Young-onset movement disorders

van Egmond, Martje Elisabeth

Stellingen behorende bij het proefschrift

Young-onset movement disorders

Genetic advances require a new clinical approach

1 Young-onset movement disorders: genetic advances require a new clinical approach. *(dit proefschrift)*

2 A dedicated tertiary multidisciplinary approach to complex young-onset movement disorders facilitates phenotyping and improves recognition of rare disorders. *(dit proefschrift)*

3 Particularly in this next-generation sequencing era, optimal dystonia classification methodologies require reasonable consensus to be useful for clinical and research purposes. *(dit proefschrift)*

4 A strategy incorporating a diagnostic algorithm is recommended to ensure that patients with myoclonus and young-onset dystonia optimally benefit from the availability of next-generation sequencing techniques. *(dit proefschrift)*

5 Early recognition of myoclonus in childhood-onset neurogenetic disorders is important, because treatment can lead to significant functional improvement. *(dit proefschrift)*

6 Clinicians should consider mutation analysis of *GOSR2* in young children with ataxia and areflexia, and in all patients with ataxia, areflexia and myoclonus. *(dit proefschrift)*

7 The art of percussion may have been replaced by ultrasound, but it will be long before any laboratory technique, including next-generation sequencing and neuroimaging, replaces a good movement disorders clinician. *(Kapil Sethi and Antony Lang, Mov Dis Clin Pract 2017)*

8 Progress in science depends on new techniques, new discoveries, and new ideas, probably in that order. *(Sydney Brenner, Nobel Prize winner in 2002)*

9 If the human brain were so simple that we could understand it, we would be so simple that we couldn't. *(Emerson Pugh, uitspraak stond ingelijst op het bureau van Michiel Staal)*

10 Domheid kan verdwijnen door het stellen van vragen en de bereidheid tot twijfel aan antwoorden. *(Baan Oterdoom)*

11 Overbeweeglijkheid van de oren (*'wiggling ears'*) kan wijzen op chorea maar is lang niet altijd pathologisch. *(Movement Disorder Congress, Stockholm, 2015)*

12 Liefde kost niets om te krijgen, maar is onbetaalbaar als je het hebt. *(Kees van Kooten)*

Martje van Egmond, mei 2018

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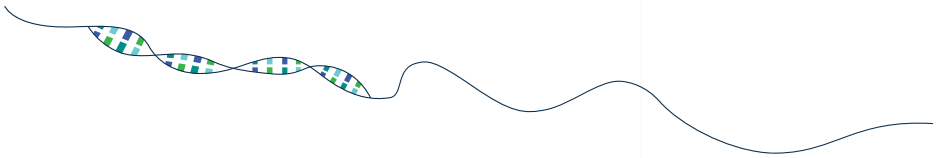

Martje van Egmond

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Promotor
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Copromotor
Dr. T.J. de Koning

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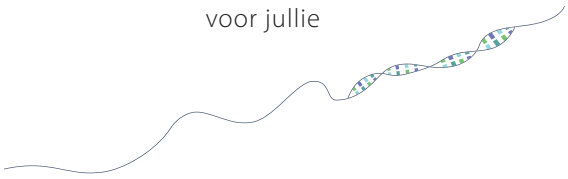

Paranimfen
Lianne van den Berg
Margriet van der Waal

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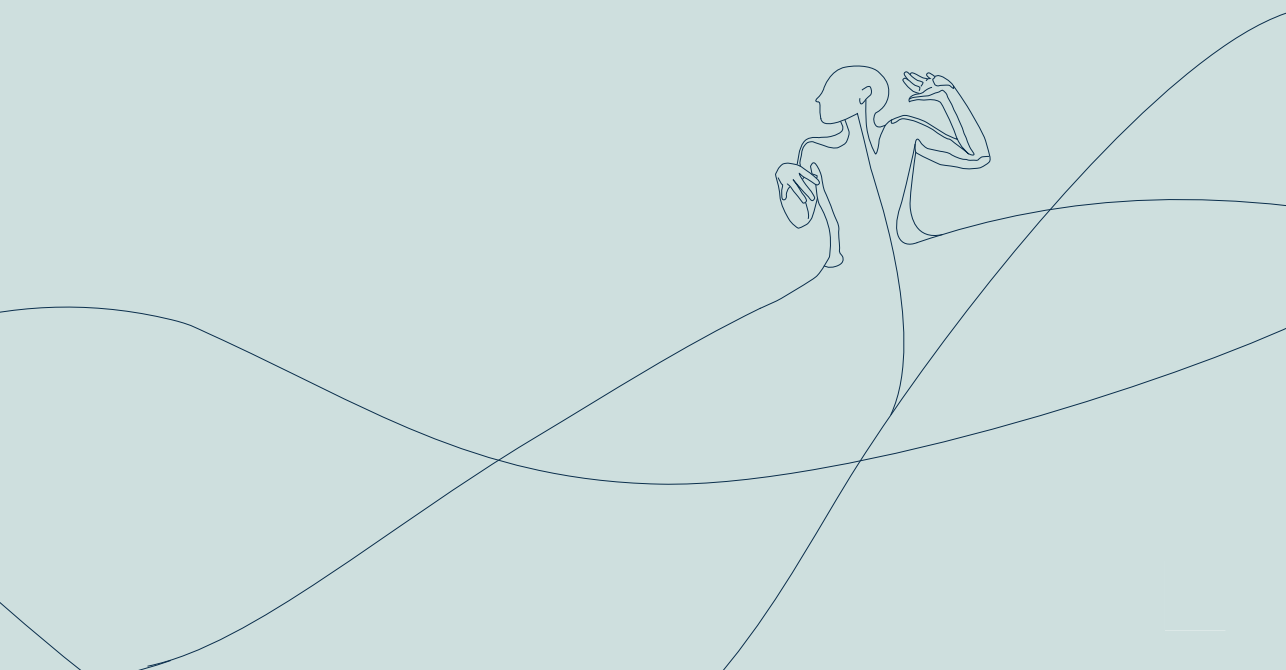


Introduction and aim

This is a thesis on young-onset hyperkinetic movement disorders (YMDs). *Hyperkinetic movement disorders* are characterized by 'too much movement'. *Young-onset* is, arbitrarily, defined as involuntary movements manifesting before the age of 18 years. This thesis focuses on two hyperkinetic YMDs, namely dystonia and myoclonus.

In this introduction, different aspects of hyperkinetic YMDs will be discussed with a focus on how recent genetic developments are transforming the practice of medicine in this field. These genetic advances require a new clinical approach to our patients.

General background

For clinicians encountering a patient with a YMD, the three main practical questions are: what do we see (phenomenology), what is the cause (etiology) and subsequently, what is the optimal treatment?[1-3] Assessing the phenomenology not only comprises classification of the movement disorder, for example whether it is dystonia or chorea but also the evaluation of other neurological and systemic features. The composite of these observable characteristics is called 'phenotype' (from the Greek word 'phainein', meaning 'to show', and 'typos', meaning 'type').[4] A phenotype results from the expression of someone's genetic code, his or her genotype, as well as the influence of environmental factors and the interactions between the two.[4]

The complete genetic code (genome) of humans comprises a six-billion-letter DNA sequence. In the last few decades the development of genetic technologies to unravel this DNA sequence took place at an incredible speed. Currently, it has been 40 years since the technique of DNA sequencing was invented.[5] Ten years ago, for the first time a complete individual human genome was analyzed through the use of next-generation sequencing (NGS) techniques.[6] These NGS techniques allow sequencing of thousands of DNA regions at the same time.[4] The DNA sequencing costs decreased dramatically from an estimated cost per genome of more than $95 million in 2001 to $1245 at the end of 2015.[7] The duration of the sequencing and interpretation of one genome dropped in a similar way from many years to less than 4-8 weeks.[8]

This revolution in molecular genetic diagnostics is transforming the practice of medicine, including neurology.[9, 10] In the field of YMDs, NGS has led to the discovery of many new YMD-associated genes, distinct phenotypes and new phenotype-genotype correlations.[11-13] Other advantages of NGS for patients with genetic YMDs are earlier diagnosis, a shorter duration of the diagnostic work-up, avoidance of other, often invasive, investigations, and lower costs for the health care system.[10, 14] An early molecular diagnosis is important as well for initiating the optimal treatment, as for providing accurate recurrence risk counselling.[9]

The wider availability of NGS requires a new approach to YMDs in clinical practice. New diagnostic strategies are needed to help clinicians to determine in which YMDs patient NGS may lead to the diagnosis, and which patients first require other investigations, for instance to exclude acquired disorders that can give rise to involuntary movements. Furthermore, NGS brings a number of new challenges and complexities of interpretations that require both genetic and clinical expertise.[10] A multidisciplinary team approach may help to face these challenges. In this thesis we will elaborate on these topics.

Young-onset movement disorders

YMDs comprise a heterogeneous group of neurological syndromes. The movement disorders start before the age of 18 years, and in almost all cases symptoms persist during adulthood. Movement disorders can be defined as impaired performance of voluntary movements, dysfunction of posture, the presence of abnormal involuntary movements, or the performance of normal-appearing movements at inappropriate or intended times.[1] YMDs often have significant impact on the lives of patients and their families[1, 15]

Movement disorders are categorized into hyperkinetic movements (dystonia, myoclonus, chorea, ballism, tremor, stereotypies and tics), hypokinetic movements (parkinsonism), and ataxia.[1, 16, 17] Occasionally, ataxic movements may appear hyperkinetic, but ataxia is by nature disorganized and poorly executed rather than truly hyperkinetic.[3]

The majority of YMDs are hyperkinetic, with tics being the most common with an estimated prevalence of 6-12% in school-aged children.[1, 18, 19] Also motor stereotypies commonly occur in children, particularly in children with a developmental delay or neurodevelopmental disorder.[20] Movement disorders with 'too less movement' (hypokinetic) are rare in young patients.

The precise neuroanatomic correlates of most YMDs are largely unknown, particularly when compared with well-studied adult-onset movement disorders such as Parkinson's and Huntington disease.[3] Traditionally, hyperkinetic YMDs have been considered as basal ganglia disorders. However, in recent years, there is increasing interest in the role of the cerebellum and both dystonia and myoclonus are increasingly conceptualized as network disorders involving both the cerebellum and the basal ganglia.[21-24] Future studies with animal models and (functional) neuro-imaging may help to delineate an integrative model of the pathophysiology of YMDs.

