosis, tremor, ataxia, and hand stereotypies.[31,32] Additionally, episodic paroxysmal kinesigenic dyskinesia consisting of dystonic/hemi-dystonic, dyskinetic, or 'shivering' episodes have also been reported.[33]

The *SCN1A*-related phenotypic spectrum is broad and includes not only Dravet syndrome but also genetic epilepsy with febrile seizures plus, EIMFS, and infantile spasms. Recently, choreoathetosis, ballismus, dystonia, orofacial dyskinesia, hand stereotypies, and even familial cases of hemiplegic migraine have been described in patients with *SCN1A*-related disease.[34–37] It has been reported that atypical movements are occasionally triggered by the sodium channel blockers phenytoin and carbamazepine.[34,38] More recently, the c.677C>T; p.(Thr226Met) variant has been described in association with a distinct epilepsy-dyskinesia phenotype, more severe than Dravet syndrome, with a prominent hyperkinetic movement disorder.[38]

FHF1 encodes a voltage-gated sodium channel binding protein which modulates channel inactivation. Mutations in *FHF1* (R52H), have been reported in patients with early onset epilepsy associated with progressive cerebellar atrophy and ataxia.[39–41]

Potassium channel genes

Autosomal dominant mutations in *KCNT1*, which encodes the sodium-activated potassium channel, are identified in a wide range of epileptic disorders from benign familial neonatal-infantile seizures and autosomal dominant nocturnal frontal lobe epilepsy to severe EOEE syndromes, such as

Ohtahara syndrome, West syndrome, and EIMFS.[26,42] Axial hypotonia is frequently present though the majority of patients do not have other pyramidal tract signs.[43] Moreover, some patients present with an early-onset choreiform movement disorder or generalized dystonia.[26,43] *KCNQ2*, encoding the voltage-gated potassium channel (KQT-like subfamily), has been associated with benign familial neonatal-infantile seizures and more recently with EOEE, including Ohtahara syndrome,[44] and West syndrome.[45] Myokymia, myoclonus, ataxia, and dystonic posturing have all been described in affected patients.[46–48] *KCNB1* mutations, affecting another voltage-gated potassium channel, have also been recently identified in patients with EOEE where hand-wringing stereotypies, chorea, and myoclonus have been reported.[49]

Gamma-aminobutyric acid-related genes

Mutations in genes encoding subunits of the gamma-aminobutyric acid (GABA) type A receptor are increasingly recognized in the epilepsy-dyskinesia spectrum. *GABRA1* mutations not only cause Dravet syndrome, Ohtahara syndrome, and West syndrome, but also juvenile myoclonic epilepsy, childhood absence epilepsy, and GTCS. Reported extrapyramidal features include myoclonus, dystonia, choreoathetosis, hand stereotypies, and bruxism.[50] Recently a de novo *GABRA2* mutation was found in a patient with EOEE, who also had severe hypotonia, and continuous choreiform movements.[51] *GABRB3* mutations, previously linked with Angelman syndrome, autism, and absence seizures, have recently been implicated in EOEE such as West syndrome and later onset epilepsy syndromes such as LGS and myoclonic atonic epilepsy.[52,53] Hypotonia, ataxia, tremor, dyskinesia, and hand stereotypies are also often reported in affected patients.[52] *GABRG2* mutations cause Dravet syndrome, genetic epilepsy with febrile seizures plus, and also later-onset types such as childhood absence epilepsy, GTCS, and LGS.[54,55] Here, patients also present with extrapyramidal features including choreoathetosis, ataxia, hand stereotypies, and atypical eye movements. Finally, mutations in *GABRB2*, recently identified in EOEE,[56] also cause a '*MECP2*-like' clinical phenotype[57] consisting of neurological regression with developmental plateauing, hand stereotypies, autonomic dysfunction, sleep disturbance, microcephaly, and GTCS. Genotype-phenotype

correlation suggests that mutations with greater impact on *GABRB2* activity appear to cause the more severe EOEE phenotype.[57] Related to GABA type A function, *ARHGEF9* encodes a protein crucial for the formation of gephyrin and gephyrin-dependent GABA type A clusters in the postsynaptic membrane. Mutations in *ARHGEF9* are reported in EOEE of variable seizure types (GTCS, tonic, focal with impaired awareness, and myoclonic seizures). Hyperekplexia and ataxia are described in some patients.[58]

