Diagnostic approach to paediatric movement disorders

Groningen Movement Disorder Expertise Centre; Brandsma, Rick; van Egmond, Martje E; Tijssen, Marina A J

Published in:
Developmental Medicine and Child Neurology

DOI:
10.1111/dmcn.14721

Publication date:
2021

For physicians only

~50% of epilepsies have some genetic basis [1,2,3]

Find the underlying cause of the seizure

Real patient with CLN2 disease

- **Some rapidly progressive neurodegenerative disorders present with subtle and non-specific symptoms**, mimicking more common paediatric epilepsies.[3]
- **CLN2 disease (TPP1 deficiency) is one devastating genetic condition** that often presents with new-onset unprovoked seizures between 2-4 years of age and/or language delay and/or motor disturbance/ataxia.[4,5]
- **Genetic testing can help identify the aetiology** of 100+ paediatric epilepsies with one test* [2]
- **Many genes are actionable:** A prompt diagnosis can be essential to adopt precise disease management strategies.[3,2]
- If you have patients with seizures of unknown cause, **no-cost genetic testing may be available** in your country.[3]

Visit paediatricseizures.com to find a no-cost test sponsored by BioMarin near you.

The list of laboratories provided does not include all laboratories that perform CLN2 genetic and enzymatic diagnostic testing. Laboratories providing the no-cost tests are supported by BioMarin and participate in commercially-sponsored diagnostic testing programs. There may or may not be a sponsored program or test in your area. The sponsors receive de-identified patient data, but no patient identifiable information. Participants of this program have no obligation to recommend, purchase, order, prescribe, administer, use or support any product or service of the sponsors.

** Number of genes tested will vary in each country, ranging from a single gene to over 400+ genes*

~ The genetic basis of epilepsy has a range according to country and publication from 14% -24.4%,[2] to 50% [1], to 70-80%[3]

References:

1) Pal DK *et al. Genetic evaluation and counseling for epilepsy. Nature Rev Neurology. 2010;6:445-453.* **2) Truty** *et al. Possible precision medicine implications from genetic testing using combined detection of sequence and intragenic copy number variants in a large cohort with childhood epilepsy. Epilepsia Open. 2019;4:397–408.* **3) Amadori** *et al. 'Targeted re-sequencing for early diagnosis of genetic causes of childhood epilepsy' Italian Journal of Pediatrics (2020) 46:92 https://doi.org/10.1186/s13052-020-00860-1* **4) Mei D, Parrini E, Marini C, Guerrini R.** *The Impact of Next-Generation Sequencing on the Diagnosis and Treatment of Epilepsy in Paediatric Patients. Mol Diagn Ther. 2017;21(4):357-373. doi:10.1007/s40291-017-0257-0* **5) Berg AT, Coryell J, Saneto RP**, *et al. Early-Life Epilepsies and the Emerging Role of Genetic Testing. JAMA Pediatr. 2017;171(9):863-871. doi:10.1001/jamapediatrics.2017.1743*

Visit paediatricseizures.com

GL/CLN2/0033 EU/CLN2/0922 August 2020

BIOMARIN®

Sponsored by BioMarin Pharmaceutical Inc.

Diagnostic approach to paediatric movement disorders: a clinical practice guide

RICK BRANDSMA[1] | MARTJE E VANEGMOND[2] | MARINA A J TIJSSEN[2] | THE GRONINGEN MOVEMENT DISORDER EXPERTISE CENTRE*

1 Department of Pediatric Neurology, University Medical Center Utrecht, Utrecht; **2** Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

Correspondence to Marina A J Tijssen at University Medical Center Groningen, 9713 GZ Groningen, the Netherlands. E-mail: m.a.j.de.koning-tijssen@umcg.nl

***Members of the Groningen Movement Disorders Expertise Centre are listed in the Acknowledgements.**

PUBLICATION DATA
Accepted for publication 2nd October 2020.
Published online

ABBREVIATIONS

IEM	Inborn error of metabolism
NGS	Next-generation sequencing
PMD	Paediatric movement disorder
WES	Whole-exome sequencing

Paediatric movement disorders (PMDs) comprise a large group of disorders (tics, myoclonus, tremor, dystonia, chorea, Parkinsonism, ataxia), often with mixed phenotypes. Determination of the underlying aetiology can be difficult given the broad differential diagnosis and the complexity of the genotype–phenotype relationships. This can make the diagnostic process time-consuming and difficult. In this overview, we present a diagnostic approach for PMDs, with emphasis on genetic causes. This approach can serve as a framework to lead the clinician through the diagnostic process in eight consecutive steps, including recognition of the different movement disorders, identification of a clinical syndrome, consideration of acquired causes, genetic testing including next-generation sequencing, post-sequencing phenotyping, and interpretation of test results. The aim of this approach is to increase the recognition and diagnostic yield in PMDs.