Phenomenology

Recognition of common movement disorders, such as tics, is relatively straightforward for most clinicians. However, diagnosis of less common and more complex YMDs, such as myoclonus or dystonia, can be difficult for both pediatric and adult neurologists.[1, 18]

In clinical practice, the diagnosis of a YMD requires careful observation of the type of movement and context.1 An overview of the hallmark features of hyperkinetic movement disorders is provided in Table 1. Making a correct movement disorder diagnosis can be facilitated by obtaining videos of the patient's movements and by using consensus definitions and classification systems.[1, 25, 26] Importantly, the phenomenology of a movement disorder is often debated, even among movement disorder experts, and video allows clinicians to view and re-view the movements of a patient together, offering the opportunity for group discussion.[27] Furthermore, video aids to identify changes in movement disorder phenomenology over time, and to document the response to intervention.[27]

Table 1. Key features of the main hyperkinetic young-onset movement disorders (adapted from Sanger et al.[25])

	Rhythmic	Repeated posture	Repeated stereotyped movement	Suppressible
Dystonia	Rarely	Yes	Sometimes	Partial or only briefly
Chorea	No	No	Rarely	No
Myoclonus	Sometimes	Sometimes	Usually	No
Tremor	Yes	No	Yes	Sometimes briefly
Tics	No	Yes	Yes	Usually
Stereotypies	Yes	Sometimes	Yes	Yes

In comparison to adult-onset movement disorders, the recognition and classification of YMDs involves some unique challenges. First, it can be difficult to perform a detailed and accurate neurological examination in poorly cooperative children.[28] Second, the clinical phenotype of YMDs is often complex. For instance, co-occurring movement disorders are common in YMDs.[25] In general, these so-called 'mixed movement disorders' are more difficult to classify compared to isolated movement disorders. Besides this, co-existence of other neurological or systemic features, including spasticity, epilepsy, mental retardation and psychiatric problems, are commonly seen in YMDs.[1, 17] Third, presentation of YMDs during early childhood may be particularly challenging for clinicians, because in young children the developing brain gives rise to a variety of motor patterns. These motor patterns would be abnormal in older children, but are in young children simply a result of immaturity of the central nervous system.[1] It is important to distinguish these transient benign motor patterns from abnormal movements. For example, choreatic movements are normal in healthy infants and toddlers, and signs of overflow dystonia and ataxia can be found in healthy school-aged children.[29, 30]

Etiology

For clinicians encountering a patient with a YMD, another challenge is that there is a long list of possible causes, both acquired and genetic. It is important to realize that some of these are treatable disorders.[18, 31, 32] For each patient with a YMD with an unknown cause, clinicians need to decide whether diagnostic work-up should include laboratory investigations, neuroimaging, neurophysiological tests, genetic diagnostics, consultation of another medical specialist, or a combination of all these diagnostic modalities.

The diagnostic journey is often long which is burdensome for patients and their families, and expensive for our health care system.[1, 9, 18, 33-35] Importantly, for some underlying disorders disease-specific treatments are available that may have life-altering effects.[32, 36] Therefore, early diagnosis in YMDs is fundamental.

For several types of heterogeneous disorders in children and adolescents including dyskinetic cerebral palsy, a beneficial effect of a multidisciplinary team approach has been described.[37-40] A multidisciplinary strategy facilitates mutual collaboration, can help to guide complex care

decisions and to standardize diagnostic protocols.[39] This might also be true in complex YMDs, as clinical phenotyping and diagnostic work-up in complex YMDs requires a broad range of skills and knowledge of clinicians.

Treatment

A brief overview of the possible treatment modalities in YMD will be given below, focused on dystonia and myoclonus. A comprehensive review of all treatment options for YMDs is beyond the scope of this thesis.

Much of the evidence for treatments in YMDs relies on small, often single arm, non- blinded, and non-randomized trials, because many of the underlying disorders are rare.[32, 41, 42] Consequently, most treatment recommendations in YMDs are based on consensus opinion guidelines or principles of good clinical practice.[32, 41-43] As Jinnah and colleagues noted: "In this situation the idealistic goals of 'evidence-based medicine' become a more practical dilemma of 'evidence-limited medicine'."[32]

Noteworthy, only for a small subgroup of YMDs are mechanism-based treatments available. For most YMDs, treatment is symptomatic with variable effect, ranging from no effect to significant improvement in daily functioning.[1, 15, 32, 42] Treatment for young-onset dystonia and myoclonus can be divided in several categories, which are briefly mentioned here.

1. *Education and counselling* is important and can provide profound benefits for the patient and their families.[1, 32]
2. *Physical and supportive therapy* may improve functioning of patients with young-onset dystonia and myoclonus. Examples are physiotherapy, speech and occupational therapy, and medical aids such as a walker to prevent falls.[43, 44]
3. A broad range of *symptomatic pharmacologic treatments* for young-onset dystonia and myoclonus has been described.[32, 41-43] . This will be discussed in more detail below. Another category of pharmacologic treatment involves immunotherapy for YMDs caused by autoimmune encephalitis.[36] YMDs induced by medication or a toxic agent will ameliorate after cessation of the inducing agent.[45, 46]
4. Local *botulinum toxin injections* have been shown to be effective in focal dystonias.[41, 43]
5. *Dietary interventions* can significantly reduce symptoms in some cases, particularly in YMDs caused by inborn errors of metabolism (IEM).
6. For some of the underlying disorders, *mechanism-based treatments* are available that can prevent, reduce or even eliminate symptoms when initiated on time.[1, 32] Penicillamine for Wilson disease and levodopa for dopa-responsive dystonia are well-known historical examples. In recent years, mechanism-based treatments have been developed for more than 30 other rare genetic movement disorders.[32] The clinical manifestations of most of these treatable disorders typically begin in childhood or adolescence.
7. For selected dystonia patients, *surgical intervention including deep brain stimulation* (DBS) may significantly reduce the involuntary movements. This will be discussed in more detail below.

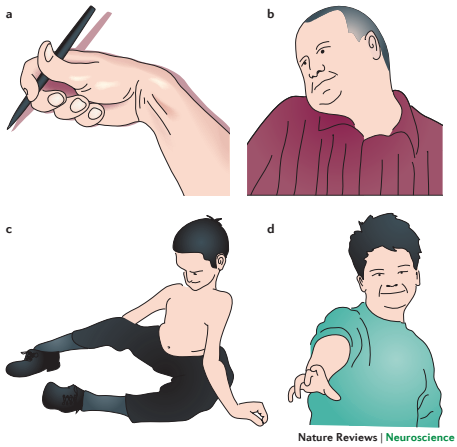
These interventions are all primarily aimed at the motor symptoms of YMDs. Importantly, recent studies have demonstrated that hyperkinetic YMDs are often accompanied by non-motor symptoms, such as psychiatric symptoms, cognitive impairment, sleep disturbances and pain.[30, 36, 47-49] Timely recognition of these symptoms and adequate management are likely to improve the quality of life of these patients.

Dystonia

Dystonia: definition and classification

Dystonia is defined as *a movement disorder 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. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation*.[26] Most patients with dystonia have a combination abnormal movements and abnormal postures.[26] Dystonia can affect one or more body regions, as illustrated by Figure 1.

Figure 1. *Images of patients with different forms of dystonia*



Legend: Examples of different forms of dystonia: (a) writer's cramp, (b) cervical dystonia, (c) young-onset generalized dystonia, (d) rapid-onset dystonia-parkinsonism which can manifest as dystonic spasms in the upper limbs with facial grimacing, but can also include parkinsonian symptoms such as slowness of movement and postural instability. Figure reprinted with permission, from Breakefield et al.[50]

Prevalence data on childhood-onset dystonia are scarce. In 2012 a meta-analysis was published showing an overall prevalence of primary (inherited or idiopathic isolated) dystonia of 16.4 per 100.000, which likely is an underestimate of the true prevalence.[51] In this meta-analysis, age-specific estimates could not be derived as a result of variable grouping of ages across the included studies.[51]

In clinical practice, an important first question in the diagnostic process is whether the movements are either dystonia or 'dystonia mimics'.[26, 52] For example, trochlear nerve palsy, congenital muscular torticollis and Sandifer syndrome are conditions that may mimic dystonia in children.

Additional features that support a diagnosis of dystonia include mirror dystonia and the presence of a sensory trick.[26, 52] Mirror dystonia is defined as a *unilateral posture or movement that is the same or similar in character to a dystonic feature that can be elicited, usually in the more severely affected side, when contralateral movements or actions are performed.*[26] A sensory trick or 'geste antagoniste' is *a voluntary action that specifically corrects the abnormal posture or alleviates the dystonic movements.*[26] Sensory tricks mostly involve a simple activity, such as light touch to the face, but some tricks can be complex and bizarre.[53] The recognition of sensory tricks forms an important aid in dystonia diagnosis.[52, 53]

Dystonia is classified according to a system based on consensus criteria, published in 2013.26 This consensus classification involves two axes: the first axis focuses on the clinical manifestations of dystonia, the second axis on etiology, see Table 2.[26]

Table 2. *Dystonia classification as proposed by Albanese et al.*[26]

Axis I. Clinical characteristics of dystonia	**Axis II. Etiology**
Age at onset	***Nervous system pathology***
• Infancy (birth to 2 years)	• Evidence of degeneration
• Childhood (3–12 years)	• Evidence of structural (often static) lesions
• Adolescence (13–20 years)	• No evidence of degeneration or structural lesion
• Early adulthood (21–40 years)	***Inherited or acquired***
• Late adulthood (>40 years)	Inherited
Body distribution	• Autosomal dominant
• Focal	• Autosomal recessive
• Segmental	• X-linked recessive
• Multifocal	• Mitochondrial
• Generalized (with or without leg involvement)	Acquired
• Hemidystonia	• Perinatal brain injury
Temporal pattern	• Infection
Disease course	• Drug
• Static	• Toxic
• Progressive	• Vascular
Variability	• Neoplastic
• Persistent	• Brain injury
• Action-specific	• Psychogenic
• Diurnal	Idiopathic
• Paroxysmal	• Sporadic
Associated features	• Familial
Isolated dystonia or combined with another movement disorder	
• Isolated dystonia	
• Combined dystonia	
Occurrence of other neurological or systemic manifestations	
• List of co-occurring neurological manifestations	

In dystonia, there is a clear relation between the age at onset, the anatomical distribution and course of the disease.[1, 3, 26, 52] Dystonia that starts in childhood is more likely to begin focally, with progression to generalized dystonia in several years.[26] Adult-onset dystonia typically starts in one body region (e.g. cervical dystonia) and may spread to an adjacent body segment, but the chance of progression to generalized dystonia is very low.[26, 52]

Once the clinical characteristics are phenomenologically classified according to the first axis, a dystonia syndrome can be defined.[26] In line with this, Fung and colleagues proposed a diagnostic strategy to dystonia involving a so-called 'syndromic approach' with the goal to assist clinicians when evaluating a patient with dystonia and to guide diagnostic testing.[54] They provided a list of 27 dystonia syndromes (see Table 3), supplemented with lists of potential etiologies for 16 of these syndromes.[54]

Table 3. Dystonia syndromes as published by Fung et al.[54]

Isolated dystonia syndromes that are red flags for the subsequent development of a combined dystonia syndrome or neurodegenerative disease
- Cranial dystonia in young adults and children
- Adult-onset lower limb dystonia
- Adult-onset non task-specific limb dystonia
- Truncal dystonia
- Adult-onset generalized dystonia
- Hemidystonia

Combined dystonia
- Dystonia with or without parkinsonism of infantile or childhood onset
- Dystonia with or without parkinsonism of adolescent and young adult
- onset
- Dystonia and parkinsonism in older adults
- Dystonia with spasticity (with or without parkinsonism)
- Dystonia with cerebellar ataxia
- Dystonia with myoclonus
- Dystonia as part of paroxysmal dyskinesia
- Dystonia with chorea
- Dystonia with tics

Dystonia with other neurological involvement
- Dystonia with deafness
- Dystonia with ophthalmological abnormalities
- Dystonia with peripheral neuropathy
- Dystonia with progressive dementia

Dystonia with systemic disease
- Dystonia with endocrine abnormalities
- Dystonia with hematological abnormalities
- Dystonia with solid organ involvement