Genes in the N-methyl-D-aspartate pathway

Mutations in *GRIN2B* (encoding the GluN2B subunit of the N-methyl-D-aspartate (NMDA) receptor) were first reported in patients with childhood-onset focal epilepsy, and more recently in patients with West syndrome. Severe hypotonia and dysphagia are described, with some patients also manifesting episodic axial hyperextension and dystonic finger movements.[59–61] For patients with EOEE and *GRIN2D* mutations, affecting the GluN2D NMDA receptor subunit, hypotonia, choreoathetoid limb movements, paroxysmal extensor posturing, and involuntary eye movements resembling oculogyric crises have been reported.[62] *GRIN1* mutations impacting the GLuN1 subunit lead to multiple epilepsy phenotypes including infantile spasms, as well as focal with impaired awareness, generalized, and myoclonic seizures.[63] Marked axial hypotonia, complex stereotypies, and a broad range of extrapyramidal features, such as fragmentary non-epileptic myoclonus, chorea, dyskinesia, and dystonia (that also affects eye movements and resembles oculogyric crises) are additional features in *GRIN1*-related disease.[63–65]

Genes involved in synaptic vesicle dynamics

Recessive mutations in *TBC1D24*, encoding a protein involved in the regulation of synaptic vesicle trafficking, have been reported in patients with EIMFS and infantile spasms, as well as early onset myoclonic, febrile, clonic, tonic, GTCS, absence, and focal seizures. Affected patients often exhibit axial hypotonia and spasticity. Dystonia, ataxia, choreoathetosis, parkinsonism, and non-epileptic myoclonus are also reported.[66,67] *STXBP1* encodes a syntaxin-binding protein which plays a crucial role in neurotransmitter release from synaptic vesicles. Mutations of *STXBP1* cause a wide range of

EOEE disorders including Ohtahara syndrome, early myoclonic encephalopathy, and West syndrome.[68] Pyramidal features, such as axial hypotonia and spasticity, and extra-pyramidal phenotypes, including ataxia, intention tremor, dyskinetic movements, and dystonia, are frequently seen in such patients.[68–70] Furthermore, parkinsonian features have also been described in older patients.[71] Stereotypies involving the hands, trunk, head, and neck, including the 'figure-of-eight' sequence,[72] also feature in *STXBP1*-related disease. *DNM1* encodes Dynamin-1, involved in synaptic and postsynaptic signalling. Mutations in this gene cause a neurodevelopmental disorder associated with West syndrome (often evolving to LGS) and choreiform hand movements, distal limb dystonia, ataxia, and tremor.[60,73,74]

Genes encoding transporters

Transportopathies are also increasingly recognized within the epilepsy-dyskinesia spectrum. Biallelic mutations in *SLC13A5*, encoding a high affinity sodium-dependent citrate transporter, are associated with EOEE, characterized by focal clonic seizures in the first week of life. The epilepsy tends to evolve into status epilepticus (hemiconvulsive, convulsive, and non-convulsive) and fever-sensitivity is frequently reported. Motor features including spasticity, ataxia, and choreoathetosis are often present.[75,76] Finally, patients with *SLC1A2* mutations, affecting the glutamate transporter EAAT2, manifest EOEE occasionally in tandem with movement disorders such as upper limb dyskinesia.[77,78]

Genes with other cellular functions

Biallelic mutations in *UBA5*, a gene involved in protein posttranslational modification, cause EOEE including Ohtahara syndrome, West syndrome, or myoclonic jerks, and axial or peripheral hypotonia. Patients also often have pronounced dystonia and athetosis.[79–81] Recessive mutations in *ARV1*, encoding for an endoplasmic reticulum transmembrane protein, have also been identified in patients presenting with Ohtahara syndrome and dystonia/ataxia.[82] Dystonic movements have been described in patients with EOEE (in particular West syndrome) due to mutations in *SPTAN1*,[83,84] a gene involved in cytoskeleton organization. Mutations in this gene are associated with spastic

quadriplegia and axial hypotonia, as well as dystonia and ataxia.[83,84] Mutations in *YWHAG*, encoding a member of the 14-3-3 protein family involved in intracellular signalling, protein trafficking, cell-cycle control, and apoptosis,[77] cause EOEE characterized by variable seizure types (focal motor, GTCS, myoclonic, absence), ataxia, and tremor. *AARS* encodes for alanyl tRNA synthetase, an enzyme important in the initial phases of protein translation. Heterozygous *AARS* mutations are an established cause of dominantly inherited Charcot Marie Tooth disease type 2N; more recently, biallelic *AARS* mutations have been described in patients with severe EOEE, peripheral neuropathy, blepharospasm, orolingual dyskinesia, limb dystonia, and chorea.[85,86]

Additionally, patients with mutations in *WWOX*, a gene with a role in apoptosis and tumour suppression,[87] present with treatment-resistant EOEE. Multiple seizure types are described, including infantile spasms, tonic, GTCS, and myoclonic seizures, while sometimes the electroclinical phenotype is compatible with LGS. Motor features include axial hypotonia, spasticity, cerebellar ataxia, and dystonia.[87,88]

INFANTILE-ONSET EPILEPTIC ENCEPHALOPATHIES ASSOCIATED WITH SEVERELY PROGRESSIVE MOVEMENT DISORDERS AND STATUS DYSTONICUS

Several conditions presenting with EOEE are associated with a markedly progressive, severe and disabling movement disorder.