In recent years, the importance of recognition and treatment of paediatric movement disorders (PMDs) has increasingly been recognized.[1] PMDs often comprise a mixed clinical picture with neurological and non-neurological features.[1] In addition, the number of possible aetiologies is growing, especially those concerning genetic causes. Owing to a variable phenotype–genotype correlation, the diagnostic process for PMDs becomes challenging and time consuming, not only for the clinician but also for patients and caregivers.[2]

Innovative next-generation sequencing (NGS) techniques have increased the diagnostic yield in paediatric neurology.[3] The use of NGS can speed up the diagnostic process and prevent unnecessary additional investigations, and shorten the time of uncertainty in patients and caregivers. Second, in some disorders, early treatment options are crucial to prevent further neurological decline.

The goal of this overview is to present a diagnostic algorithm that can serve as a framework for paediatricians and/or (paediatric) neurologists with less experience in PMDs (Fig. 1).

CLINICAL PHENOTYPE

Step 1. Is it a movement disorder?

The first step is to distinguish normal, physiological developmental motor patterns and pathological movement disorders. Infantile fidgety movements and startles resembling chorea and myoclonus normally disappear around the age of 3 months.[4] Dystonic-like features may appear from birth and can persist until the age of 16 years.[4] The development of goal-directed movements (3–6mo) coincides with the occurrence of ataxic-like features which can persist until the age of 12 years.[4] It may be difficult to distinguish physiological developmental motor patterns from pathological movement disorders. Children should be monitored to evaluate how the movement pattern develops. In general, physiological patterns will subside with typical psychomotor development. Besides developmental features, other neurological diseases (such as epilepsy) may resemble movement disorders.

Step 2. Classify the movement disorder phenotype and which movement disorder is the most prominent

The second step is to classify the movement disorder phenotype and denote which movement disorder is the most prominent. Clinical clues can be used to distinguish between different movement disorder phenotypes. Movement disorders are classified into three major groups: hyperkinetic and hypokinetic movement disorders and ataxia. In children, hyperkinetic movement disorders are more prevalent and include tics, dystonia, chorea, myoclonus, stereotypies, and tremor. Hypokinetic movement disorders, including Parkinsonism, are rare in children. Ataxia is not a hypo- or hyperkinetic movement disorder, but includes disorganized and poorly executed movements, and is relatively common in children.[5]

Hyperkinetic movement disorders

Tics. Tics are defined as sudden, rapid, recurrent, nonrhythmic movements or vocalizations (Video S1, online

 DOI: 10.1111/dmcn.14721

supporting information; descriptions of the videos are found in Appendix S1, online supporting information).[6] A distinction is made between motor and phonic tics and each is subdivided as simple or complex. Simple motor tics comprise a single muscle or localized muscle group, such as eye blinking. Complex motor tics involve either a cluster of simple actions or a coordinated sequence of movements. Simple phonic tics include sounds and noises such as humming or sniffing, whereas complex phonic tics comprise the repetition of words, syllables, or phrases. Positive clues are a waxing and waning course, worsening by stress or excitement, the report of a premonitory sensation, and brief voluntary suppressibility followed by a rebound.[1,7]

Dystonia. Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous (Video S2, online supporting information). Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation. Symptoms can be present in one body part (focal), additional/adjacent body parts (segmental), unilateral (hemidystonia), or generalized. Slow, continuous, involuntary writhing movements that prevent maintenance of a stable posture, previously known as athetosis, are considered as part of a dystonic phenotype. Features supporting the diagnosis dystonia include mirror movements and a sensory trick.[8] These features may help clinicians to differentiate between dystonia and 'dystonia mimics'.[8] The most important dystonia mimic is spasticity. Key features in distinguishing spasticity from dystonia are the presence of velocity-dependent hypertonia, hyperreflexia, and pathological plantar responses. Spastic posturing reveals prominent flexion of the elbow and wrist with adduction of the thumb.