Syndromes according to brain imaging
- Dystonia with MRI evidence of neuronal brain iron accumulation
- Dystonia with basal ganglia lesions
- Dystonia with leucoencephalopathy
- Dystonia with basal ganglia calcification

Progressive dystonia with normal brain MRI or generalized atrophy

Dystonia: etiology

Axis II of the dystonia classification focuses on etiology.[26] There are many possible causes of dystonia, including acquired and genetic causes.[26, 45] The third etiological group comprises the idiopathic dystonias, which are dystonias with an unknown cause. Compared to adult- onset dystonia, young-onset dystonia is more likely to have an identifiable cause, both acquired and genetic.[26, 52] The most common acquired cause of childhood-onset dystonia is dyskinetic cerebral palsy, which is defined as *a group of permanent disorders causing impairment of movement and posture, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.*[55]

Finding the cause of dystonic symptoms can be difficult and estimates are that at least half of all patients with dystonic symptoms may go undiagnosed.[52] In clinical practice, experienced movement disorder specialists will often use a combination of diagnostic strategies, including pattern recognition, recognition of red flags and delineating phenotypic syndromic patterns.[32]

Dystonia: treatment

Treatment categories for (young-onset) dystonia are listed above. For focal forms of dystonia, local botulinum toxin injections are the treatment of choice. Frequently used oral medication in generalized dystonia include anticholinergic drugs, dopamine modulators, baclofen and benzodiazepines.[41] Recently, gabapentin and clonidine have been shown to significantly improve dystonia severity and quality of life in children.[56, 57] In many cases however, the benefit of medication in dystonia often is disappointingly limited. For some patients with dystonia, DBS can be an effective treatment.[58] This therapy uses a small device similar to a pacemaker, called a neurostimulator, to send mild electrical pulses to small regions of the brain.

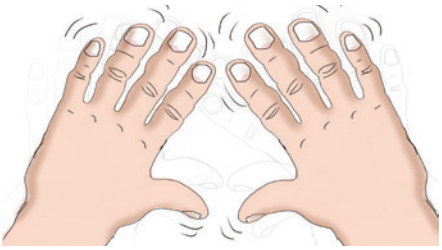
Strong (level B) evidence supports the use of DBS for inherited or idiopathic, isolated generalized, segmental or cervical dystonia (both childhood-onset and adult-onset) with a mean improvement of dystonia severity of 40% to 60%.[40, 59, 60] Lesser benefit is generally seen in dystonia secondary to structural brain damage, such as in dyskinetic cerebral palsy.[61] Thus, DBS therapy can be considered in a selected group of dystonia patients, when dystonic symptoms are not adequately controlled with medication.[58]

Myoclonus

Myoclonus: definition and classification

Myoclonus is defined as *a sudden, brief, and shock-like involuntary movement*, either due to muscular contraction (positive myoclonus) or due to a temporary pause in muscle activity (negative myoclonus) (Figure 2).[62] The severity may range from extremely disabling to very mild. Epidemiological data on myoclonus are scarce, one study performed in the United States reported a lifetime prevalence of myoclonus of 8.6 cases per 100.000 people.[63] Myoclonus may affect people of all age groups and the prevalence rate increases with age.[64]

Figure 2. *Myoclonus: brief and shock-like involuntary movements*



Reference: www.clipart-library.com

The first step in the diagnostic process of myoclonus is to assess whether the involuntary movements are actually myoclonus or mimics of myoclonus.[46]

Several clinical aspects may help clinicians to distinguish myoclonus from other hyperkinetic movements, and may provide clues to the anatomical origin. These aspects include body distribution, temporal pattern and the relation to motor activity and unexpected stimuli.58 For instance, myoclonus can occur at rest (*spontaneous myoclonus*) or during voluntary action (*action-induced myoclonus*). Reflex myoclonus can be provoked by unexpected visual, auditory or tactile stimuli, and during bed side examination a tactile stimulus given to the distal part of the fingers may induce a series of myoclonus.[58] Negative myoclonus is often harder to recognize than positive myoclonus and requires that the patient makes a tonic movement.[64] Myoclonus can be rhythmic, for instance in familial cortical myoclonic tremor. This *rhythmic myoclonus* may easily be mistaken for tremor.[65]

Young-onset myoclonus needs to be distinguished from other hyperkinetic jerky movements that can occur in childhood, such as chorea, dystonic jerks and tics.[1] Myoclonus-dystonia syndrome may closely resemble benign hereditary chorea and distinguishing the phenomenology of these two entities may be challenging, even for expert clinicians.[66, 67] Multiple classification schemes have been proposed for myoclonus, taking into account clinical, anatomical and etiological aspects (Table 4).[16, 65] These strategies are overlapping and not mutually exclusive.

Table 4. Different classification schemes for myoclonus (adapted from Eberhardt and Dijk)[42, 65]

Body distribution	Clinical features	Anatomical origin	Etiology
Focal	Positive or negative	Cortical	Physiological
Segmental	Spontaneous (at rest)	Subcortical	Essential
Multifocal	Action-induced	• Brainstem	Epileptic
Generalized	Stimulus induced	• Myoclonus dystonia	Symptomatic
	Rhythmic	Spinal	
		• Segmental	
		• Propriospinal	
		Peripheral	

Note: in this table functional (psychogenic) myoclonus has not been included, because in this thesis we consider functional myoclonus as a mimic of myoclonus.

The most commonly used second step in the evaluation of myoclonus is to define the anatomical locus, which will require electrophysiological testing in the vast majority of cases.[42] Myoclonus can be generated at several levels in the nervous system, ranging from the cerebral cortex to the peripheral nerve.[64] This anatomical classification usually guides diagnostic work-up in clinical practice, because the origin of myoclonus is associated with specific clinical and electrophysiological features that can be connected to a list of potential etiologies.[58, 64] Moreover, the anatomical locus may aid in selecting symptomatic therapies for myoclonus.[42]

Myoclonus: etiology

A plethora of causes of myoclonus have been described.[65] As a consequence, elucidating the etiology in an individual with myoclonus can be difficult. In children, myoclonus most commonly manifests with co-occurring neurological features such as epilepsy or encephalopathy, or with other movement disorders e.g. dystonia and ataxia. Isolated myoclonus is uncommon in childhood.[1] As a result, pediatric neurologists or movement disorder specialists may use the presence of myoclonus in a child as one of several key factors in clinical decision making.[1] At the same time, it is important to realize that myoclonus in childhood-onset neurogenetic disorders frequently may go unnoticed, because it is overshadowed by other neurological features.[15, 33]

One of the many possible causes of young-onset myoclonus is North Sea Progressive Myoclonus Epilepsy (NSPME), a genetic disorder characterized by progressive myoclonus, young-onset ataxia, seizures and areflexia. Currently, worldwide less than 30 patients with NSPME have been described.[68-72] The disorder is called NSPME because all patients described come from countries bounding the North Sea.[69] Thus, the prevalence of some genetic forms of myoclonus may differ according to ethnic background and region of the world.

Myoclonus: treatment

Of the aforementioned treatment categories for YMDs, pharmacological treatment is by far the most used option for patients with myoclonus, with variable efficacy. In both children and adults, the mainstay of symptomatic treatment are antiepileptics (most used are sodium valproate, levetiracetam and piracetam), as well as benzodiazepines (particularly clonazepam). A comprehensive overview of the evidence and efficacy of pharmacological treatment for different subtypes of myoclonus can be found elsewhere.[42]

Aim and outline

The main objective of this thesis is to explore new diagnostic strategies to YMDs that clinicians can apply in light of the paradigm shift that has occurred in molecular genetics.

In the first part of the thesis we describe the benefits of a multidisciplinary diagnostic approach to complex YMDs in a tertiary referral center (**Chapter 2**). In the second part of the thesis, we aim to investigate new diagnostic strategies to (young-onset) dystonia, taking into account the advances that have recently been made in molecular diagnostics. In **Chapter 3** we present a systematic review of the literature on dystonia in children and adolescents and we propose a new diagnostic algorithm to young-onset dystonia incorporating NGS diagnostics. In **Chapter 4** the results of a post hoc study on the use of a NGS technique for the diagnosis of dystonia described, namely gene panel analysis. In line with this study, we investigated the inter-rater agreement among experienced clinicians on the dystonia classification and the dystonia syndrome (**Chapter 5**), because for both clinical and research purposes reasonable consensus is needed, particularly in this NGS era. Lastly, we report on three individual patients to illustrate how appropriate treatment can improve debilitating symptoms in two genetic forms of dystonia (**Chapter 6**). The third part of the thesis describes new strategies to myoclonus. In **Chapter 7** we describe a new diagnostic algorithm to myoclonus, again taking into account the full potential of NGS diagnostics, based on a systematic review of the literature. **Chapter 8** comprises a case series on myoclonus in young-onset neurogenetic disorders, demonstrating the importance of early identification of myoclonus and its treatment, also when a molecular diagnosis has already been established. **Chapter 9** is dedicated to NSPME, a rare genetic disorder in which young-onset myoclonus is one of the key features. In the first section of this chapter we report on the results of careful phenotyping, describing the clinical characteristics of five patients with NSPME. The second section focuses on treatment: we present the results of a prospective open-label study on the efficacy of the modified Atkins diet in NSPME. **Chapter 10** provides a discussion of the findings of this thesis. This chapter ends with recommendations for future research and concluding remarks.

References

1 Singer HS, Mink J, Gilbert D, et al. Movement Disorders in Childhood. Philadelphia: Saunders: Elsevier 2010.

2 Abdo WF, van de Warrenburg BP, Burn DJ, et al. The clinical approach to movement disorders. Nat Rev Neurol. 2010;6(1):29-37.

3 Brownstein CA, Beggs AH, Homer N, et al. An international effort towards developing standards for best practices in analysis, interpretation and reporting of clinical genome sequencing results in the CLARITY Challenge. Genome Biol. 2014;15(3):R53.

4 Keogh MJ, Daud D, Chinnery PF. Exome sequencing: how to understand it. Pract Neurol. 2013;13(6):399-407.

5 Kohane IS, Masys DR, Altman RB. The incidentalome: a threat to genomic medicine. JAMA. 2006;296(2):212-5.

6 Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19(4):484.

7 Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19(2):249-55.

8 Bonifati V. Will New Genetic Techniques Like Exome Sequencing and Others Obviate the Need for Clinical Expertise? Yes. Movement Disorders Clinical Practice. 2017;4(1):36-8.

9 Warman Chardon J, Beaulieu C, Hartley T, et al. Axons to Exons: the Molecular Diagnosis of Rare Neurological Diseases by Next-Generation Sequencing. Curr Neurol Neurosci Rep. 2015;15(9):64.

10 Foley AR, Donkervoort S, Bonnemann CG. Next-generation sequencing still needs our generation's clinicians. Neurol Genet. 2015;1(2):e13.

11 de Koning TJ, Tijssen MA. Movement disorders in 2014. Genetic advances spark a revolution in dystonia phenotyping. Nat Rev Neurol. 2015;11(2):78-9.

12 Olgiati S, Quadri M, Bonifati V. Genetics of movement disorders in the next- generation sequencing era. Mov Disord. 2016;31(4):458-70.

13 Skogseid IM. Pallidal deep brain stimulation is effective, and improves quality of life in primary segmental and generalized dystonia. Acta Neurol Scand Suppl. 2008;188:51-5.