ARX encodes for a transcription factor with a pivotal role in the forebrain, pancreas, and testicular embryogenesis.[89] *ARX* mutations are reported in a broad range of EOEE including Ohtahara syndrome, infantile spasms, and myoclonic seizures.[89–91] Atypical motor semiology is often reported, with features of spasticity, as well as extra-pyramidal movement disorders such as progressive generalized dystonia, four limb dyskinesia, and non-epileptic myoclonic jerks.[92] Status dystonicus has also been reported.[91]

Mutations in *GNAO1*, encoding the alpha-subunit of a heterotrimeric G protein implicated in the modulation of synaptic transmission,[93] result in early onset epilepsy syndromes, such as EOEE, Ohtahara syndrome, and EIMFS-like phenotypes. Prominent movement disorders such as chorea,

dystonia, facial, and orolingual dyskinesia and complex stereotypies are very commonly reported.[93–95] Many affected patients present with progressive, potentially life-threatening episodic exacerbations, which often necessitate hospitalization in an intensive care setting. During periods of exacerbation atypical facial movements, orolingual dyskinesia, and complex stereotypies are also reported.[93,95,96] Lasting from minutes to days or even months such exacerbations are commonly triggered by infection, pyrexia, heightened emotion, stress, and anxiety. Moreover, dysautonomic manifestations, such as tachycardia, hyperthermia, hypertension, and diaphoresis, are often described.[93,95,96]

CHILDHOOD-ONSET GENETIC EPILEPSY SYNDROMES WITH MOVEMENT DISORDERS

Potassium channel genes

KCNA2-related epilepsy presents with childhood-onset epilepsy of multiple seizure types including GTCS, myoclonic, and absence seizures. Patients also manifest ataxia and tremor, 4-limb dystonia, midline hand stereotypies, and myoclonic movements.[97–99] Moreover, autosomal recessive *KCNJ10* mutations cause epilepsy, ataxia, sensorineural deafness, and tubulopathy syndrome. Patients present with infantile-onset GTCS,[100–102] while non-progressive ataxia is evident from the first year of life. Finally, *KCND3* mutations, traditionally linked with ataxia, cognitive impairment, tremor, myoclonus, and neuropathy (Spinocerebellar Ataxia 19/22), have also been described in patients with parkinsonian features, dysarthria, dysphagia, and childhood/adult-onset generalized or focal seizures with impaired awareness.[103]

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors

Mutations in *GRIA4***,** which encodes an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit (GluR4) found on excitatory glutamatergic synapses, cause a spectrum of phenotypes from an early infancy or childhood onset neurodevelopmental disorder (with or without seizures and a clumsy or stiff gait) to EOEE with intractable seizures in the first weeks of life. Spastic quadriplegia, choreiform, and stereotypic hand movements and ataxia are also reported.[104]

Recently, mutations in *FRRS1L*, which encodes an important component of the outer core of the AMPA receptor accessory proteins, were identified in patients with childhood onset epilepsy associated with regression of skills, choreoathetosis, dystonia, and, later on in life, rigidity and hypokinesia.[105] Seizure types included multifocal, GTCS, and tonic, while some patients evolve into LGS.

Genes encoding transporters

Mutations in genes leading to aberrant function of cellular transporters can also present with childhood-onset epilepsy and movement disorders. *SLC6A1* encodes one of the major brain transporters of GABA; mutations lead to childhood-onset myoclonic-atonic epilepsy as well as autistic features, stereotypies, ataxia, and tremor.[106] Mutations in the *SLC9A6* gene, which encodes a sodium-hydrogen exchanger, cause Christianson syndrome, an X-linked intellectual disability syndrome. Some children present with phenotypes reminiscent of Angelman syndrome,[107] characterized by intellectual disability, early-onset epilepsy, ataxia with progressive cerebellar atrophy, and progressive neurological dysfunction associated with tau-deposition.[108]

Genes involved in degradation/turnover of intracellular and extracellular components