Chorea. Chorea is characterized by an excess of brief, continuous, unpatterned involuntary movements (Video S3, online supporting information).[9] The continuous, non-suppressible movements give the appearance of restlessness. The presence of involuntary movements at rest, worsening during action, and incorporation of excessive movements in voluntary movements are clues for this phenotype.

Myoclonus. Myoclonus is the fastest movement disorder, characterized by brief involuntary, irregular jerks caused by muscle contraction (positive myoclonus) or loss of muscle activity in active postural muscles (negative myoclonus) (Video S4, online supporting information). Myoclonus is classified according to the anatomical origin into cortical, subcortical, spinal, and peripheral myoclonus.[10] Cortical myoclonus is the most common myoclonus subtype whereas peripheral myoclonus is rare.[10] Clinical features and electrophysiological testing can help to differentiate between myoclonus subtypes and tremor.[11]

Stereotypies. Stereotypies encompass non-goal-directed fixed movement patterns or vocalizations that are repeated continuously for a period of time (seconds to minutes) in the same form (Video S5, online supporting information). These patterns occur on multiple occasions, are purposeless, and are typically distractible.[12] Examples are hand/arm flapping and head nodding.[12] Stereotypies usually manifest before the age of 3 years.[13] The movements are triggered by excitement, stress, or fatigue. Stereotypies are frequently upsetting to caregivers, but usually of little concern to the child.[1]

Tremor. Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body part (hands, legs, head, or jaw) or the voice (Video S6, online supporting information).[14] It can occur at rest, during sustained postures, during movements, and at the end of intentional movements.

What this paper adds

- An up-to-date description and diagnostic framework for testing of paediatric movement disorders is presented.
- The framework helps to determine which patients will benefit from next-generation sequencing.

Hypokinetic movement disorders

Parkinsonism. Parkinsonism is characterized by the core symptom bradykinesia with the occurrence of tremor, rigidity, or both (Video S7, online supporting information).[1,15] Parkinsonism can be recognized by a generalized slowness of movements. When patients with bradykinesia are asked to perform repetitive movements, the amplitude decreases and becomes less rhythmic. The tremor in juvenile Parkinsonism is frequently a rest tremor, but postural or action tremor can also be found.[15]

Ataxia

Ataxia is characterized by the presence of uncoordinated movements (Video S8, online supporting information). The symptoms are subdivided in four domains: (1) gait and stance with a broad-based gait, staggering, and swaying; (2) kinetic ataxia with an intentional tremor, dysmetria, and dysdiadochokinesis; (3) eye movements with nystagmus, saccadic intrusions, and dysmetria; and (4) cerebellar dysarthria.[16] The difficulties in coordination are mainly present when turning during walking and the execution of faster, goal-directed movements. At rest, there are no involuntary movements.

Step 3. Could the movement disorder be functional?

Functional movement disorders can either be hyper- or hypokinetic, with the first being much more prevalent. The diagnosis of a functional movement disorder is no longer made per exclusion, but should be a positive diagnosis, based on features in the history and examination.[17] These features are abrupt onset, varying (severity of) symptoms, and a temporary decrease of symptoms when the patient is distracted. Specifically in the case of tremor or jerky movements, entrainment can be objectified, a phenomenon in which the involuntary movements copy the rhythm of an externally cued voluntary movement (like finger-tapping).[18] In functional dystonia, the posturing is frequently fixed instead of mobile.[18] Additional features pointing in the direction of a functional movement

