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RESEARCH ARTICLE

Movement Disorders in Patients With Genetic Developmental and Epileptic Encephalopathies

Sterre van der Veen, MD,* Gabrielle T.W. Tse, MD,* Alessandro Ferretti, MD, Giacomo Garone, MD, Bart Post, MD, PhD, Nicola Specchio, MD, PhD, Victor S.C. Fung, MBBS, PhD, Marina Trivisano, MD, PhD, and Ingrid E. Scheffer, MBBS, PhD

Correspondence
Dr. Scheffer
scheffer@unimelb.edu.au

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Abstract

Background and Objectives

Movement disorders (MDs) are underrecognized in the developmental and epileptic encephalopathies (DEEs). There are now more than 800 genes implicated in causing the DEEs; relatively few of these rare genetic diseases are known to be associated with MDs. We identified patients with genetic DEEs who had MDs, classified the nature of their MDs, and asked whether specific patterns correlated with the underlying mechanism.

Methods

We classified the type of MDs associated with specific genetic DEEs in a large international cohort of patients and analyzed whether specific patterns of MDs reflected the underlying biological dysfunction.

Results

Our cohort comprised 77 patients with a genetic DEE with a median age of 9 (range 1–38) years. Stereotypies (37/77, 48%) and dystonia (34/77, 44%) were the most frequent MDs, followed by chorea (18/77, 23%), myoclonus (14/77, 18%), ataxia (9/77, 12%), tremor (7/77, 9%), and hypokinesia (6/77, 8%). In 47% of patients, a combination of MDs was seen. The MDs were first observed at a median age of 18 months (range day 2–35 years). Dystonia was more likely to be observed in nonambulatory patients, while ataxia was less likely. In 46% of patients, therapy was initiated with medication (34/77, 44%), deep brain stimulation (1/77, 1%), or intrathecal baclofen (1/77, 1%). We found that patients with channelopathies or synaptic vesicle trafficking defects were more likely to experience dystonia; whereas, stereotypies were most frequent in individuals with transcriptional defects.

Discussion

MDs are often underrecognized in patients with genetic DEEs, but recognition is critical for the management of these complex neurologic diseases. Distinguishing MDs from epileptic seizures is important in tailoring patient treatment. Understanding which MDs occur with different biological mechanisms will inform early diagnosis and management.

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Introduction

Developmental and epileptic encephalopathies (DEEs) are the most severe group of epilepsies, characterized by drug-resistant seizures, epileptiform activity on electroencephalography, and developmental plateauing or regression.[1] With advances in next-generation sequencing, the genetic basis is determined in almost 40%–50% of DEEs with more than 800 DEE genes identified.[2-4] These genes implicate a wide range of neurobiological processes.[5,6]

*These authors contributed equally to this work.

From the University Medical Center Groningen (S.v.d.V.), the Netherlands; Austin Health (G.T.W.T.), Melbourne, Australia; Bambino Gesù Children's Hospital (A.F., M.T.); Bambino Gesù Children's Hospital (G.G.), Tor Vergata University, Rome, Italy; Radboud UMC (B.P.), Nijmegen, the Netherlands; Ospedale Pediatrico Bambino Gesù (N.S.), Rome, Italy; Westmead Hospital (V.S.C.F.); and University of Melbourne, Austin Health and Royal Children's Hospital (I.E.S.), Australia.

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Glossary

DBS = deep brain stimulation; **DEE** = developmental and epileptic encephalopathy; **MD** = movement disorder.

As larger cohorts of patients with a specific genetic DEE are identified, a phenotypic spectrum typically emerges. While there has been a major focus on seizure types, EEG, and MRI findings in individuals with DEEs, less attention has been given to movement disorders (MDs), which may be subtle or missed. Distinguishing MDs from seizures can be challenging, yet critically important for management of both facets of the DEE.