Deficient expression of the maternal copy of the *UBE3A* gene, encoding a protein involved in the ubiquitin/proteasome system, leads to Angelman syndrome. Phenotypic features include intellectual disability, speech impairment, epilepsy (with a characteristic EEG pattern and multiple seizure types typically presenting in childhood), and a behavioural profile of hyperexcitability, happy demeanour, and frequent laughter. Additionally, patients with Angelman syndrome also exhibit jerkiness, ataxia, tremor, mouthing of objects, stereotypies,[109] and, towards adolescence or adulthood, non-epileptic myoclonus.[110] Mutations in a gene encoding a protein with similar function (*HACE1*), were also recently found to cause neurodevelopmental delay and childhood onset epilepsy characterized by GTCS, myoclonic, and focal seizures, with hypotonia, lower limb spasticity, ataxia, and dystonia.[111,112] *HACE1* not only functions as an E3 ubiquitin ligase but also represses the transcriptional activity of retinoic acid receptors and, hence, downstream pathways

that are involved in a range of cellular processes including neuronal differentiation/regeneration and stimulation of neurite outgrowth.[111]

Defects in autophagy, another innate cellular system of cargo disposal and recycling, also lead to mixed epilepsy/movement disorder phenotypes. Mutations in *WDR45* cause beta-propeller protein-associated neurodegeneration, a subtype of neurodegeneration with brain iron accumulation. Beta-propeller protein-associated neurodegeneration manifests with epilepsy of multiple seizure types (febrile, focal with impaired awareness, absences, atonic, tonic, epileptic spasms, GTCS, and myoclonic, or even EOEE or West syndrome),[113] *MECP2*-like hand wringing stereotypies, and, later in the disease course, neurological regression, dystonia, and prominent parkinsonian features.[114] *EPG5* mutations lead to Vici syndrome, a multisystemic condition encompassing seizures, which are often severe and can present as EOEE or LGS, as well as atypical motor semiology including dystonia and choreoathetosis.[115] More recently, mutations in another autophagy gene, *SNX14*, have been found to cause delayed development, hypotonia, absent speech, progressive cerebellar atrophy, ataxia, and seizures.[116]

DNAJC6 has recently been added to the expanding spectrum of genes causing later-onset epilepsy-dyskinesia. *DNAJC6* encodes the brain-specific isoform of auxilin, a protein with a well-established role in clathrin-mediated endocytosis and synaptic vesicle recycling. Prominent tremor, bradykinesia, rigidity, and dystonia commonly starts in childhood or early adolescence. Some patients also have epilepsy characterized by generalized EEG discharges, the onset of which can either occur before[117] or after[118] the parkinsonian features manifest clinically. Psychiatric features including hallucinations, sometimes linked to levodopa administration, have also been reported.[117–119]

Genes involved in postsynaptic cell signalling

GNB1 mutations have been recently identified in patients with childhood or adolescence-onset epilepsy, neurodevelopmental delay, tics, hypotonia, dystonia, ataxia, and intermittent action-induced myoclonus.[120–122] Gβ1 is the β-subunit of a guanine nucleotide–binding protein that forms

heterotrimeric complexes with G protein subunits α and γ. Gβ1 is involved in the same cellular pathway as *GNAO1* (Section 3) and interacts with GNAL (encoded by the gene mutated in *DYT25* dystonia),[121] which might provide a causative link to the combined epilepsy and movement disorder phenotype seen in these patients.

In addition, mutations in *SYNGAP1*, which encodes a protein that constitutes a downstream component of the NMDA receptor-associated signalling complex, have been shown to cause epilepsy and atypical movements.[123] Affected patients present with late infantile-onset seizures, drop attacks, myoclonic jerks, atonic seizures, myoclonic absences, or absences, in tandem with hypotonia and ataxia.

THE PROGRESSIVE MYOCLONIC EPILEPSIES

The progressive myoclonic epilepsies are a genetically and clinically heterogeneous group of disorders characterized by epilepsy of varying degrees, and associated with neurological decline with ataxia and dementia.[124] Metabolic aetiologies, such as neuronal ceroid lipofuscinoses,[125] are well recognized in progressive myoclonic epilepsies, but many other genetic causes have also been described including mutations in *CSTB* (Unverricht-Lundborg disease), *EPM2A* (Lafora disease), *GOSR2*, *KCNC1*, *PRICKLE1*, *SCARB2*, and *KCTD7*.[126–131] These genes encode proteins with a wide variety of cellular functions, such as intracellular trafficking (GOSR2),[132] lysosomal function (SCARB2), and sodium channels (KCNC1). Stimulus-sensitive or action myoclonus (with and without EEG correlate), ataxia, and tonic-clonic seizures are consistent features in all progressive myoclonic epilepsies, while significant associated dementia is encountered in some subtypes (e.g. Lafora disease and neuronal ceroid lipofuscinoses).[127] Muscle biopsies often have characteristic appearances and prove useful when investigating or suspecting such disorders.[125]