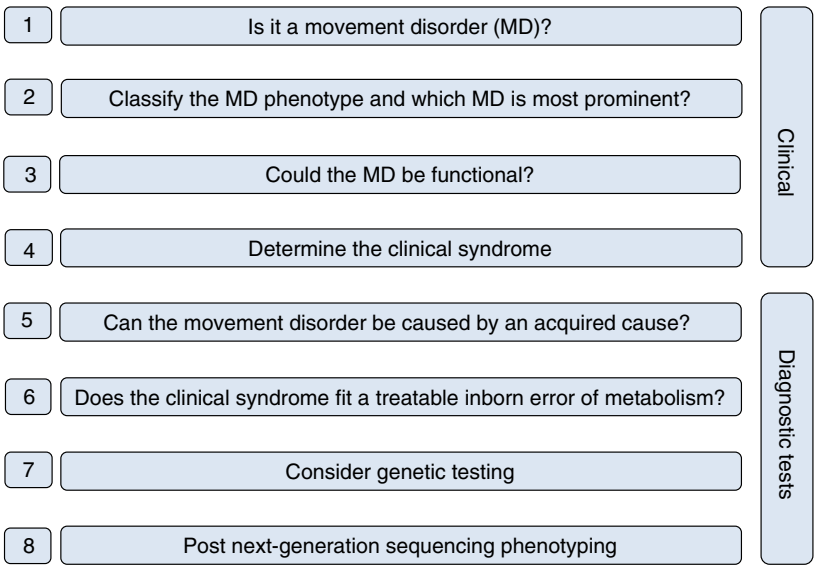

Figure 1: A diagnostic approach to paediatric movement disorders (PMDs). The diagnostic approach of PMDs divided in a clinical part (history and examination) and diagnostic part (diagnostic testing). Each step of this approach is explained in the text.]

disorder include a history of unexplained medical symptoms, prominent pain, paroxysmal symptoms, and sometimes a physical or psychosocial trigger and selective disability.[19] Despite these characteristics, it sometimes remains difficult to distinguish functional movement disorders from non-functional ones, and they can coincide in the same patient.

Step 4. Determine the clinical syndrome

We denote the clinical syndrome as the constellation of all clinical features, including different movement disorders, as well as additional neurological signs (such as spasticity, epilepsy, polyneuropathy, deafness, blindness, and cognitive difficulties) and non-neurological signs (including dysmorphisms, skin and psychiatric abnormalities [e.g. obsessive–compulsive disorder, behavioural changes, apathy]). Sometimes the clinical syndrome strongly points to a specific diagnosis and prompts directed genetic testing. However, in children, clinical syndromes are usually less distinct. In these cases, it is advisable to select the main movement disorder as the starting point for diagnostic testing. In the following section we outline the basic approach grouped by the main movement disorder phenotype. We also provide references to diagnostic algorithms for some specific movement disorders.

Tics

Tics are divided into either primary or secondary tic disorders. Primary tic disorders are the most common. Transient tic disorder is the most frequent primary tic disorder in children followed by Tourette syndrome. Secondary tic disorders are rare and can be caused by acquired or genetic disorders (chromosomal or heredo-degenerative). It has been hypothesized that an acute onset of tics with neuropsychiatric symptoms (such as obsessive–compulsive disorder) might be associated with an aberrant immune response to an infectious episode, described as paediatric auto-immune neuropsychiatric disorder associated with streptococcal infection; however, the true relation with streptococcal infection is still debated.[5] If the patient has an isolated tic disorder, further diagnostic testing is not necessary.

Dystonia

The aetiology of dystonia can be divided into acquired or genetic. Acquired causes can be divided in structural lesions, vascular insults, and infectious or auto-immune disorders. For genetic dystonia the list of causes is extensive.[8] Classification of the clinical characteristics of dystonia is important, because of the implications for diagnostic testing and treatment.[8,20] van Egmond et al. described a diagnostic algorithm to help clinicians decide which patients would benefit from NGS technologies or whether they would require other initial investigations.[8]

Chorea

To facilitate diagnosis, a (sub-)acute onset should be distinguished from chronic chorea. (Sub-)acute chorea is the most common form in children; the aetiology is frequently acquired and can be subdivided into auto-immune (Sydenham chorea), infectious/inflammatory, vascular, hypoxic, and drug- or toxin-induced. Chronic chorea is categorized as primary (isolated genetic chorea) or secondary (perinatal hypoxic ischemic injuries, neurodegenerative, and metabolic or auto-immune disorders). The secondary aetiologies are mainly multisystem diseases in which chorea can

be the main symptom, but it is often accompanied by other (non-)neurological symptoms.[1,21] In particular in the latter case, further genetic diagnostic work-up with NGS is warranted (see Step 6).