The association between genetically determined epilepsies and MDs has become increasingly apparent. There has been considerable interest in paroxysmal MDs that occur with self-limited epilepsies, such as paroxysmal kinesigenic dyskinesia and self-limited familial infantile epilepsies, which co-occur in the epilepsy syndrome of infantile convulsions choreoathetosis, due to *PRRT2* pathogenic variants.[7,8] For the DEEs, MDs have been identified in some specific genetic diseases; however, the range of chronic and paroxysmal MDs in genetic DEEs has not been addressed in a large cohort of patients.

A clearer understanding of the range of MDs seen in association with DEE genes also has implications for MD specialists. For some genes usually associated with a DEE phenotype, rare patients with only mild,[9] or without,[10] epilepsy have been reported. Such patients may present to MD neurologists, so it is important to include DEE genes in the diagnostic workup.

We aimed to understand which MDs are associated with different genetic DEEs. We characterized the pattern of MDs in patients with genetic DEEs.

Methods

Patients with genetic DEEs and a co-existing MD were recruited to the University of Melbourne Epilepsy Genetics Research Program (Melbourne, Australia) and the Department of Neuroscience at the Bambino Gesù Children's Hospital (Rome, Italy). Only patients with an identified molecular diagnosis were included, whereas patients with an acquired or unknown cause were excluded.

Patients with DEEs were included in the study when we identified a MD in the setting of a known genetic etiology. Video recordings of each patient's MD were reviewed by MD neurologists, and the nature of the MD was classified for each patient. Videos were obtained from video-EEG recordings, video recordings by the physician, or home video provided by family members or carers. A small number of patients were included where their neurologist described the MD(s) but a video was not available. We classified MDs into hyperkinetic MD phenotypes of stereotypies, dystonia, chorea, myoclonus, and tremor in addition to hypokinetic and ataxic MDs.[11]

We determined the age at onset at which the abnormal movements were first noticed by parents or carers or documented in the medical record, whichever was earlier. We reviewed the clinical course of the MD and patients' seizure types, severity of intellectual disability (ID), impairment in gait and speech, and abnormalities on brain MRI. The severity of ID was determined by IQ scores (where available) or information on the level of functioning in accordance with the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.[12] An epilepsy syndrome diagnosis was made where possible.[13]

Data were analyzed in MATLAB R2022a (MathWorks, Natick, MA) with descriptive analyses for clinical characteristics. Comparison of categorical data among groups was performed using a χ^2 test to determine the level of significance ($p < 0.05$).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Austin Health Human Research Ethics Committee. Written informed consent was obtained for research participation and video recording of the MD from all patients or their parents or legal guardians in the case of minors or adults with ID.

Data Availability

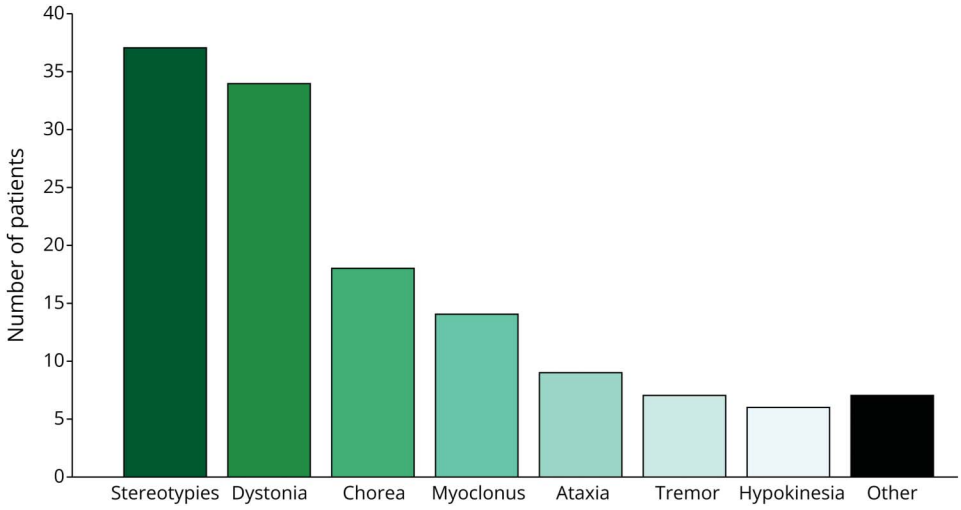
Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

We identified 77 patients (41 female, 53%) with a genetic DEE and a co-existing MD. They had a median age of 9 years (range 1–38 years); 3 (4%) patients were deceased at ages 3, 3, and 12 years, respectively.