14 Hennekam RC, Biesecker LG. Next-generation sequencing demands next-generation phenotyping. Hum Mutat. 2012;33(5):884-6.

15 van Egmond ME, Elting JW, Kuiper A, et al. Myoclonus in childhood-onset neurogenetic disorders: The importance of early identification and treatment. Eur J Paediatr Neurol. 2015;19(6):726-9.

16 Fahn S. Classification of movement disorders. Mov Disord. 2011;26(6):947-57.

17 Delgado MR, Albright AL. Movement disorders in children: definitions, classifications, and grading systems. J Child Neurol. 2003;18 Suppl 1:S1-8.

18 Bäumer T, Sajin V, Münchau A. Childhood-Onset Movement Disorders: A Clinical Series of 606 Cases. Movement Disorders Clinical Practice. 2017;4(3):437-40. 16

19 Lines MA, Jobling R, Brady L, et al. Peroxisomal D-bifunctional protein deficiency: three adults diagnosed by whole-exome sequencing. Neurology. 2014;82(11):963-8.

20 Barry S, Baird G, Lascelles K, et al. Neurodevelopmental movement disorders - an update on childhood motor stereotypies. Dev Med Child Neurol. 2011;53(11):979-85.

21 Koy A, Timmermann L. Deep brain stimulation in cerebral palsy: Challenges and opportunities. Eur J Paediatr Neurol. 2017;21(1):118-21.

22 Ganos C, Kassavetis P, Erro R, et al. The role of the cerebellum in the pathogenesis of cortical myoclonus. Mov Disord. 2014;29(4):437-43.

23 Frank M, Prenzler A, Eils R, et al. Genome sequencing: a systematic review of health economic evidence. Health Econ Rev. 2013;3(1):29.

24 Kubu CS, Ford PJ. Beyond Mere Symptom Relief in Deep Brain Stimulation: An Ethical Obligation for Multi-faceted Assessment of Outcome. AJOB Neurosci. 2012;3(1):44-9.

25 Sanger TD, Chen D, Fehlings DL, et al. Definition and classification of hyperkinetic movements in childhood. Mov Disord. 2010;25(11):1538-49.

26 Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863-73.

27 Kubu CS, Cooper SE, Machado A, et al. Insights gleaned by measuring patients' stated goals for DBS: More than tremor. Neurology. 2017;88(2):124-30.

28 McMichael G, Bainbridge MN, Haan E, et al. Whole-exome sequencing points to considerable genetic heterogeneity of cerebral palsy. Mol Psychiatry. 2015;20(2):176- 82.

29 Brandsma R, Spits AH, Kuiper MJ, et al. Ataxia rating scales are age-dependent in healthy children. Dev Med Child Neurol. 2014;56(6):556-63.

30 Lim WH. Cerebral palsy: Causes, pathways, and the role of genetic variants. Am J Obstet Gynecol. 2016;214(5):670-1.

31 Garcia-Cazorla A, Wolf NI, Serrano M, et al. Inborn errors of metabolism and motor disturbances in children. J Inherit Metab Dis. 2009;32(5):618-29.

32 Jinnah HA, Albanese A, Bhatia KP, et al. Treatable inherited rare movement disorders. Mov Disord. 2018;33(1):21-35.

33 Eggink H, Kuiper A, Peall KJ, et al. Rare inborn errors of metabolism with movement disorders: a case study to evaluate the impact upon quality of life and adaptive functioning. Orphanet J Rare Dis. 2014;9:177.

34 Aquino CC, Lang AE. Tardive dyskinesia syndromes: current concepts. Parkinsonism Relat Disord. 2014;20 Suppl 1:S113-7.

35 Gasiunas G, Barrangou R, Horvath P, et al. Cas9-crRNA ribonucleoprotein complex mediates specific DNA cleavage for adaptive immunity in bacteria. Proc Natl Acad Sci U S A. 2012;109(39):E2579-86.

36 Jinek M, Chylinski K, Fonfara I, et al. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science. 2012;337(6096):816-21.

37 Bent N, Tennant A, Swift T, et al. Team approach versus ad hoc health services for young people with physical disabilities: a retrospective cohort study. Lancet. 2002;360(9342):1280-6.

38 Shapiro BS, Cohen DE, Covelman KW, et al. Experience of an interdisciplinary pediatric pain service. Pediatrics. 1991;88(6):1226-32.

39 Ladner TR, Mahdi J, Attia A, et al. A multispecialty pediatric neurovascular conference: a model for interdisciplinary management of complex disease. Pediatr Neurol. 2015;52(2):165-73.

40 Kupsch A, Benecke R, Muller J, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. N Engl J Med. 2006;355(19):1978-90.

41 Cong L, Ran FA, Cox D, et al. Multiplex Genome Engineering Using CRISPR/Cas Systems. Science (New York, N.Y.). 2013;339(6121):819-23.

42 Dijk JM, Tijssen MA. Management of patients with myoclonus: available therapies and the need for an evidence-based approach. Lancet Neurol. 2010;9(10):1028-36.

43 Roubertie A, Mariani LL, Fernandez-Alvarez E, et al. Treatment for dystonia in childhood. Eur J Neurol. 2012;19(10):1292-9.

44 Mali P, Yang L, Esvelt KM, et al. RNA-guided human genome engineering via Cas9. Science. 2013;339(6121):823-6.

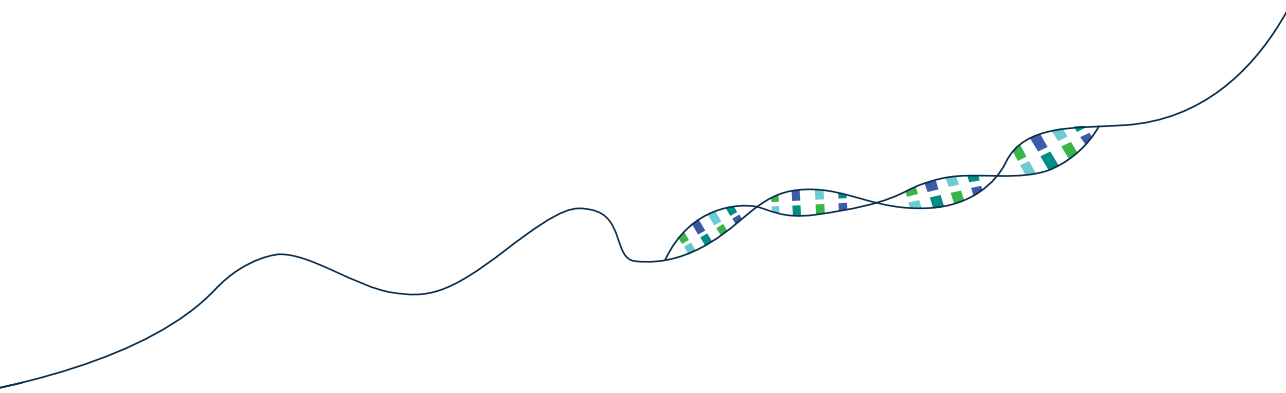
45 van Egmond ME, Kuiper A, Eggink H, et al. Dystonia in children and adolescents: a systematic review and a new diagnostic algorithm. J Neurol Neurosurg Psychiatry. 2015;86(7):774-81.

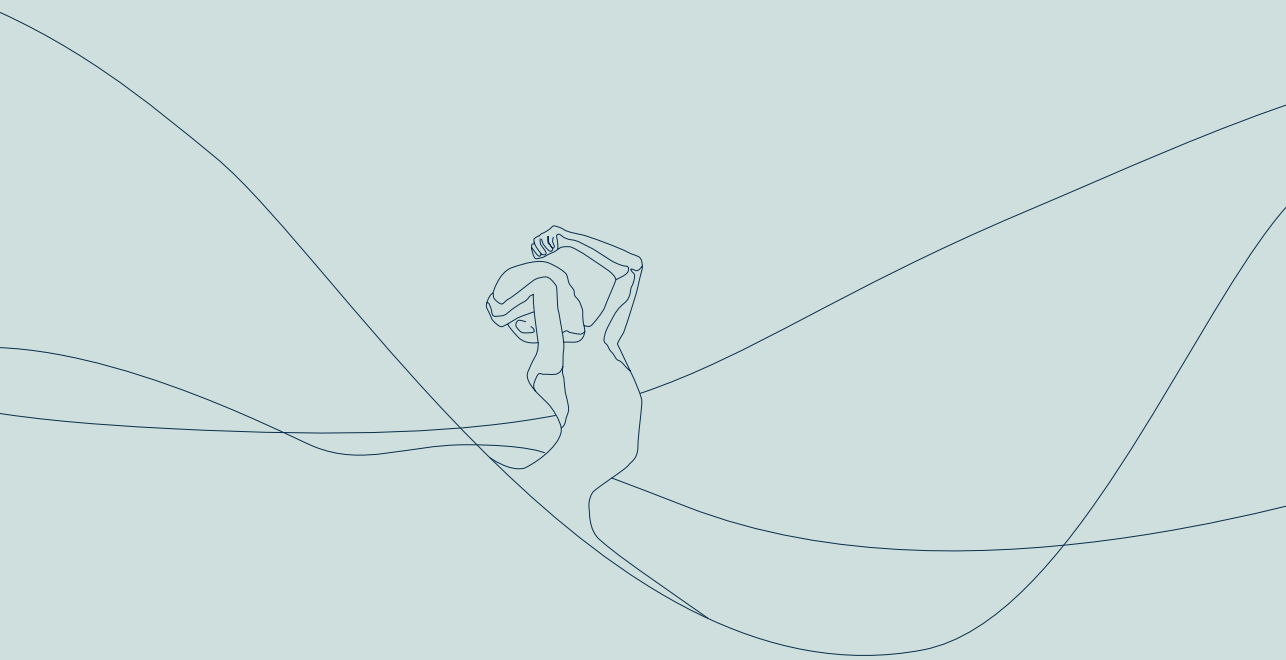
46 Zutt R, van Egmond ME, Elting JW, et al. A novel diagnostic approach to patients with myoclonus. Nat Rev Neurol. 2015;11(12):687-97.
47 Peall KJ, Kuiper A, de Koning TJ, et al. Non-motor symptoms in genetically defined dystonia: Homogenous groups require systematic assessment. Parkinsonism Relat Disord. 2015;21(9):1031-40.
48 Peall KJ, Ritz K, Waite AJ, et al. SGCZ mutations are unlikely to be associated with myoclonus dystonia. Neuroscience. 2014;272:88-91.
49 Komaroff AL. Gene Editing Using CRISPR: Why the Excitement? JAMA. 2017;318(8):699-700.
50 Komor AC, Kim YB, Packer MS, et al. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. Nature. 2016;533:420.
51 Kim YB, Komor AC, Levy JM, et al. Increasing the genome-targeting scope and precision of base editing with engineered Cas9-cytidine deaminase fusions. Nat Biotechnol. 2017;35(4):371-6.
52 Bertram KL, Williams DR. Diagnosis of dystonic syndromes--a new eight-question approach. Nat Rev Neurol. 2012;8(5):275-83.
53 Ramos VF, Karp BI, Hallett M. Tricks in dystonia: ordering the complexity. J Neurol Neurosurg Psychiatry. 2014;85(9):987-93.
54 Fung VS, Jinnah HA, Bhatia K, et al. Assessment of patients with isolated or combined dystonia: an update on dystonia syndromes. Mov Disord. 2013;28(7):889-98.
55 Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007;109:8-14.
56 Liow NY, Gimeno H, Lumsden DE, et al. Gabapentin can significantly improve dystonia severity and quality of life in children. Eur J Paediatr Neurol. 2016;20(1):100-7.
57 Nakou V, Williamson K, Arichi T, et al. Safety and efficacy of high-dose enteral, intravenous, and transdermal clonidine for the acute management of severe intractable childhood dystonia and status dystonicus: An illustrative case-series. Eur J Paediatr Neurol. 2017;21(6):823-32.
58 Wolters EC, Van Laar T, Berendse HW. Parkinsonism and Related Disorders. Amsterdam: VU University Press; 2008.
59 Schneider SA, Bhatia KP. Secondary dystonia-clinical clues and syndromic associations. J Mov Disord. 2009;2(2):58-63.
60 Volkmann J, Wolters A, Kupsch A, et al. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. Lancet Neurol. 2012;11(12):1029-38.
61 Vidailhet M, Yelnik J, Lagrange C, et al. Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study. Lancet Neurol. 2009;8(8):709-17.
62 Fahn S, Marsden CD, Van Woert MH. Definition and classification of myoclonus. Adv Neurol. 1986;43:1-5.
63 Caviness JN, Alving LI, Maraganore DM, et al. The incidence and prevalence of myoclonus in Olmsted County, Minnesota. Mayo Clin Proc. 1999;74(6):565-9.
64 Lozsadi D. Myoclonus: a pragmatic approach. Pract Neurol. 2012;12(4):215-24.
65 Eberhardt O, Topka H. Myoclonic Disorders. Brain Sci. 2017;7(8).
66 Schrag A, Quinn NP, Bhatia KP, et al. Benign hereditary chorea--entity or syndrome? Mov Disord. 2000;15(2):280-8.
67 Asmus F, Devlin A, Munz M, et al. Clinical differentiation of genetically proven benign hereditary chorea and myoclonus-dystonia. Mov Disord. 2007;22(14):2104-9.
68 Corbett MA, Schwake M, Bahlo M, et al. A mutation in the Golgi Qb-SNARE gene GOSR2 causes progressive myoclonus epilepsy with early ataxia. Am J Hum Genet. 2011;88(5):657-63.
69 Boisse Lomax L, Bayly MA, Hjalgrim H, et al. 'North Sea' progressive myoclonus epilepsy: phenotype of subjects with GOSR2 mutation. Brain. 2013;136(Pt 4):1146-54.