EPILEPSY SYNDROMES ASSOCIATED WITH PROMINENT STEREOTYPIES

Mutations in *MECP2*, encoding a transcription factor highly expressed in the brain, cause a neurodevelopmental disorder historically known as Rett syndrome. After a period of typical development, neurological regression (including loss of purposeful hand skills and language) and

postnatal microcephaly ensue. Epilepsy of multiple seizure types, focal with impaired awareness, absence, atonic, tonic, GTCS, myoclonic, occurs in the majority of cases. Movement disorders, including ataxia, dystonia, chorea, myoclonus, tremor, rigidity, hand stereotypies typically involving the midline,[133] can be prominent with hyperkinetic movements more common in younger patients and parkinsonian features in older ones.[133,134]

FOXG1 mutations share some overlapping features with *MECP2*-related disease. The encoded protein is also a transcription factor involved in fetal telencephalic development and postmitotic neuron survival.[134] Unlike the *MECP2* X-linked inheritance pattern (and consequential female predominance) both sexes are relatively equally affected. *FOXG1*-related disease is characterized by global neurodevelopmental delay, rather than neurological regression, often accompanied by poor feeding, irritability, hypotonia, postnatal microcephaly, lack of purposeful hand use, and visual inattention. Epilepsy with multiple seizure types including GTCS, myoclonic, and focal seizures with impaired awareness presents in infancy, often as EOEE and/or infantile spasms, or as childhood-onset epilepsy.[108,135] Hyperkinetic movement disorders are a cardinal and important disease feature with a combination of choreoathetosis, dystonia, myoclonus, orolingual dyskinesia, and distinct (mainly unilateral) hand stereotypies being present in all patients, even in the absence of epilepsy. Dystonia-parkinsonism is reported in older patients.[134]

Mutations in *CDKL5,* which is involved in transcriptional regulation/DNA modification and repair, are also associated with a clinical phenotype encompassing both epilepsy and atypical motor stereotypies. Similarly to *MECP2* there is X-linked inheritance with most patients being female. Postnatal microcephaly and poor purposeful hand use are key disease features. Epileptic seizures of early onset often include EOEE, infantile spasms, myoclonic seizures, and prolonged GTCS (although less severe forms have also been described), while atypical movements mainly consist of hand stereotypies and bruxism,[5] ataxia, chorea, dystonia, and myoclonus.[18,136]

PCDH19 mutations, which encodes a protein highly expressed in the brain, important for cell-cell adhesion, axon guidance, and dendrite self-avoidance,[137] are well known to lead to EOEE

and later-onset epilepsy in females, characterized by focal and/or generalized seizures that typically occur in clusters. Other associations also include autistic features and behavioural issues, sleep disturbance, and hand stereotypies.[138]

Dystonia, dyskinesia, chorea, *MECP2*-like features, and hand stereotypies in childhood are described in patients with *MEF2C* mutations, who also manifest EOEE and childhood-onset epilepsy including myoclonic, atonic seizures, and infantile spasms.[139]

Similar to *MECP2*, a number of genes causing epilepsy syndromes with prominent stereotypies encode for transcription factors, or proteins involved in transcriptional regulation. First, *HNRNPU* encodes a protein that facilitates interactions between genes, mRNA, and proteins during mRNA processing thereby regulating gene expression.[140] Mutations in the gene cause EOEE (including infantile spasms, West syndrome, and LGS) and childhood-onset epilepsy with seizures initially occurring in the context of febrile episodes.[140–142] Neurological regression is reported in some patients, and hand-flapping stereotypies appear to be a common feature. *TBL1XR1* also encodes a protein that localizes to the nucleus and plays a role in transcription mediated by nuclear receptors.[143] Mutations are associated with West syndrome, hand stereotypies, developmental delay, and autistic or *MECP2*-like features.[18,144] Moreover, *PURA* mutations, a gene encoding a protein with multiple regulatory functions in processes like DNA replication, transcription, mRNA transport, DNA repair, and a role in neuronal development and differentiation, have recently been described in *PURA* syndrome.[145] The condition is multisystemic with central nervous system involvement including several seizure types: GTCS, focal, absence, tonic seizures, infantile spasms, drop attacks, and, over time, evolution to LGS. Atypical motor features include hypotonia, spasticity, *MECP2*-like stereotypies, chorea, dystonia, and ataxia.[145] Loss of function mutations in *SMC1A*, with a role in chromosome segregation during cell division, cause drug-resistant tonic seizures or GTCS often occurring in clusters, infantile spasms, and EIMFS, and psychomotor regression. Patients also manifest hypotonia, spasticity, and midline hand wringing stereotypies.[146–150] Finally, *SETD5*, which encodes for a methyltransferase enzyme highly expressed in the brain,[151]

was initially described in association with intellectual disability and dysmorphic features, gastrointestinal malformations, and behavioural problems including obsessive-compulsive or autistic features as well as stereotypical hand flapping.[151] Mutations were also recently identified in patients with West syndrome with, again, associated hand stereotypes.[18]