The most common MDs were stereotypies occurring in 37 (48%) and dystonia in 34 (44%) patients, followed by chorea in 18 (23%), myoclonus in 14 (18%), ataxia in 9 (12%), tremor in 7 (9%), and hypokinesia in 6 (8%) patients (Figure 1). In patients with chorea, the movements were predominantly choreoathetosis in 11 and ballistic in 7 patients. In 41 (53%) patients, a single MD was observed, with stereotypies being most common (18 patients) (Figure 2). In the remaining 36 (47%) patients, more than 1 MD was observed of which chorea with dystonia, hypokinetic rigidity syndrome with dystonia, and dystonia with spasticity were most frequent. While stereotypies were the most common finding, they co-occurred at times with all the other MDs apart from spasticity (Figure 2), without a distinctive association emerging. The MDs were paroxysmal in 10/71 (14%), with

Figure 1 Frequency of Movement Disorders in a Cohort of 77 Patients With Genetic DEEs



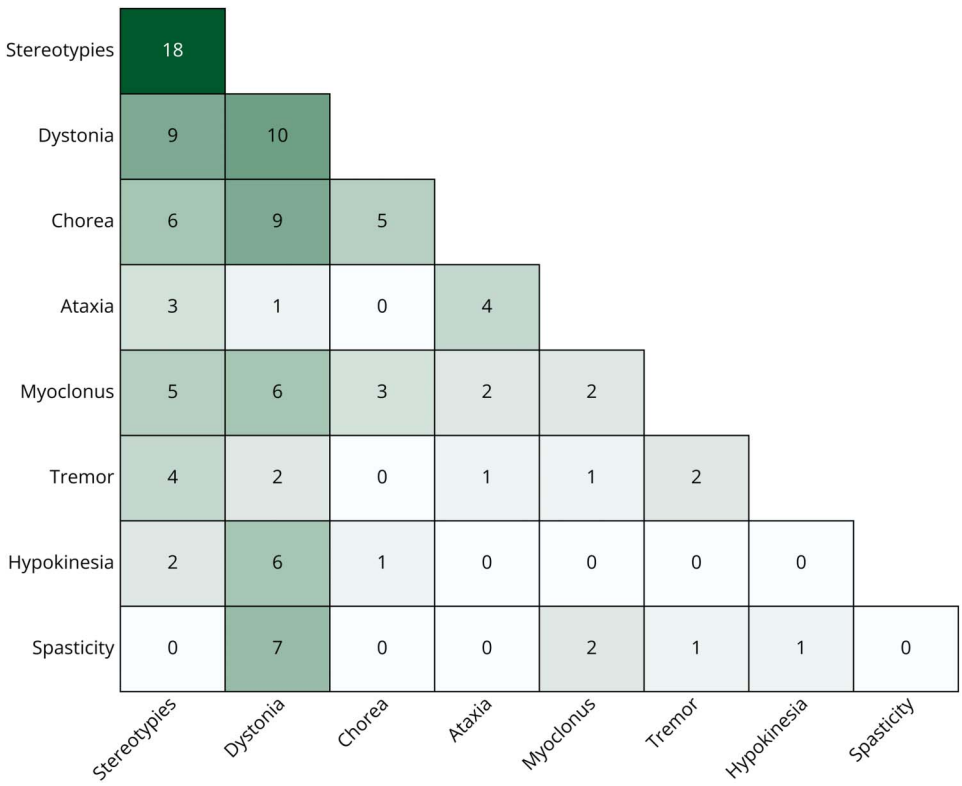
The "other" box refers to movement disorders such as dyskinetic exacerbations (n = 3), dyskinetic eye blinking (n = 2), orofacial dyskinesias (n = 1), and an exaggerated startle reflex (n = 1). DEE = developmental and epileptic encephalopathy.

dystonia (8/10), ataxia (1/10), and tremor (1/10), while showing chronic persistence in the remainder of patients.