70 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(4):569-75.
71 Anderson DG, Németh AH, Fawcett KA, et al. Deep Brain Stimulation in Three Related Cases of North Sea Progressive Myoclonic Epilepsy from South Africa. Movement Disorders Clinical Practice. 2017;4(2):249-53.
72 Praschberger R, Balint B, Mencacci NE, et al. Expanding the Phenotype and Genetic Defects Associated with the *GOSR2* Gene. Movement Disorders Clinical Practice. 2015;2(3):27

A multidisciplinairy approach to young onset-movement disorders

Part I





Crossing barriers: a multidisciplinary approach to children and adults with young-onset movement disorders

Chapter 2

M.E. van Egmond *, H. Eggink *, A. Kuiper, D.A. Sival,
C.C. Verschuuren-Bemelmans, M.A.J. Tijssen, T.J. de Koning
*Shared first authors

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Abstract

Background

In contrast to common motor tics, diagnosis of less common young-onset movement disorders is often challenging, requiring a broad spectrum of skills of clinicians regarding phenotyping, normal and abnormal development and the wide range of possible acquired and genetic etiologies. This complexity often leads to considerable diagnostic delays, paralleled by uncertainty for patients and their families. Therefore, we hypothesized that these patients may benefit from a multidisciplinary approach. We report on the first 100 young-onset movement disorders patients who visited our multidisciplinary outpatient clinic.

Methods

Clinical data were obtained from the medical records of patients with disease- onset before age 26. We investigated whether the multidisciplinary team, consisting of a movement disorder specialist, pediatric neurologist, pediatrician for inborn errors of metabolism and clinical geneticist, revised the movement disorder classification, etiological diagnosis, and/or treatment.

Results

The patients (56 males) had a mean age of 12.5 ± 6.3 years and mean disease duration of 9.2 ± 6.3 years. Movement disorder classification was revised in 58/100 patients. Particularly dystonia and myoclonus were recognized frequently and supported by neurophysiological testing in 24/29 patients. Etiological diagnoses were made in 24/71 (34%) formerly undiagnosed patients, predominantly in the genetic domain. Treatment strategy was adjusted in 60 patients, of whom 43 (72%) reported a subjective positive effect.

Conclusions

A dedicated tertiary multidisciplinary approach to complex young-onset movement disorders can facilitate phenotyping and improve recognition of rare disorders, with a high diagnostic yield in a relatively short period of time, providing clear benefits for the patients and their families.

Background

Young-onset movement disorders (YMDs) is a relatively new field in neurology, comprising clinical neurological syndromes presenting with involuntary movements manifesting before the age of 18 years. As with movement disorders (MDs) in adults, YMDs are subdivided into hyperkinetic movements (dystonia, myoclonus, chorea, ballism, tremor and tics), hypokinetic (parkinsonism) movements, and ataxia.[1-4] Recognition of common YMDs, such as tics and stereotypies, is usually straightforward for most clinicians. However, diagnosis of less common and more complex YMDs, such as disorders presenting primarily with myoclonus or dystonia, is often difficult, both for pediatric and adult neurologists.[1, 5, 6]

The recognition and classification of YMDs present some unique challenges. First, YMDs are often embedded in a complex clinical phenotype. For example, the occurrence of mixed MDs (more than one MD present) or co-existence of a variety of symptoms such as psychomotor retardation or behavioral abnormalities are commonly seen.[4, 7, 8] Second, in young children the developing nervous system may produce a variety of motor patterns that would be labeled as pathologic in older children and adults, but are simply a manifestation of brain immaturity in younger patients.[1] For instance, chorea is a normal feature in healthy infants and toddlers, and (subtle) signs of overflow dystonia and ataxia are found in healthy children up till the age of 12 years or even older.[9, 10] Finally, YMDs can be caused by a broad spectrum of both acquired and genetic disorders, including infections, auto-antibody and auto-immune disorders, as well as rare metabolic disorders and other inherited defects.[6, 11- 13]

The challenges within the field of YMDs have been increasingly recognized over the past decades, which has resulted in a growing number of pediatric neurologists specialized in YMDs. Despite these developments, the diagnostic process in complex YMDs often remains challenging, a burden for patients and their families, and costly for our health care system as patients often remain undiagnosed for many years.[1, 5, 6, 13, 14] This has been reflected in a recent study in a tertiary referral center that showed a mean delay of diagnosis of 11.1 ± 12,5 years in a cohort of 260 patients with non-tic YMDs.[6]

In other heterogeneous or rare diseases in children, a beneficial effect of a multidisciplinary approach has been reported.[15-17] We hypothesized that also patients with complex YMDs may benefit from a multidisciplinary approach, integrating not only pediatric and adult neurology, but all expertise areas required for both children and young adults with MDs. A multidisciplinary team enables to overcome the three difficulties experienced in this patient group: a complex clinical phenotype (movement disorder specialist), the variety of motor patterns produced by the developing brain (pediatric neurologist), and a broad spectrum of both acquired and genetic disorders (pediatrician for inborn errors of metabolism and a clinical geneticist).

Here, we report on the first 100 patients with YMDs who visited our multidisciplinary outpatient clinic. Our aim was to investigate whether this new multidisciplinary approach was beneficial regarding to MD classification, diagnostic yield and targeted treatment strategies.

Methods

Design and setting of the study

In this retrospective, single center, observational study we evaluated the first consecutive 100 patients who visited our multidisciplinary outpatient clinic for YMDs. It is situated in a tertiary referral center, the University Medical Center Groningen, in the Netherlands. The study was performed according to the ethical standards and regulations of our institute.

Patients

All patients had a confirmed or suspected MD with an onset before the age of 18 years and were referred for an expert opinion regarding MD classification, etiology or treatment of involuntary movements (Table 1).

Multidisciplinary outpatient clinic

The clinic was initiated in 2012 with a team consisting of an adult neurologist specialized in MDs (MT), a pediatric neurologist specialized in developmental neurology and YMDs especially ataxia (DS), a pediatrician specialized in metabolic diseases (TK) and a clinical neuro-geneticist (CV). In addition, clinical fellows in movement disorders and residents attend the clinic to gain skills and knowledge from the different medical specialties involved as part of their clinical training.

Referrals were selected by the pediatrician as the coordinating medical specialist. Prior to the consultation, referral letters and medical reports containing previous diagnostic and treatment strategies were read carefully by the clinical fellow, who sent a summary to all team members.

During the consultation, patients were seen by all team members at once. In a separate meeting, the team members reviewed the video images, discussed the movement disorder classification and the results of the additional investigations, and developed joint diagnostic and therapeutic recommendations. In all cases the team members reached consensus. The main diagnostic steps were laboratory investigations, (neuro-)imaging, clinical neurophysiology or genetic testing. The key therapeutic options comprised pharmacological treatment, botulinum toxin injections, paramedical interventions, ketogenic diet, and deep brain stimulation.

The primary purpose of the multidisciplinary team was not to take over the clinical care provided by the referring medical specialist, but to see a patient only once at our tertiary center and provide an all-in-one expert opinion. In most cases, the management and follow-up was continued by the referring specialist and patients were only seen more than once if there were still unresolved issues.

Data collection

We evaluated the first 100 patients who visited our multidisciplinary clinic for YMDs between June 2012 and May 2014. Medical records were reviewed for patient characteristics and previous phenotypical classifications. The severity of the YMDs present was assessed by the team members using the global clinical impression scale of severity (GCI-S). This commonly used 7-point scale enables a clinician to rate the extent movement disorders with no movement disorder (1), slight (2), mild (3), moderate (4), marked (5), severe (6), and among the most severest (7).[18] We

compared the classification of the most prominent MD and etiological diagnosis before and after assessment by the multidisciplinary team. In addition, we studied the treatment strategies and whether the patients or their caregivers reported any positive effects of therapies 3-6 months after initiation. Since many patients were not under our primary care, and/or living at a distance from our center, we performed follow-up using a semi-structured interview during a telephone consultation. Patients and/or caregivers were asked (1) whether they experienced benefit with regard to motor symptoms, (2) since when they experienced this, (3) extent of improvement (none/slight/moderate/good), and (4) if any adverse effects are present.

Results

Patient characteristics

A total of 56 male and 44 female patients visited the multidisciplinary clinic (Table 1). Patients had a mean age of 12.5 years (SD 6.3) and a mean duration of symptoms of 9.2 years (SD 6.3). Referring specialists were predominantly pediatric neurologists, pediatricians and rehabilitation doctors with questions concerning the MD classification, etiology or treatment options. We had 36 patients referred with an unclassified MD, documented as dyskinesias, trembling, involuntary movements, or restlessness. A confirmed etiological diagnosis (17 inherited, 12 acquired) already explained the phenotype of 29 patients upon referral.