Genes with regulatory roles in synaptic activity have also been linked with *MECP2*-like phenotypes. First, mutations in *IQSEC2* are associated with regression, stereotypical hand movements, spasticity, postnatal microcephaly, and epilepsy, including EOEE, atypical absences, and infantile spasms phenotypes.[152,153] *IQSEC2* has an essential role in modulating the cytoskeleton and vesicle transport at the postsynaptic density and hence is a crucial modifier of synaptic plasticity.[153] Interestingly, *IQSEC2* escapes X-inactivation in females and the phenotype can therefore be related to the severity of loss-of-function, as in autosomal genes.[154] *AP3B2* encodes the neuronal-specific subunit of a protein mediating the sorting and transport of vesicle membrane proteins between the neuronal cell body and nerve terminus.[155] *AP3B2* mutations are now reported in EOEE characterized by infantile spasms, tonic-clonic, and tonic seizures. Patients also exhibit axial hypotonia and atypical movements such as midline hand stereotypies, dystonia, and chorea.[155]

Choreoathetosis[156] and stereotypies[157] have been described in patients with recessive *SZT2* mutations presenting with EOEE. SZT2 regulates the mechanistic target of rapamycin complex 1 signalling pathway,[158] malfunction of which is implicated in several central nervous system developmental abnormalities.[159]

Finally, stereotypies are increasingly recognized as a feature in other genetic disorders including *WDR45*-, *GRIN1*-, and *GABRB2*-related epilepsy; these have all been described in previous sections.[56,63,114]

PARKINSONISM IN CHILDHOOD-ONSET GENETIC EPILEPSIES

Paediatric movement disorders are mainly hyperkinetic. Hypokinetic movement disorders are less commonly described, encountered more frequently in older patients. This is exemplified by patients with *MECP2* mutations, where early disease is characterized by hyperkinetic movements, and

parkinsonian features manifest later on in the disease course.[133] Similarly, mutations in other epilepsy-related genes (*KCND3, STXBP1, DNAJC6, FOXG1, WDR45, FRRS1L, TBC1D24, ATP1A3)* can cause hypokinesia and parkinsonism,[66,71,105,114,117,133,134,160] usually manifesting later in childhood, adolescence, or adulthood.

PAROXYSMAL DYSKINESIAS AND EPILEPSY

Paroxysmal dyskinesias are characterized by the episodic occurrence of involuntary extrapyramidal movements. Based on the precipitating factor, these can be subdivided into three clinical syndromes: paroxysmal kinesigenic dyskinesia, paroxysmal non-kinesigenic dyskinesia, and paroxysmal exercise-induced dyskinesia.[23,35] They are often associated with epilepsy, manifesting in patients with mutations in genes encoding synaptic proteins/receptors (*PRRT2, CHRNA4),* ion channels (*KCNA1, KCNMA1, SCN8A, CACNA1A*), and transporters (*SLC2A1, SLC16A2, ATP1A2, ATP1A3*).[161]

The clinical features of paroxysmal kinesigenic dyskinesia, paroxysmal non-kinesigenic dyskinesia, and other paroxysmal dyskinesias are detailed in Table 1. In the context of epilepsy, paroxysmal kinesigenic dyskinesia is reported in patients harbouring mutations in *PRRT2,*[162,163] *SCN8A,*[31,33] *SLC16A2,*[164,165] and *CHRNA4.*[166] Additionally, epilepsy occurs in tandem with paroxysmal non-kinesigenic dyskinesia in *CACNA1A*[167] and *KCNMA1*-related disease,[168–170] while paroxysmal exercise-induced dyskinesia is often described in cases of *SLC2A1*-related glucose transporter type 1 protein deficiency.[23] Other paroxysmal movement disorders include hemiplegic migraine and the episodic ataxias. *CACNA1A*, *SCN1A*, and *ATP1A2* mutations are mainly responsible for co-occurrence of familial hemiplegic migraine and epilepsy,[35,171] while a combination of episodic ataxias and epileptic seizures is reported in *PRRT2,*[23,163] *CACNA1A,*[167] and *KCNA1*[35,172,173] mutation-positive patients.[34,174] Finally, *ATP1A3* mutations manifest in a broad clinical spectrum encompassing alternating hemiplegia of childhood, rapid-onset dystonia-parkinsonism, and epilepsy.[35,175]

A DIAGNOSTIC APPROACH

Approaching the epilepsy-dyskinesia spectrum from a diagnostic perspective can be challenging in view of the clinical and genetic heterogeneity, non-specific or atypical presentations, and lack of clinical awareness of rarer entities. Clinicians should therefore have a low threshold for referring such complex cases to appropriate specialist clinics, where available.