The age at onset of the MD was known in 67/77 patients and began at a median age of 18 months (range day 2–35 years). In the patients who only had a single MD, the age at onset for stereotypies was 21 months (range 6 months–14 years), dystonia 14.5 months (range 6 months–13 years), and chorea 12 months (range 4 months–13 years).

The median age at onset of epileptic seizures in our cohort was 4 months (range day 1–11 years). The most common epileptic seizure types were epileptic spasms (36/75), tonic seizures (34/75), myoclonic seizures (30/75), and tonic-clonic seizures

Figure 2 Co-occurrence of Different Types of Movement Disorders and Spasticity in 77 Patients With Genetic DEEs



DEE = developmental and epileptic encephalopathy.

(30/75). Thirty-seven of 77 patients had an early infantile DEE with onset by 3 months of age,[13] while 30/77 had an infantile-onset DEE by age 2 years, with 10/77 having later onset. Epilepsy syndrome diagnoses in 25/77 (32%) patients included Lennox-Gastaut syndrome (8/77), Dravet syndrome (5/77), infantile epileptic spasms syndrome (4/77), epilepsy in infancy with migrating focal seizures (4/77), epilepsy with myoclonic-atonic seizures (3/77), and progressive myoclonus epilepsy (1/77).

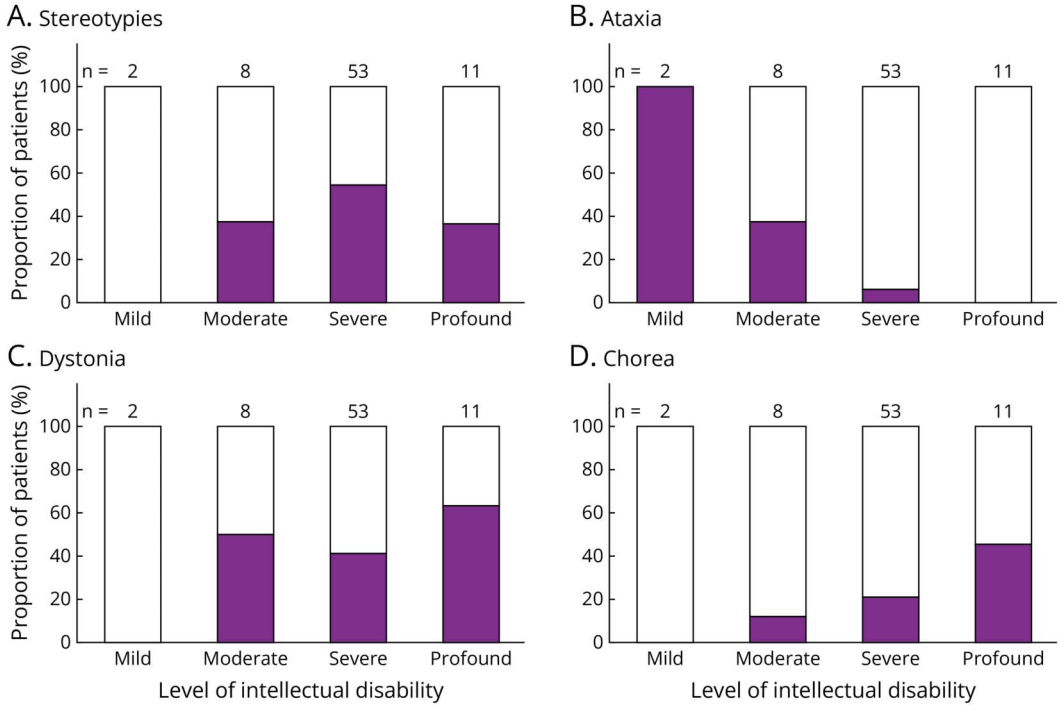
ID was severe in 53/74 (72%) patients, profound in 11/74 (15%), with a smaller proportion having moderate (8/74) or mild (2/74) ID. In 3 patients, the severity of their ID was not available. The correlation between type of MD and severity of ID was examined and found that ataxia was less frequently associated with severe ID ($\chi^2 = 24.96$, $p < 0.0001$, Figure 3). By contrast, stereotypies and dystonia were observed evenly across different severity levels of ID.