Table 1. Baseline characteristics

Patient characteristics	
Sex (male/female)	55/46
Age (years)*	12.5 ± 6.3; 1-33
Age (years)*	3.3 ± 4.6; 0-19
Duration of symptoms (years)*	9.2 ± 6.3; 1-32
Referral questions	
Movement disorder classification	50
Etiology	38
Treatment	42
MD classification	
Ataxia	9
Dystonia	32
Myoclonus	11
Other**	12
Unclassified	36
Etiological diagnosis	
Inherited etiologies	17
Monogenic	
ARX mutation	1
Ataxia telangiectasia	1
Coffin Lowry syndrome	1
Glutaric aciduria type 1	2
GLI2 mutation	1
GOSR2 mutation	1
GTPCH deficiency (DYT5)	1
Proprionacidemia	1
SCN1A mutation	2
THAP1 mutation (DYT6)	2
TITF1 mutation	1
Structural chromosomal abnormality	
Microdeletion 19p13.2p13.13 *(NFIX* and *CACNA1A* gene)	1
Partial deletion chromosome 7q (*SCGE* gene)	1
Uniparental disomia chromosome 7 (*SCGE* gene)	1
Acquired etiologies	12
Infectious	2
Perinatal asphyxia	9
Functional	2

** Age in years ± standard deviation; range*

*** Chorea, tics, tremor, parkinsonism and if no MD was present*

Abbreviations: ARX, Aristaless related homeobox; GOSR2, Golgi SNAP receptor complex member 2; GTPCH, Guanosine Triphosphate Cyclohydrolase; SCN1A, sodium channel voltage gated type I alpha subunit; TITF1, Thyroid transcription factor-1; NFIX, nuclear factor I/X; CACNA1A, calcium channel voltage-dependent, P/Q type, alpha 1A subunit; SCGE, epsilon-sarcoglycan.

Movement disorder classification

Mean severity of the MDs present was 4.3 ± 1.7 on the global clinical impression scale (range 1–7), corresponding with a moderate to marked MD severity. The multidisciplinary team revised the initial classification in 58/100 patients (Table 2). These revisions reduced the number of patients with an unclassified MD from 36 down to 4. Compared to the referring clinicians, the team more frequently classified the patients' involuntary movements as dystonia (from 32 to 41) and myoclonus (from 11 to 31). The number of ataxic and tremor patients dropped (from 9 to 1 and 6 to 1, respectively), whereas the number of patients with chorea increased (from 4 to 6). The multidisciplinary team observed no MDs in eleven patients (e.g. the movements were related to agitation or caused by behavioral abnormalities).

Simultaneous non-invasive surface electroencephalography/electromyography (EEG/EMG) was performed in 29 predominantly myoclonic patients and this confirmed or supported the MD classification observed by the team in 24/29 patients. In the remaining five cases, EEG/EMG was not conclusive due to an absence of symptoms during registration (n = 3) or the patient being unable to comply with the registration protocol (n = 2).

Table 2. *Overview of classification of most prominent MD before and after visiting the multidisciplinary outpatient clinic*

		Observed MD classification by the multidisciplinary team					
		Dystonia	**Myoclonus***	**Ataxia**	**Other****	**Unclassified**	**Total**
Referral MD classification	Dystonia	26	1	0	4	1	**32**
	Myoclonus*	0	10	0	1	0	**11**
	Ataxia	0	8	0	1	0	**9**
	Other**	2	5	0	5	0	**12**
	Unclassified	13	7	1	12	3	**36**
	Total	**41**	**31**	**1**	**23**	**4**	**100**

** Isolated myoclonus, myoclonus ataxia and myoclonus dystonia*

*** Comprises chorea, tics, tremor, parkinsonism and if no MD was present*

Associated neurological and non-neurological features

Only 26/100 patients presented with a (mixed) MD without associated features, whereas the majority of patients also had additional neurological symptoms (n = 35), non-neurological symptoms (n = 9) or both (n = 30). The most important additional features were intellectual disability, epilepsy, spasticity, skin abnormalities, deafness, dysmorphias, and skeletal and growth abnormalities.

Etiological diagnosis

At presentation, 29/100 patients had a confirmed genetic or acquired cause explaining their phenotype (Table 1). The multidisciplinary team established a diagnosis in 24 additional patients (Table 3), particularly in the genetic domain, where the number of diagnoses more than doubled from 17 to 37. Monogenetic etiologies were found using single-gene testing in nine cases, by targeted resequencing in three cases and using whole exome sequencing in five cases. Biochemical testing led to a diagnosis of non-ketotic hyperglycinemia in one case in which confirmation of the molecular defect is still pending.

Among the acquired causes, oral contraceptive-induced chorea was diagnosed in one patient and three patients turned out to have functional MDs. Despite an increase in confirmed etiological diagnoses from 29 to 53, we still had 35 patients categorized with a suspected genetic diagnosis (defined as strong suspicion of a genetic cause based on a severe clinical phenotype, early onset, family history, and absence of any of the known acquired causes). In these cases, multiple genetic tests, including whole exome sequencing, have not yet revealed a causative molecular defect. For 21 of these 35 patients we are awaiting elucidation of the causal mutation in a research setting, the other 14 patients (or their caregivers) decided not to participate in this research.

Treatment strategies

More than half of the 100 patients (61%) had not been given any specific treatment for their MD before visiting our clinic. The multidisciplinary team initiated or changed the treatment strategy in 60/100 of the patients. Table 4 gives an overview of changes in the treatment strategy, categorized by MD type. In 30/60 cases (50%), the new treatment strategy was based on the revised MD classification. In the other 30 patients the team initiated or adjusted the treatment strategy, despite an unchanged MD classification: for example symptomatic treatment with trihexyphenidyl in dystonic cerebral palsy. We advised six patients to stop their medication, which led to unchanged clinical symptoms in two patients and an improvement of symptoms in three others. An example of the latter was advice to stop taking oral contraceptives, which led to an almost complete disappearance of adolescent-onset chorea. In the group of 60 patients who had new or adjusted treatment, 72% of them or their caregivers reported a positive effect therapy after 3-6 months. Five patients were advised to stop their medication at the 3-6 months evaluation, because of limited benefit and or potential aggravation of other symptoms and side effects, such as effects on mood, behavior or constipation.

Table 3. Confirmed etiological diagnoses after assessment by the multidisciplinary team

Diagnosis	**N**
Inherited etiologies	*20*
Monogenic	
ACTB mutation	1
CTNNB1 mutation	1
GLRA1 mutation	1
GOSR2 mutation	6
HSD17B10 mutation	1
MECP2 mutation	1
OFD-1 mutation	1
OTC-deficiency	1
PRRT2 mutation	1
SPTBN2 mutation	1
TH mutation	1
TITF-1 mutation	1
Laboratory abnormalities	
Non-ketotic hyperglycinemia	1
Syndrome diagnosis	
Gilles de la Tourette	1
Linear naevus syndrome	1
Acquired etiologies	4
Drug-induced	1
Functional	3

Abbreviations: ACTB, beta-actin; CTNNB1, catenin (cadherin-associated protein) beta 1; GLRA1, glycine receptor alpha 1; GOSR2, Golgi SNAP receptor complex member 2; HSD17B10, 17beta-hydroxysteroid dehydrogenase type 10; MECP2, methyl CpG binding protein 2; OFD-1, oral-facial-digital syndrome 1; OTC, ornithine carbamoyltransferase; PRRT2, proline-rich transmembrane protein 2; SPTBN2, spectrin beta non- erythrocytic 2; TH, tyrosine hydroxylase; TITF1, thyroid transcription factor-1; HSD17B10 or 2-methyl-3- hydroxybytyryl-CoA dehydrogenase deficiency

Table 4. Overview of treatment strategies that were changed by the multidisciplinary team

Movement disorder	Treatment category	Treatment specifics	N	Positive effect (*n*)
Dystonia				
	Pharmacological			
		Clonazepam	1	1
		Gabapentin	3	3
		L-dopa	2	1
		Trihexyphenidyl	8	3
		Cessation of drug	1	1
	Botulinum toxin		5	5
	Deep brain stimulation		5	4
	Paramedical		2	2
	Total dystonia		27	20
Myoclonus				
	Pharmacological	Clonazepam	10	10
	Ketogenic diet		4	1
	Paramedical		4	2
	Total myoclonus		18	12
Other				
	Pharmacological			
		L-dopa	4	4
		Acetozolamide	1	1
		Cessation of drug	4	2
	Botulinum toxin		1	1
	Paramedical		3	2
	Total other		13	10
Difficult to classify			2	
	Pharmacological	L-dopa	2	1
Total			**60**	**43**

Discussion

To our knowledge, this is the first study to systematically examine the effects of a multidisciplinary team approach for children and adults with YMDs. Our results showed that this multidisciplinary approach was beneficial with regard to MD classification, diagnostic yield and targeted treatment strategies.

The multifaceted nature of YMDs served as the impulse for setting up our multidisciplinary outpatient clinic, because the complexity of YMDs often leads to a time- consuming and burdensome diagnostic process.[1, 5, 6] This issue is reflected by a mean symptom duration of 74% of our patients' life spans, which is in line with the results of a previous study.[6]

The results of our study show that in 58% of the patients with YMDs the multidisciplinary team revised the MD classification or defined another MD as the most prominent clinical symptom. We think this high percentage of revisions may be due to the combined expertise of a pediatric neurologist, trained to distinguish normal developmental from abnormal movements, and a movement disorder specialist, trained to establish the phenomenology of clinical MD syndromes.[1,7] Although we are aware that there is no gold standard for clinical MD classification, additional investigations such as EEG/EMG for myoclonus confirmed the clinical diagnosis in 24/29 of our cases.[19] The presence of non-neurological features in 39% of our YMD cohort underscores the complexity of the clinical presentations in a significant part of this population, and the combined expertise of a pediatrician and a clinical geneticist to include all symptoms, facilitated the diagnostic process.

The multidisciplinary approach led to a confirmed etiological diagnosis in 24/71 (34%) previously undiagnosed patients, of which 17 were found to have monogenetic disorders. This is a high diagnostic yield compared to previous literature. In a recent study with 260 patients with non-tic YMDs in a tertiary referral center, a definitive genetic diagnosis was made by a neurologist specialized in YMDs in 44 of 260 (17%) patients with non-tic YMDs.[6] Another study on complex MDs showed similar diagnostic yields.[20] We hypothesize that the high diagnostic yield in our study is the result of the team's broad and combined expertise and of the process of clinical decision-making through a consensus meeting. Importantly, a multidisciplinary team strategy facilitates immediate decision-making in comparison to the normal serial process involving multiple referrals, therefore minimizing the burden for the patients and their families. In the near future, third-generation technologies (real-time DNA sequencing) may lead to tremendous improvement in the speed and capacity of the diagnostic process.[21] Also in this context, we think a solid understanding of the whole phenotype is of great importance and can only be accomplished by a close collaboration between clinicians.