Thorough history taking and clinical examination is paramount, while the use of mobile phones and/or video capturing (either in hospital or at home) is useful, especially in the case of paroxysmal movement disorders. Detailed neuroimaging should also be considered early on not only for potential diagnostic clues but also to exclude structural abnormalities that could explain the constellation of symptoms and signs.

Additionally, IEM should always be considered, and where appropriate sufficiently excluded, with an important emphasis on searching for treatable conditions. A combination of atypical motor semiology and epilepsy is frequently encountered in many metabolic conditions.[7] Hence, relevant investigations should be initiated as required, depending on the clinical presentation.

For neurogenetic conditions presenting with movement disorders and epilepsy accurate electroclinical characterization of the epileptic events and phenotypic delineation of the atypical motor semiology will enable more targeted biochemical, radiological, and neurophysiological investigations and subsequent genetic testing. Even in the era of next generation sequencing such clinical characterization will aid the interpretation of genetic data, especially for genetic variants of unknown significance.

Microarray-based comparative genomic hybridization should be a first-line genetic investigation, as copy number variants encompassing key gene(s) may indeed be responsible for the observed clinical phenotypes. The diagnostic yield from microarray is reported to be significant for both epilepsy[27] and movement disorders.[176] Next generation sequencing approaches such as gene panels and whole exome or genome sequencing are now usually second line genetic investigations. Rarely, targeted single gene testing may be undertaken in cases of high clinical or biochemical

suspicion; this should be initiated early on in the diagnostic process. Conversely, more invasive investigations such as tissue biopsies are often expensive and of comparatively low yield[177,178] and could, therefore, be considered ever further down the investigative process. A suggested diagnostic algorithm is summarized in Figure S1 (online supporting information).

PUTATIVE PATHOGENIC MECHANISMS

Intriguingly, similar clinical phenotypes encompassing both epilepsy and movement disorders are caused by an ever-expanding compendium of genes, encoding for proteins with very diverse functions (Fig. 1, Table S2 online supporting information). The exact mechanism through which this occurs is unclear, but it is likely to be multifactorial. It is plausible that the affected protein functions may be ubiquitous and/or indispensable throughout the central nervous system. For example, genes involved in toxic cargo removal or recycling are likely to be of key importance in non-regenerating, postmitotic neurons. Hence, mutations in genes such as *WDR45, EPG5, SNX14*, *UBE3A*, or *HACE1*,[109,111,116] might lead to broad cellular dysfunction in multiple neuronal subtypes, which, in turn, would clinically manifest as a combination of neurological features, including epileptic seizures and motor abnormalities. Additionally, genes involved in synaptic function (neurotransmission, synaptic vesicle cycle, G-protein-coupled signal transduction) would also be predicted to affect multiple neuronal subtypes within both cortical and subcortical networks, hence leading to a complex clinical picture with epilepsy and motor defects. Finally, genetic epilepsy-dyskinesia may be attributed to genes that either cause radiologically discernible structural brain abnormalities or preferentially affect specific parts of the brain involved in motor control and coordination. For example, *FOXG1* mutations lead to both forebrain underdevelopment and atypical basal ganglia gene expression.[134] Beta-propeller protein-associated neurodegeneration (due to *WDR45* mutations) preferentially affect the substantia nigra and globus pallidus, as evident on brain magnetic resonance imaging[114] and neuropathology studies.[179] Moreover, some genes (for instance *SPTAN1*,[83] *SLC9A6*,[107] and *SNX14)*[116] are associated with cerebellar atrophy, which may impact key corticothalamic pathways and other important motor networks, thereby leading to both epilepsy

and a movement disorder.

CONCLUSIONS

Our review summarizes the 'genetic epilepsy-dyskinesia' spectrum and describes a genetically and clinically heterogeneous group of conditions caused by mutations in genes encoding proteins with a diverse set of neuronal functions. These disorders are often under-recognized, mainly because of their rarity and heterogeneity, and, therefore, delays in diagnosis and appropriate management are common. This issue is becoming increasingly relevant, with a number of promising disease-specific treatments either already available or currently being developed in preclinical studies and clinical trials.[180–182] With the advent of next generation sequencing and enhanced clinical phenotyping, it is likely that the genetic epilepsy-dyskinesia spectrum will further expand. Clinical awareness is paramount, to achieve a more focused diagnostic approach. Robust interpretation of genetic data will facilitate accurate prognostication and genetic counselling. Ultimately establishing the exact underlying molecular defect will lead to initiation of appropriate management strategies, and more precision medicine approaches in the future.