Fifty-three of 77 (70%) patients were nonambulant. The inability to walk was more likely in patients with dystonia (30/34, $\chi^2 = 9.98$, $p = 0.002$) while, understandably, ataxia was much less likely to be observed in nonambulatory individuals (2/9, $\chi^2 = 10.92$, $p \leq 0.001$). Chorea, myoclonus, and stereotypies were not associated with severity of motor impairment.

Fewer than half (34/74, 46%) of the patients were treated with medication for their MD. In general, drugs were initiated for dystonia, chorea, and myoclonus, but not for stereotypies, tremor, and hypokinesia. They received trihexyphenidyl (15/34), tetrabenazine (12/34), clonazepam (7/34), clonidine (6/34), baclofen (6/34), gabapentin (4/34), levodopa (3/34), botulinum toxin (3/34), tizanidine (1/34), and propranolol (1/34). Limited information on drug responsiveness was available in 16/34 patients. Levodopa was ineffective for dystonia in 3/3 patients. Tetrabenazine improved dystonia and chorea in patients with pathogenic variants in *GNAO1* and *UGDH*, but was ineffective in 3 patients with different sodium channel DEEs (*SCN1A*, *SCN2A* and *SCN8A*). Paroxysmal dystonia was treated in 3/10 patients; 2 patients showed mild improvement on treatment with tetrabenazine and combination therapy (baclofen, clonazepam, and lorazepam) in another. Invasive therapies were performed in 2 patients, both with symptom improvement: deep brain stimulation (DBS) of the bilateral globus pallidus internus in a patient with *GNAO1*-DEE causing chorea and dystonia[14] and an intrathecal baclofen pump in a patient with an *SCN2A* early infantile DEE causing dystonia.

Our patient cohort had 38 different genetic diseases, with *STXBP1*[15-18] and *CDKL5* most frequently seen (7 patients each), followed by *SCN1A* (6/77),[19,20] *SCN2A* (5/77),[21] *MECP2* (4/77), *KCNQ2* (3/77), *GNAO1* (3/77),[14,22] *CHD2* (3/77), and *ALG13* (3/77).[22] The remaining 29 genes were identified in 2 patients (7/38) or single (22/38) cases. All 7 patients with *CDKL5*-DEE had stereotypies, and 3/3 patients with *GNAO1*-DEE had chorea and acute dyskinetic

Figure 3 Proportion of 77 Patients With Genetic DEEs With the 4 Most Common Movement Disorders According to Severity of Intellectual Disability



DEE = developmental and epileptic encephalopathy.

exacerbations. We looked for consistent MD patterns in 3 or more cases with a specific genetic disease (Table). We found that 4/5 patients with *SCN2A*-DEE had dystonia, 3/6 with *SCN1A*-DEE had ataxia, 4/7 with *STXBP1*-DEE had stereotypies, and 3/7 had dystonia.

Discussion

The presence of MDs is often not appreciated in patients with DEEs because they can be subtle with the major clinical focus being on drug-resistant seizures.[1] In this study, our international collaborative effort ascertained 77 patients with a genetic DEE who had a concomitant MD. Stereotypies and dystonia were most common, followed by chorea, myoclonus, ataxia, tremor, and hypokinesia. MDs can be observed from as early as the second day of life or as late as the fourth decade and are associated with a wide range of genetic diseases. Approximately half of our patients required treatment for their MDs, especially those with dystonia or chorea, with limited effect.