After critical appraisal of phenotype and etiology, therapeutic strategies were considered and tailored to individual patient needs. The team gave specific advice on treatment for 60% of patients, with 72% (n = 42) of them or their caregivers reporting a subjective positive effect of the suggested treatment on follow-up. The effectiveness of treatment was only assessed through a semi-structured questionnaire and it was therefore not possible to draw more detailed conclusions on objective and/or long-term outcome measures of its effectiveness. Nevertheless, the large number of patients in which treatment was initiated at our clinic may reflect a potential

under-treatment of YMDs, likely to significantly impact the patient's quality of life. The low number of patients that were already treated for their MD is remarkable, in particular when taking into account that the mean MD severity of these 60 cases was significant (5 on a scale of 7). Low treatment rates and potential under-treatment have also been reported in MDs in children with inborn errors of metabolism,12 despite the fact that it has been shown that symptomatic treatment may significantly improve patients' daily functioning and quality of life.[22, 23]

All patients in our study had an age at onset before 18 years. For diagnostic approaches distinguishing early-onset and later-onset MDs can be useful.[2, 3] However, age at presentation may not fit within the upper limit of 18 years for pediatric care, as is reflected in our population (range 1-33 years). A broad expertise is likely to be beneficial in the approach of both young adults and children with YMDs. Therefore, we propose to consider YMDs as a spectrum, with arbitrary age limits, crossing barriers between pediatric and adult neurology, and allowing all complex YMD patients to benefit from the combined expertise of a multidisciplinary team.

In conclusion, our results demonstrate that a multidisciplinary approach can facilitate phenotyping in complex YMDs. Consequently, this approach improves recognition of rare disorders, with a high diagnostic yield and a minimal diagnostic delay. We expect that in the coming years a multidisciplinary approach for both children and adults with complex YMDs will become more common in tertiary centers.

Future studies are needed to investigate which subgroups of YMDs patients benefit most from a multidisciplinary approach in comparison to regular subspecialty care and to explore the long term benefits, preferably using a study design with standardized clinical assessments to systematically evaluate treatment effects.

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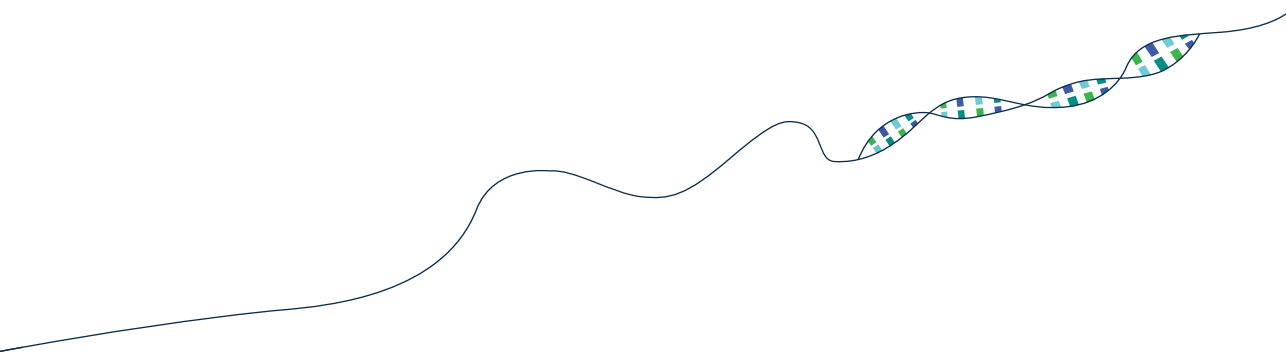
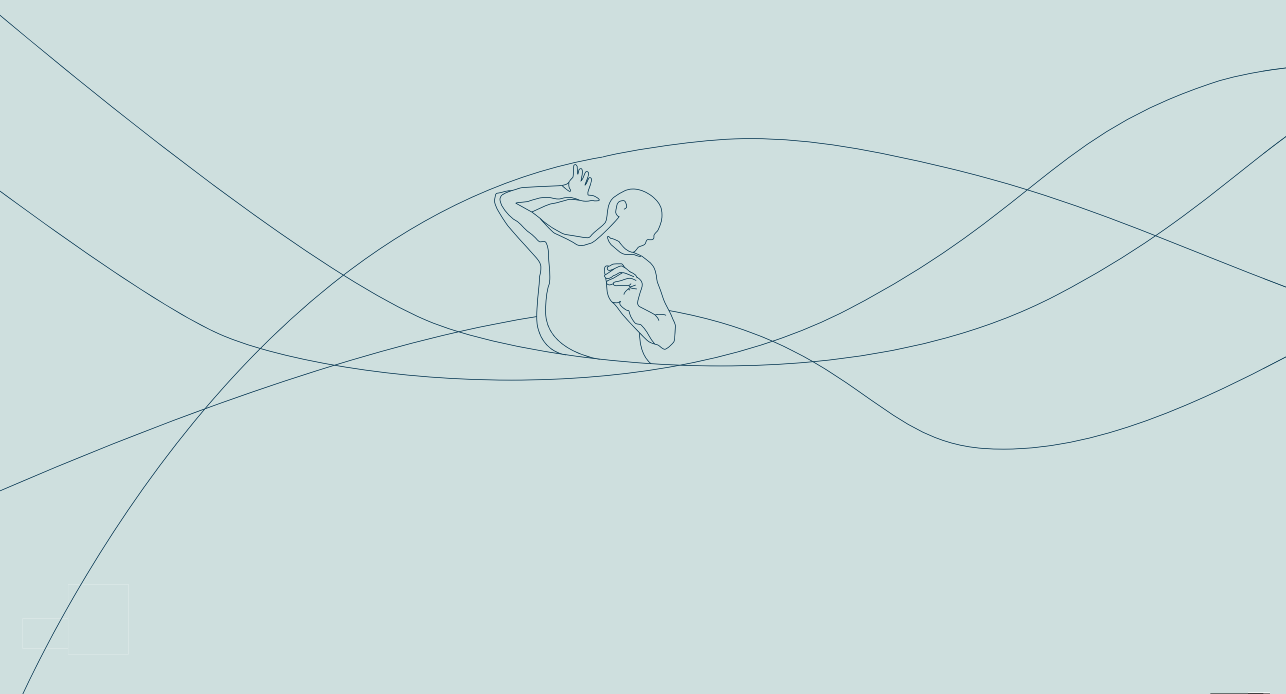
References

1 Singer HS, Mink JW, Gilbert DL, Jankovic J.. Movement Disorders in Childhood. Philadelphia: Saunders: Elsevier 2010.
2 Fahn S. Classification of movement disorders. Mov Disord. 2011;26(6):947-57.
3 Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863-73.
4 Delgado MR, Albright AL. Movement disorders in children: definitions, classifications, and grading systems. J Child Neurol. 2003;18 Suppl 1:S1-8.
5 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(7):774-81.
6 Bäumer T, Sajin V, Münchau A. Childhood-Onset Movement Disorders: A Clinical Series of 606 Cases. Movement Disorders Clinical Practice. 2017;4(3):437-40.
7 Abdo WF, van de Warrenburg BP, Burn DJ, et al. The clinical approach to movement disorders. Nat Rev Neurol. 2010;6(1):29-37.
8 Sanger TD, Chen D, Fehlings DL, et al. Definition and classification of hyperkinetic movements in childhood. Mov Disord. 2010;25(11):1538-49.
9 Brandsma R, Spits AH, Kuiper MJ, et al. Ataxia rating scales are age-dependent in healthy children. Dev Med Child Neurol. 2014;56(6):556-63.
10 Kuiper MJ, Vrijenhoek L, Brandsma R, et al. The Burke-Fahn-Marsden Dystonia Rating Scale is Age-Dependent in Healthy Children. Movement Disorders Clinical Practice. 2016;3(6):580-6.
11 Gascon GG, Ozand PT, Brismar J. Movement disorders in childhood organic acidurias. Clinical, neuroimaging, and biochemical correlations. Brain Dev. 1994;16 Suppl:94-103.
12 Garcia-Cazorla A, Wolf NI, Serrano M, et al. Inborn errors of metabolism and motor disturbances in children. J Inherit Metab Dis. 2009;32(5):618-29.
13 Eggink H, Kuiper A, Peall KJ, et al. Rare inborn errors of metabolism with movement disorders: a case study to evaluate the impact upon quality of life and adaptive functioning. Orphanet J Rare Dis. 2014;9:177.
14 Bertram KL, Williams DR. Diagnosis of dystonic syndromes--a new eight-question approach. Nat Rev Neurol. 2012;8(5):275-83.
15 Shapiro BS, Cohen DE, Covelman KW, et al. Experience of an interdisciplinary pediatric pain service. Pediatrics. 1991;88(6):1226-32.
16 Bent N, Tennant A, Swift T, et al. Team approach versus ad hoc health services for young people with physical disabilities: a retrospective cohort study. Lancet. 2002;360(9342):1280-6.
17 Ladner TR, Mahdi J, Attia A, et al. A multispecialty pediatric neurovascular conference: a model for interdisciplinary management of complex disease. Pediatr Neurol. 2015;52(2):165-73.
18 Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4(7):28-37.
19 Zutt R, van Egmond ME, Elting JW, et al. A novel diagnostic approach to patients with myoclonus. Nat Rev Neurol. 2015;11(12):687-97.
20 Neveling K, Feenstra I, Gilissen C, et al. A post-hoc comparison of the utility of sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. Hum Mutat. 2013;34(12):1721-6.
21 Bonifati V. Will New Genetic Techniques Like Exome Sequencing and Others Obviate the Need for Clinical Expertise? Yes. Movement Disorders Clinical Practice. 2017;4(1):36-8.
22 van Egmond ME, Elting JW, Kuiper A, et al. Myoclonus in childhood-onset neurogenetic disorders: The importance of early identification and treatment. Eur J Paediatr Neurol. 2015;19(6):726-9.
23 Liow NY, Gimeno H, Lumsden DE, et al. Gabapentin can significantly improve dystonia severity and quality of life in children. Eur J Paediatr Neurol. 2016;20(1):100-7.

Dystonia

Part II





Dystonia in children and adolescents: a systematic review and a new diagnostic algorithm

Chapter 3

M.E. van Egmond, A. Kuiper, H. Eggink, R.J. Sinke, O.F. Brouwer,
C.C. Verschuuren-Bemelmans, D.A. Sival, M.A.J. Tijssen, T.J. de Koning

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Abstract

Early etiological diagnosis is of paramount importance for childhood dystonia because some of the possible underlying conditions are treatable. Numerous genetic and non-genetic causes have been reported, and diagnostic workup is often challenging, time consuming and costly. Recently, a paradigm shift has occurred in molecular genetic diagnostics, with next- generation sequencing techniques now allowing us to analyze hundreds of genes simultaneously. To ensure that patients benefit from these new techniques, adaptation of current diagnostic strategies is needed. On the basis of a systematic literature review of dystonia with onset in childhood or adolescence, we propose a novel diagnostic strategy with the aim of helping clinicians determine which patients may benefit by applying these new genetic techniques and which patients first require other investigations. We also provide an up-to-date list of candidate genes for a dystonia gene panel, based on a detailed literature search up to 20 October 2014. While new genetic techniques are certainly not a panacea, possible advantages of our proposed strategy include earlier diagnosis and avoidance of unnecessary investigations. It will therefore shorten the time of uncertainty for patients and their families awaiting a definite diagnosis.

Introduction

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.[1] For dystonia in children and adolescents, here referred to as dystonia of childhood (DC), the list of possible genetic and non-genetic causes is extensive.[2, 3] For clinicians encountering a young patient with dystonia, an important practical question is how to manage the diagnostic work-up, which is often challenging, time-consuming and costly.