Myoclonus

Myoclonus can be the symptom of a wide variety of acquired and genetic disorders. A (sub-)acute onset and fast progression points towards acquired causes, whereas young-onset and a slow progressive course is more characteristic of a genetic disorder. The most common acquired causes include drug-induced, metabolic derangements, infection, or auto-immune disorders. In genetic disorders, myoclonus is often accompanied by ataxia, dystonia, or other movement disorders. Isolated myoclonic jerks can be seen in epileptic encephalopathies and familial cortical myoclonic tremor with epilepsy; for a comprehensive overview of genetic myoclonus disorders, see van der Veen et al.[22] A diagnostic approach to patients with myoclonus can be found in Zutt et al.[23]

Stereotypies

Causes of stereotypies can be divided into four groups. Physiological and primary stereotypies are seen during typical development and they will disappear over time. Secondary stereotypies are seen in children with a variety of underlying disorders, such as developmental delay, autism, (para)infectious, paraneoplastic, auto-immune, drug induced, or they are due to sensory deprivation. Only in rare cases are stereotypies due to genetic causes, including Rett syndrome.[12] In a typically developing child, stereotypies will not need further diagnostic work-up. Further diagnostic work-up (such as infectious, auto-immune, and/or genetic testing) is indicated only if additional features are present.

Tremor

In patients with tremor it is advisable to look for additional signs, such as dystonia, Parkinsonism, and cerebellar or brainstem signs, pointing towards a combined clinical syndrome that warrants specific diagnostic tests.[14] If no additional signs are present, the patient has an isolated tremor syndrome, such as essential or enhanced physiological tremor. Enhanced physiological tremor can be caused by several reversible conditions, such as anxiety, fatigue, hyperthyroidism, and numerous drugs.[14] Essential tremor is familial in half of the patients.[24]

Parkinsonism

Isolated Parkinsonism is rare in childhood and is observed in young-onset Parkinson disease; in most cases there is a positive family history. In children, Parkinsonism is frequently accompanied by other movement disorders or other neurological signs (cognitive decline, behavioural disturbances).[15] Parkinsonism can be due to acquired (e.g. medication, toxins, infectious) or genetic/metabolic causes, including Wilson disease, neurodegeneration with brain iron accumulation, and neurotransmitter disorders. Importantly, juvenile Parkinsonism can be caused by different trinucleotide disorders (such as Huntington disease and spinocerebellar ataxia type 3). It is important to realize that these disorders are not identified by current NGS techniques and require specific genetic testing. In case of Parkinsonism the first step will be to perform magnetic resonance imaging (MRI) with susceptibility-weighted images to give guidance to further diagnostic work-up, especially genetics.

Ataxia

Paediatric-onset ataxia is also caused by acquired or genetic disorders.[25] Acquired causes are recognized by the (sub)-acute onset as genetic disorders reveal a more insidious onset. Acquired causes can be medication, toxins, (para-)infectious, paraneoplastic, vascular, or auto-immune. Many genetic disorders can cause a mixed ataxic disorder, which is combined with other movement disorders or (non)-neurological signs. The most prevalent ataxic disorder in children, Friedreich ataxia, which is a trinucleotide disorder, will not be picked up by current NGS techniques. For a diagnostic approach of ataxia in children, see Brandsma et al.[26]

Case example (steps 1–4 of the algorithm)

A 2-year-old male presented to the outpatient clinic with slowly progressive balance disturbances and frequent falls. The symptoms did not start after a febrile episode. Besides these complaints, there were no other problems. Cognitive development was typical. He was born at a gestational age of 40+3 weeks after an uncomplicated pregnancy. Apgar scores postpartum were normal. Gross motor development was delayed. Communicative skills and fine motor skills were normal. Family history was negative for movement disorders, epilepsy, or developmental disorders.

Neurological examination revealed a severely unsteady and very broad-based gait. Beside the broad-based gait there were fast abrupt jerks of the extremities and the trunk resulting in more balance problems. During finger pointing these jerks were also present, without clear dysmetria. Reflexes were normal with normal plantar responses. Physical examination showed no abnormalities of the skin or signs of other organ involvement.

The findings of the history and neurological examination were compatible with prominent gait ataxia combined with jerky movements, probably myoclonus. Therefore, we defined the clinical syndrome as a progressive ataxia with myoclonus.

DIAGNOSTIC TESTING

Step 5. Can the movement disorder be caused by an acquired cause?