MDs are classically divided into paroxysmal, where they occur episodically and may be triggered by a specific task, such as initiation of movement or exercise, or constant, which may still be intermittent in nature, as seen with stereotypies or dystonia. In both instances, a differential diagnosis of an epileptic seizure may need to be considered. For example, all 3 patients with *GNAO1*-DEE had paroxysmal dyskinetic exacerbations that need to be distinguished from motor seizures.[23] In patients with hyperkinetic MDs, such as *DNM1*-DEE,[24] distinction from myoclonic seizures can be challenging; whereas stereotypies are frequent in *CDKL5*-DEE and may be hard to distinguish from focal motor seizures.[25] With the widespread availability of smart phones, multiple videos of an event of concern can be illuminating. Several videos of an event allow the clinician to take into account the context of the abnormal movements, including any potential triggers, and whether the episodes are stereotyped. Where distinction is challenging, video-EEG monitoring, preferably with EMG recording, can make a definitive diagnosis and guide management.

Dystonia occurred in isolation or in combination with chorea, myoclonus, a hypokinetic rigidity syndrome, or spasticity. Of interest, the 4/34 patients who were ambulatory did not receive therapy for dystonia, whereas, 19/30 nonambulatory patients had a trial of medical or surgical therapy. A wide range of pharmacologic drugs was trialed for dystonia, including trihexyphenidyl, tetrabenazine, baclofen, gabapentin, levodopa, and botulinum toxin. Two of our patients received invasive therapies with improvement of symptoms: DBS of the bilateral globus pallidus internus for a boy with *GNAO1*-DEE and an intrathecal baclofen pump for a girl with *SCN2A* early infantile DEE. While DBS has been shown to be a safe and effective treatment for dystonia, clinical outcomes vary according to different genetic pathologies.[26] DBS is most effective for *TOR1A* disease, which causes dystonia but not epilepsy; lower efficacy has been reported for genetic diseases due to *ATP1A3* and *ADCY5* pathogenic variants.[27] In *GNAO1*-related dyskinesias, DBS has been shown to be effective, especially for preventing severe hyperkinetic exacerbations and *status dystonicus*; however, the long-term benefit on the baseline MD requires further study.[28] Thus, understanding the genetic etiology is crucial when considering whether DBS would be suitable for a child with a DEE and dystonia, although large cohorts of each genetic DEE are needed to draw definitive conclusions. Intrathecal baclofen is well established for severe secondary generalized dystonia but has rarely been reported in pediatric neurodegenerative diseases.[29,30] The marked clinical benefit of intrathecal baclofen for extreme distress associated with dystonia in our patient with *SCN2A* early infantile DEE led to significant improvement in quality of life for the patient and her family because it alleviated her extremely severe irritability through the first 18 months of life.

Ataxia occurred more frequently in ambulatory patients with mild to moderate ID. Because dysmetria or intention tremor require goal-directed movements, it may not be possible to identify these features in patients with more severe impairment. Similarly, dysarthria is difficult to determine in patients who only speak a few words or are nonverbal. Therefore, detection of cerebellar features is much more likely in those with milder disability and may be present, but not assessable, in severely impaired individuals.

Differentiation between types of MDs can be challenging, especially in complex neurologic disorders with features of spasticity, rigidity, hypotonia, or cognitive impairment.[31] The blanket terms "hyperkinetic" and "dyskinetic" are often applied to several types of MDs. In this study, we distill MDs into MD phenotypes of stereotypies, dystonia, chorea, myoclonus, and tremors.[11,31]

A broad range of neurobiological mechanisms has been implicated in the DEEs associated with MDs.[32-34] These include channelopathies, synaptic defects, transcriptional dysregulation, impairment in posttranslational modifications, transporter and signaling dysfunction, and metabolic disorders.[33] We found that patients with sodium (*SCN1A*, *SCN2A*, and *SCN8A*), potassium (*KCNQ2*), and calcium (*CACNA1E*) channelopathies were more likely to experience dystonia, as were patients with synaptic vesicle trafficking disorders (*STXBP1*, *DNM1*, and *DNM1L*) (Figure 4). While stereotypies were also frequently seen with synaptic vesicle trafficking disorders (*STXBP1*, *DNM1*, and *DNM1L*), stereotypies were the most frequent MD in our cohort with transcriptional defects (*CHD2*, *MECP2*, *MEF2C*, *BRAT1*, *CDKL5*, and *MBD5*). More mixed pictures were observed in patients with posttranslational defects and transporter and signaling disorders.