Acknowledgements

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

Supporting information

The following additional material may be found online:

Table S1: Summary of clinical manifestations in epilepsy-dyskinesia disorders

Table S2: Function of genes implicated in the genetic epilepsy-dyskinesia spectrum

Figure S1: Proposed diagnostic approach for children presenting with epilepsy and movement disorders.

Video S1-5: Videos demonstrating movement phenotypes in patients with mutations to *GNAO1, FOXG1, KCNA2, IQSEC2,* and *SCN2A*.

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[FIGURE LEGENDS]

Figure 1: Pathophysiology of genetic epilepsy-dyskinesia phenotypes. The genetic epilepsy-dyskinesia spectrum is associated with mutations in genes encoding proteins with a wide variety of cellular functions (Table S1). Mutations in these genes lead to dysregulation of multiple key cellular processes and neuronal dysfunction, that ultimately manifests clinically as epilepsy and motor deficits. Pathways and processes involved include: gene transcription, posttranslational protein modification, autophagy, ubiquitin-mediated proteolysis, endosomal function, axon myelination, the synaptic vesicle cycle, ion and/or nutrient transport, receptor function, and postsynaptic signal transduction. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Ca++, calcium; DAT, dopamine transporter; H+, hydrogen ion; K+, potassium; Na+, sodium; GDP, guanosine diphosphate; Glu, glucose; GTP, guanosine triphosphate; P, phosphate; RBC, red blood cell; T3, triiodothyronine; α, β, γ, alpha, beta, and gamma subunits of guanine nucleotide-binding proteins (G proteins).

Table 1: Summary of clinical manifestations in epilepsy-paroxysmal dyskinesias disorders

Gene	Inheritance	OS	WS/IS	EIFMS	EOEE	LGS	Other seizure types	Dystonia	Chorea/athetosis	Orofacial involvement	Myoclonus	Stereotypies	Ataxia	Tremor	Parkinsonism	Paroxysmal movement disorders	Other key phenotypic features
ATP1A2	AD	-	-	-	-	-	Generalized, febrile, GEFS+	-	-	-	-	-	+	-	-	HM	-
ATP1A3	AD	-	-	-	+	-	GTCS, tonic, atonic, focal with impaired awareness, myoclonic, EOEE, status epilepticus	+	+	+	-	-	+	-	+	AHC, rapid-onset dystonia-parkinsonism, EA	CAPOS syndrome
CACNA1A	AD	-	+	-	+	+	Febrile, GEFS+, absence, generalized, focal, status epilepticus, posttraumatic	+	+	-	-	-	+	+	-	PNKD, EA, HM, benign paroxysmal torticollis	Cerebellar atrophy, ASD features, nystagmus
CHRNA4	AD	-	-	-	-	-	Febrile, GEFS+, myoclonic, GTCS	+	+	-	-	-	-	-	-	PKD	-
KCNA1	AD	-	-	-	-	-	GTCS, focal	+	+	-	-	-	+	-	-	EA, PKD, myokymia, neuromyotonia	Migraine, vertigo, dysarthria, weakness
KCNMA1	AD	-	-	-	-	-	Absence, GTCS, clonic, atonic	+	+	-	-	-	-	+	-	PNKD	Cerebellar and corticospinal tract atrophy
PRRT2	AD	-	-	-	-	-	BFIS	+	+	-	-	-	-	-	-	PKD, PNKD, PED, EA, benign paroxysmal torticollis, HM	Response to low dose antiepileptic medications
SLC16A2	X	-	-	-	-	-	Febrile, myoclonic, GTCS	+	-	+	+	+	+	-	-	PKD	Male predominance, myopathic face, dysmorphic features, high free T3, normal/low free T4, high TSH

Causative genes are listed in alphabetical order. *SCN1A*, *SCN8A*, and *SLC2A1*-related phenotypes are also associated with paroxysmal movements, as already detailed in Table SI (online supporting information). OS, Ohtahara syndrome; WS, West syndrome; IS, infantile spasms; EIMFS, epilepsy of infancy with migrating focal seizures; EOEE, early-onset epileptic encephalopathy; LGS, Lennox-Gastaut syndrome; AD, autosomal dominant, GEFS+, generalized epilepsy with febrile seizures plus; HM, hemiplegic migraine; GTCS, generalized tonic-clonic seizures; AHC, alternating hemiplegia of childhood; EA, episodic ataxia; CAPOS, cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss; PNKD, paroxysmal non-kinesigenic dyskinesia; ASD, autistic spectrum disorder; PKD, paroxysmal kinesigenic dyskinesia; BFIS, benign familial infantile seizures; PED, paroxysmal exercise-induced dyskinesia; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.