Almost all movement disorders can be caused by acquired causes, but, as previously discussed, the onset in acquired movement disorders is more (sub)-acute. In this section we briefly discuss the additional investigations besides careful

Table 1: Medication with movement disorders as side effects

Medication	Parkinsonism	Myoclonus	Dystonia	Ataxia	Tremor	Chorea
Anticonvulsants	✓	✓	✓	✓	✓	✓
Antipsychotics	✓	✓	✓		✓	
Antidepressants		✓	✓	✓	✓	
Antihypertensives		✓				
Antiparkinson drugs		✓	✓			
Antibiotics		✓			✓	
Antineoplastic		✓		✓	✓	
Opiates		✓				
Anxiolytics		✓		✓		
Anaesthetics		✓				
Oral contraceptives						✓
Anti-emetics			✓		✓	
Immunosuppressants				✓	✓	
Corticosteroids			✓		✓	

The table shows groups of medication known to cause different movement disorders. The list is not complete and only shows the main classes of drugs that may induce movement disorders.

history taking including prescribed medication (Table 1) and intoxication.

MRI

The first step in identifying an acquired cause is to perform MRI of the brain. Vascular and traumatic causes can be visualized. MRI might give clues for auto-immune disorders and some genetic/metabolic disorders.

Laboratory testing

Especially in the case of infectious or auto-immune disease, laboratory testing can be helpful by determining infectious and auto-immune parameters. Serological testing of viral and bacterial agents is also useful.

Cerebrospinal fluid

The presence of a pleiocytosis in cerebrospinal fluid points to an infectious or auto-immune disorder. Additional serological testing and determining auto-immune antibodies in cerebrospinal fluid can be performed thereafter.

Step 6. Does the clinical syndrome fit a treatable inborn error of metabolism?

Clinicians should be aware that, especially in children with more than one movement disorder, involvement of multiple organs, and/or cognitive difficulties, the underlying aetiology could be an inborn error of metabolism (IEM). Worsening of symptoms after dietary changes, fasting, or fever can be important clues for an IEM.

Treatment options are increasing for metabolic disorders and more therapies are expected. A fast recognition of a treatable IEM is crucial as timely treatment can prevent or lessen (brain) damage.[27] Therefore, in many countries, several treatable IEMs are included in newborn screening programmes and treatment can be started before symptoms have occurred. It is important to realize that IEMs comprise a large group of disorders which are all based on genetic mutations and can be detected by NGS techniques similar to other genetic disorders.

Therapeutic options for IEMs are divided into reduction of toxic substances, dietary interventions, vitamin supplementation, avoidance or management of triggers, specific medications, and others.[28] For a list of treatable metabolic disorders that can present with movement disorders, see Table S1 (online supporting information).[27–29]

Step 7. Consider genetic testing

If acquired causes are excluded, genetic testing should be the next step. Below, we discuss which genetic testing is most appropriated to perform first. (1) In the case of a clear phenotype/genotype correlation or in case of a positive family history, the performance of directed genetic testing of a single gene (Sanger sequencing) is warranted. (2) If there is no clear phenotype/genotype correlation, a first-tier test in PMD can be comparative genomic hybridization. The diagnostic yield will increase if patients have a movement disorder combined with cognitive difficulties, autism, and/or dysmorphisms. (3) We recommend that when there is a genetic differential diagnosis of two or more genes it is cheaper (and faster) to perform NGS instead of single gene analysis.

Whole-exome sequencing (WES) is the most applied basic technique for NGS.[30] In general, the first step in the genetic diagnostic process of PMDs is the use of a WES with a movement-disorder-specific filter. In these cases, a filter with predefined genes associated with the main movement disorder phenotype will be analysed. When the diagnosis is not established by using this filter, an analysis of the data set of all the genes captured (open WES) can be performed next.

When using NGS techniques one should be aware of the limitations: (1) the genes in the filter need to be selected carefully and be update regularly; (2) trinucleotide repeat expansion disorders, large rearrangement deletions and duplications, mutations in the non-coding part of the genome (such as deep intronic regions or promotor regions) are not detected;[30] (3) mitochondrial diseases due to mutations in mitochondrial DNA are not detected by most laboratories using WES; one should realize that the

current diagnostic yield of NGS techniques is only 15% to 40%, but probably will increase in forthcoming years.

Step 8. Post-NGS phenotyping

The results of NGS techniques can be difficult to interpret. Frequently, results reveal variants of unknown significance or heterozygotic mutations in a gene associated with a recessive disease. In these cases, it is extremely important that focused phenotyping for specific movement disorder features is performed. If the movement disorder phenotype is congruent with the phenotype of the disease (in which a variant of unknown significance or heterozygous mutation is present), further genetic investigations will be necessary to determine whether the variant(s) found explain the clinical phenotype of the patient. This includes a multiplex ligation-dependent probe amplification of the gene involved to find structural rearrangements such as duplications or deletions, which in combination with a heterozygous mutation may explain the phenotype. Also, genetic testing of parental DNA (for de novo mutations) and functional studies of the candidate gene may be warranted. Unfortunately, a definitive diagnosis cannot always be made with the help of post-NGS phenotyping.