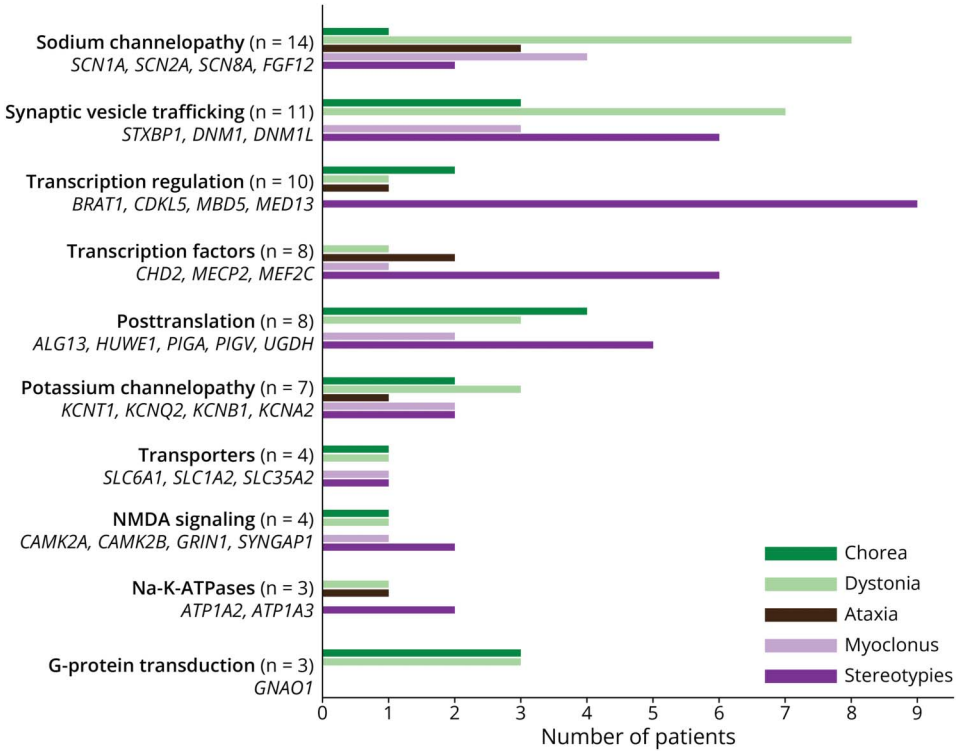
The cross-sectional nature of this study prevents us from analyzing the evolution of MDs over time in individual patients. Furthermore, distinctive patterns for specific genetic diseases did not emerge because the phenotype varied

Table Type of Movement Disorders in 77 Patients With Genetic DEEs

Gene	No. of patients	Already described in literature	Stereotypies	Dystonia	Chorea	Ataxia	Myoclonus	Hypokinesia	Other
ALG13	3	1 case[22]	1	0	2	0	0	0	Dyskinesia
ATP1A2	1		1	0	0	0	0	0	Dyskinesia
ATP1A3	2	1 case[35]	1	1	0	1	0	1	Paroxysmal MD
BRAT1	1		1	1	0	0	0	0	Tremor
CACNA1E	1		0	1	1	0	0	0	No
CAMK2A	1		0	1	1	0	1	0	No
CAMK2B	1		1	0	0	0	0	0	No
CDKL5	7		7	0	1	1	0	0	Tremor, dyskinesia
CHD2	3		2	0	0	0	0	0	Tremor
DNM1	2	2 case[24]	2	2	1	0	0	0	Eye blinking
DNM1L	2		0	2	0	0	2	0	Spasticity, paroxysmal MD
FGF12	1	1 case[36]	1	0	0	0	0	0	Dyskinesia
FRRS1L	1		0	1	0	1	0	0	No
GNAO1	3	3 cases[14,22]	0	3	3	0	0	0	Acute dyskinetic exacerbations
GRIN1	1		0	1	0	0	0	0	No
HUWE1	1		0	1	0	0	0	0	No
KCNA2	1		0	0	0	1	1	0	No
KCNB1	1		0	1	0	0	0	0	No
KCNQ2	3		2	0	2	0	1	0	No
KCNT1	2		0	2	0	0	0	0	Spasticity
LIS1	1		0	1	0	0	0	0	Paroxysmal MD
MBD5	1	1 case[37]	1	0	0	0	0	0	No
MECP2	4		3	1	0	1	0	0	Crouch gait
MED13	1		0	0	1	0	0	0	No
MEF2C	1	1 case[17]	1	0	0	1	1	0	No
PIGA	2	1 case[38]	2	1	2	0	0	1	No
PIGV	1		1	0	0	0	1	0	No
PLPBP	1		1	0	0	0	0	0	No
SCN1A	6	2 cases[19,20]	1	2	1	3	2	0	Crouch gait, tremor
SCN2A	5	2 cases[21]	0	4	0	0	1	1	Tremor, exaggerated startle, paroxysmal MD
SCN8A	2	2 cases[39]	0	2	0	0	1	1	Spasticity, paroxysmal MD
SLC2A1	2		0	1	0	0	1	0	Crouch gait, paroxysmal MD
SLC35A2	1		0	0	1	0	0	0	No
SLC6A1	1	1 case[40]	1	0	0	0	0	0	Stereotypies are tics
STXBP1	7	4 cases[15-18]	4	3	2	0	1	2	Tremor, dyskinesia
SYNGAP1	1		1	0	0	0	0	0	No
UGDH	1		1	1	0	0	1	0	Paroxysmal MD

Abbreviations: DEE = developmental and epileptic encephalopathy; MD = movement disorder.

Figure 4 Patterns of the 5 Most Common Movement Disorders Grouped According to the Biological Mechanisms Causing Genetic DEEs (in 3 or More Individuals)



DEE = developmental and epileptic encephalopathy.

between patients and each genetic cohort was relatively small. A prospective natural history study of specific genetic DEEs may identify consistent patterns over time, together with determining the efficacy of therapeutic approaches.

Recognition of MDs is critical in managing patients with complex neurologic conditions because seizures need targeted management that differs from treatment of MDs. MDs may severely affect quality of life. We analyzed the types of MDs in individuals with genetic DEEs to identify patterns associated with different biological mechanisms. Recognition of DEE-MD patterns will aid in identification of specific genetic etiologies. With the promise of precision medicine for genetic DEEs, MDs will need to be addressed in concert with drug-resistant seizures and developmental impairment.

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Appendix Authors

Name	Location	Contribution
Sterre van der Veen, MD	University Medical Center Groningen, the Netherlands	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Gabrielle T.W. Tse, MD	Austin Health, Melbourne, Australia	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Alessandro Ferretti, MD	Bambino Gesù Children's Hospital, Rome, Italy	Major role in the acquisition of data
Giacomo Garone, MD	Bambino Gesù Children's Hospital, Tor Vergata University, Rome, Italy	Major role in the acquisition of data
Bart Post, MD, PhD	Radboud UMC, Nijmegen, the Netherlands	Major role in the acquisition of data
Nicola Specchio, MD, PhD	Ospedale Pediatrico Bambino Gesù, Rome, Italy	Major role in the acquisition of data
Victor S.C. Fung, MBBS, PhD	Westmead Hospital, Australia	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design
Marina Trivisano, MD, PhD	Bambino Gesù Children's Hospital, Rome, Italy	Major role in the acquisition of data
Ingrid E. Scheffer, MBBS, PhD	University of Melbourne, Australia	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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