Case example (steps 5–8 of the algorithm)

Brain MRI revealed slight hypoplasia/atrophy of the superior part of the vermis of the cerebellum, with no other cerebellar or cerebral abnormalities. Laboratory investigations were all normal. We performed genetic testing by using a WES technique with an ataxia filter (the most prominent movement disorder). This revealed a heterozygotic pathogenic mutation in the *KCNC3* gene (c.1268G>A, p.[Arg423His]) compatible with autosomal dominant spinocerebellar ataxia type 13.

However, spinocerebellar ataxia type 13 is not associated with (negative) myoclonus. By post-phenotyping with the help of a polymyography, we found that the jerky movements did not fit with myoclonus but were more compatible with an intention tremor, changing the clinical syndrome to a purer ataxic disorder.

TREATMENT

With or without a diagnosis, one should always consider treatment options. In movement disorders, mechanism-based treatment modalities for specific (especially metabolic) disorders or symptomatic treatment for the main movement disorder can be chosen.

CONCLUSION

PMDs concern a large group of disorders with heterogeneous phenotypes and genotypes, and diagnostic work-up can be challenging and time-consuming. In this paper, we have presented an up-to-date overview of PMDs and provided a diagnostic framework to facilitate early recognition of movement disorder phenotypes and guidance during the diagnostic process.

ACKNOWLEDGEMENTS

The members of the Groningen Movement Disorders Expertise Centre are as follows: H Eggink, J M Gelauff, L H Koens (all University of Groningen, University Medical Center Groningen, Department of Neurology, Groningen, the Netherlands) T J de Koning (University of Groningen, University Medical Center Groningen, Department of Neurology, Groningen, the Netherlands and Pediatrics, Department of Clinical Sciences, Lund University, Sweden), D A Sival, A M M van der Stouwe, S van der Veen (all University of Groningen, University Medical Center Groningen, Department of Neurology, Groningen, the Netherlands), and R Zutt (Haga Teaching Hospital, Department of Neurology, The Hague, the Netherlands).

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

Two (or more) of the/several author(s) of this publication is/are (a) member(s) of the European Reference Network for Rare Neurological Diseases - Project ID No 739510.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

SUPPORTING INFORMATION

The following additional material may be found online:

Video S1: Tics.
Video S2: Dystonia.
Video S3: Chorea.
Video S4: Myoclonus.
Video S5: Stereotypies.
Video S6: Tremor.
Video S7: Parkinsonism.
Video S8: Ataxia.
Appendix S1: Legends to the videos.
Table S1: Treatable inborn errors of metabolism that can present with pediatric movement disorders

REFERENCES

1. Singer HS, Mink JW, Gilbert DL. Movement Disorders in Childhood. 2nd edn. Philadelphia, PA: Saunders Elsevier, 2016.
2. van Egmond ME, Eggink H, Kuiper A, et al. Crossing barriers: a multidisciplinary approach to children and adults with young-onset movement disorders. *J Clin Mov Disord* 2018; **5**: 3.
3. van Egmond ME, Lugtenberg CHA, Brouwer OF, et al. A post hoc study on gene panel analysis for the diagnosis of dystonia. *Mov Disord* 2017; **32**: 569–75.
4. Kuiper MJ, Brandsma R, Lunsing RJ, et al. The neurological phenotype of developmental motor patterns during early childhood. *Brain Behav* 2019; **9**: e01153.
5. Schlaggar BL, Mink JW. Movement disorders in children. *Pediatr Rev* 2003; **24**: 39–51.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th edn. Washington DC: American Psychiatric Publishing, 2013.
7. Jankovic J, Lang AE. Diagnosis and assessment of Parkinson disease and other movement disorders. In:

Jankovic J, Mazziotta J, Pomeroy S, editors. Bradley's Neurology in Clinical Practice. 7th edn. Philadelphia, PA: Elsevier, 2014.

8. van Egmond ME, Kuiper A, Eggink H, et al. Dystonia in children and adolescents: a systematic review and a new diagnostic algorithm. *J Neurol Neurosurg Psychiatry* 2015; **86**: 774–81.
9. Donaldson I, Marsden CD, Schneider SA, Bhatia K. Clinical approach to movement disorders. In: Donaldson I, Marsden CD, Schneider SA, Bhatia KB, editors. Marsden's Book of Movement Disorders. Oxford: Oxford University Press, 2012: 140–1.
10. Zutt R, Tijssen MAJ, Elting JW. Myoclonus. Parkinson Disease and other Movement Disorders. 1st edn. Amsterdam: Wolters, 2014: 513–33.
11. Zutt R, Elting JW, van der Hoeven JH, Lange F, Tijssen MAJ. Myoclonus subtypes in tertiary referral center. Cortical myoclonus and functional jerks are common. *Clin Neurophysiol* 2017; **128**: 253–9.
12. Edwards MJ, Lang AE, Bhatia KP. Stereotypies: a critical appraisal and suggestion of a clinically useful definition. *Mov Disord* 2012; **27**: 179–85.
13. Katherine M. Stereotypic movement disorders. *Semin Pediatr Neurol* 2018; **25**: 19–24.
14. Bhatia KP, Bain P, Bajaj N, et al. Consensus statement on the classification of tremors from the task force on tremor of the International Parkinson and Movement Disorder Society. *Mov Disord* 2018; **33**: 75–87.
15. Niemann N, Jankovic J. Juvenile parkinsonism: differential diagnosis, genetics, and treatment. *Parkinsonism Relat Disord* 2019; **67**: 74–89.
16. Ghez C, Thach WT. Cerebellum. In: Kandel E, Schwartz J, Jessel T, editors. Principles of Neural Sciences. 4th edn. New York, NY: Mc Graw Hill, 2000: 823–50.
17. Stone J, Carson A. Functional neurologic symptoms: assessment and management. *Neurol Clin* 2011; **29**: 1–18.
18. van der Stouwe AMM, Elting JW, van der Hoeven JH, et al. How typical are 'typical' tremor characteristics? Sensitivity and specificity of five tremor phenomena. *Parkinsonism Relat Disord* 2016; **30**: 23–8.
19. Ferrara J, Jankovic J. Psychogenic movement disorders in children. *Mov Disord* 2008; **23**: 1875–881.
20. Fung VSC, Jinnah HA, Bhatia K, Vidailhet M. Assessment of patients with isolated or combined dystonia: an update on dystonia syndromes. *Mov Disord* 2013; **28**: 889–98.
21. Gilbert DL. Acute and chronic chorea in childhood. *Semin Pediatr Neurol* 2009; **16**: 71–6.
22. van der Veen S, Zutt R, Klein C. Nomenclature of genetically determined myoclonus syndromes: recommendations of the International Parkinson and Movement Disorder Society Task Force. *Mov Disord* 2019; **34**: 1602–13.
23. Zutt R, van Egmond ME, Elting JW, et al. A novel diagnostic approach to patients with myoclonus. *Nat Rev Neurol* 2015; **11**: 687–97.
24. Haubenberger D, Hallett M. Essential tremor. *N Engl J Med* 2018; **378**: 1802–10.
25. Klockgether T, Ludtke R, Kramer B, et al. The natural history of degenerative ataxia: a retrospective study in 466 patients. *Brain* 1998; **121**: 589–600.
26. Brandsma R, Verschuuren-Bemelmans CC, Amrom D, et al. A clinical diagnostic algorithm for early onset cerebellar ataxia. *Eur J Paediatr Neurol* 2019; **23**: 692–706.
27. Ebrahimi-Fakhari D, Van Karnebeek C, Münchau A. Movement disorders in treatable inborn errors of metabolism. *Mov Disord* 2019; **34**: 598–613.
28. Jinnah HA, Albanese A, Bhatia KP, et al. Treatable inherited rare movement disorders. *Mov Disord* 2018; **33**: 21–35.
29. Ferreira CR, Hoffmann GF, Blau N. Clinical and biochemical footprints of inherited metabolic diseases. I. Movement disorders. *Mol Genet Metab* 2019; **127**: 28–30.
30. Keogh MJ, Daud D, Chinnery PF. Exome sequencing: how to understand it. *Pract Neurol* 2013; **13**: 399–407.