Recently, a paradigm shift has occurred in molecular genetic diagnostics, with next- generation sequencing (NGS) techniques now allowing us to analyze hundreds of genes simultaneously. NGS diagnostic strategies are particularly effective in heterogeneous conditions, including movement disorders, significantly increasing the diagnostic yield at lower costs.[4, 5] As a significant proportion of DC cases is estimated to be genetic, a 'genetics first' diagnostic approach for all patients with DC seems logical and appealing. However, there are two groups of patients for whom another initial approach should be considered. First, in children and adolescents who may have acquired dystonia, and second, in patients in whom the cause may be a treatable inborn error of metabolism (IEM), because for most of these IEMs biochemical investigations will be a faster diagnostic method than genetic testing.

We first provide a systematic literature review of the phenomenology, classification, and etiology of DC. We then propose a novel diagnostic strategy that will help clinicians determine which patients may benefit from NGS technologies and which patients require other initial investigations. Finally, we give an up-to-date list of dystonia gene candidates to enhance the development of NGS diagnostics for DC (Supplement 1).

Methods

We systematically reviewed all papers regarding DC up to October 20th 2014, both genetic and nongenetic, in three age groups (infancy, childhood and adolescence), as proposed in the latest dystonia classification.[1] For details of our systematic search, see Supplement 2.

DYSTONIA IN CHILDREN AND ADOLESCENTS: STATE OF THE ART

Phenomenology: Is it dystonia?

The first step in diagnosing DC is the identification of a hyperkinetic movement as being 'dystonic'. Dystonia is defined as *"a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both. Dystonic movements are typically patterned or twisting, and may be tremulous. They are often initiated or worsened by voluntary action and associated with overflow muscle activation."*[1] This definition of dystonia is identical for adults and children[1, 3] and similar to the definition of dystonia published by the Taskforce on Childhood Movement Disorders.[6] In children, dystonia is more often generalized compared with adult-onset dystonia.

Correct identification of dystonia involves both an understanding of classification systems and visual pattern recognition. Three important, characteristic, clinical features of dystonia are: (1) patterned, predictable contractions of the same muscles; (2) exacerbation when performing voluntary movements (eg, walking, running, writing) and (3) the so-called *geste antagoniste*, or sensory trick. This phenomenon is characterized by the relief of dystonic movements by lightly touching the relevant or adjacent part of the body. A sensory trick is particularly frequent in cranial and cervical dystonia, whereas limb and trunk involvement more often predominate in children. Therefore, a sensory trick is not an obligatory feature in DC; however, when observed, it strongly favors a diagnosis of dystonia.[1, 6]

In children, movements should be evaluated in relation to their developmental age. For instance, a healthy toddler can have normal overflow movements that may look like dystonia, diminishing as the child's development progresses.[3] In addition to these normal movements, abnormal movements may also mimic dystonia (Table 1). For example, children with focal, stereotyped movements of the eyelids, face, or neck, are more likely to have tics than focal dystonia.[7, 8]

Reliable diagnostic criteria for different body localizations of dystonia are needed to help clinicians accurately differentiate dystonia from conditions mimicking dystonia. Recently a diagnostic guideline for diagnosing blepharospasm has been validated;[9] however, blepharospasm is a form of focal dystonia that rarely occurs in childhood or adolescence. For other body localizations of dystonia specific diagnostic criteria are an unmet need.

Table 1. Mimics of dystonia in children and adolescents

Type of dystonia	Mimics
Mimics of facial dystonia	• Tics • Stereotypies • Functional
Mimics of cervical dystonia (head tilt)	• Tics • Stereotypies • Trochlear nerve palsy • Vestibulopathy • Spasmus nutans • Acquired nystagmus • Congenital muscular torticollis • Sternocleidomastoid injuries • Benign paroxysmal torticollis of infancy • Posterior fossa tumors • Tumors in the pineal region • Chiari malformation • Atlanto axial subluxation (e.g. syndrome of Grisel) • Cervical tumors (in cervical cord, bone or soft tissue) • Upper spinal cord syringomyelia • Juvenile rheumatoid arthritis • Sandifer syndrome • Klippel-Feil syndrome • Functional
Mimics of trunk dystonia	• Scoliosis • Stiff person syndrome • Functional
Mimics of limb dystonia (posturing)	• Overflow movements in toddlers (normal developmental movements) • Stereotypies • Shoulder subluxation • Dystonic (tonic) tics • Myotonia • Neuromyotonia • Cramp • Satayoshi syndrome • Rigidity • Spasticity • Focal tonic seizures • Spasms (hypocalciemia, hypomagnesemia, alkalosis) • Deafferentation (pseudoathetosis) • Functional
Mimics of generalized dystonia	• Self-stimulation • Opisthotonus • Stiff person syndrome • Functional

Classification of dystonia

The most recent general classification scheme of dystonia identifies two distinct axes: Axis I - clinical characteristics, and Axis II – etiology.[1] Axis I describes the clinical features by (1) age at onset, (2) body distribution, (3) temporal pattern, (4) coexistence of other movement disorders and (5) other neurological or systemic manifestations. Axis II addresses the etiology via two components: (1) nervous system pathology and (2) whether the dystonia is inherited or acquired. Classification of etiology into the categories 'inherited' or 'acquired' differs from traditional classification schemes in which dystonia was classified into primary genetic dystonia or secondary dystonia.1 The reason for this change was that primary dystonias, heredodegenerative dystonias and dystonia-plus syndromes are all in fact genetic disorders.[1] These three categories are now considered together as 'inherited'. In this review, we elaborate on this recent change in etiologic classification.

Etiology of dystonia

There are many possible etiologies of DC. For this review, we highlight acquired dystonias and treatable IEMs because an initial approach other than NGS testing needs to be considered for these conditions. All other genetic causes can be tested at the same time by means of NGS diagnostics.

Table 2. *Drugs and toxic agents that may cause dystonia in children and adolescents*

Drugs	
Dopamine receptor blocking drugs	• (neuroleptics, antiemetics)
Dopamine depleting drugs	• (e.g. tetrabenazine)
Dopamine receptor stimulants	• (L-dopa, dopamine receptor agonists)
Antihistaminic drugs	
Tricyclic antidepressants	
Serotonin reuptake inhibitors	
Cholinergic agonists	• (e.g. trihexyphenidyl)
Antiepileptic drugs	• (especially phenytoin and carbamazepine)
Antimalarials	• (e.g. chloroquine, amodiaquine)
Calcium channel blockers	
Disulfiram	
Lithium	
Cocaine	
Toxins	**Main source**
Carbon monoxide	• Smoke inhalation, poorly functioning heating systems or fuel-burning devices
Cyanide	• Inhalation of smoke, ingestion of toxic household and workplace substances or cyanogenic foods
Manganese	• Drinking water with a high concentration of manganese, long-term parenteral nutrition
Methanol	• Ingestion of certain industrial products such as antifreeze solution or cleaners
Organophosphate	• Exposure to or ingestion of insecticides

Acquired dystonias

We focus on acquired forms of dystonia that are relatively common and/or treatable. Drugs and toxic agents that may cause DC are listed in Table 2. For other causes of acquired DC, clinical clues and recommended investigations are summarized in Table 3.

Drugs and toxic agents

DC can be induced by certain drugs and toxic agents, most commonly neuroleptics and antiemetics (Table 2).[7, 8] Drug-induced dystonias are categorized into acute dystonic reactions and tardive (chronic use) dystonia. The latter is a well-recognized disorder in adults, but may also occur in children.[7] Acute forms of dystonia may arise after taking a few doses or even after one administration or accidental ingestion.[8] The dystonia usually disappears rapidly on withdrawing the offending drug.

Cerebral palsy

Dyskinetic cerebral palsy (CP) is the most common cause of acquired DC.[10] CP is a clinical diagnosis, encompassing a group of permanent disorders that cause impairment of movement and posture, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.[11] Dyskinetic CP is characterized by the presence of choreoathetosis and dystonia[11] and possible etiologies are heterogeneous.[8, 12] It is most common in children, born at term, who have experienced adverse perinatal effects, since the basal ganglia are particularly vulnerable to pathogenic events toward the end of gestation.[12] There are guidelines to help identify whether an acute intrapartum event was the likely cause of any particular case of CP.[13] Due to the aggressive treatment of perinatal hyperbilirubinemia, it is now rare to see kernicterus as a cause of dyskinetic CP.[12]

In dyskinetic CP, the hyperkinetic movements are usually bilateral and mostly begin after the first year of life, and progress slowly for several years.[7, 8] In children with severe CP, dystonia may be so profound and sustained that it manifests as hypertonia rather than abnormal involuntary movements.[3] Brain MRI demonstrates abnormal findings in about 80% of individuals with CP.[14] Genetic analysis is recommended in those cases where no specific cause can be determined, as several monogenic disorders can present with clinical features similar to CP.[15]

Table 3. Clinical clues suggesting acquired dystonia

Clinical clue	Differential diagnosis	Recommended initial investigations
Acute onset dystonia or rapidly progressive course	Structural lesion External insult[a] Autoantibody-associated movement disorder ADEM Infection	Neuroimaging Neuroimaging Autoantibodies in serum and CSF Neuroimaging, CSF Neuroimaging, serum, CSF
Unilateral dystonia[b]	Structural lesion External insult[a] Autoantibody-associated movement disorder Demyelinating disease[c] Antiphospholipid syndrome[d] CP	Neuroimaging Neuroimaging Autoantibodies in serum and CSF Neuroimaging, CSF Serum investigations Neuroimaging
Psychiatric symptoms (de novo)	Autoantibody-associated movement disorder Infection	Autoantibodies in serum and CSF Neuroimaging, serum, CSF
Seizures (de novo)	Structural lesion Autoantibody-associated movement disorder Rasmussen's syndrome[e] Infection	Neuroimaging Autoantibodies in serum and CSF Neuroimaging Neuroimaging, serum, CSF
Signs of meningo-encephalitis or encephalitis	Autoantibody-associated movement disorder Infection	Autoantibodies in serum and CSF Neuroimaging, serum, CSF
Abnormal birth or perinatal history	CP	Neuroimaging
Local signs of autonomic disturbances and pain	CRPS I	Clinical diagnosis[f]

[a] External insults include head trauma and hypoxic insults caused by near-drowning, cardiac arrest or status epilepticus.

[b] Unilateral dystonia comprises either focal or hemidystonia.

[c] Demyelinating diseases including ADEM, multiple sclerosis and neuromyelitis optica.

[d] Antiphospholid syndrome with or without associated rheumatic disease such as systemic lupus erythematosus should be considered in all children with hemidystonia of unknown origin.

[e] In Rasmussen's syndrome dystonia can be an accompanying sign or the presenting feature.

[f] Criteria for CRPS are described by Mersky et al, see Supplemental references (Supplement 4). Abbreviations: ADEM, acute disseminated encephalomyelitis; CP, cerebral palsy; CRPS I, complex regional pain syndrome type I.

Acquired structural lesions

Structural lesions, such as stroke, neoplasms or structurally abnormal vessels including arteriovenous malformations, may result in unilateral DC (focal or hemidystonia).[7, 8] Childhood stroke may result in dystonia if the caudate, lenticular nucleus or thalamus are involved.[7, 8] In most cases, the dystonia develops months or even years after the incident.

Autoantibody-associated and autoimmune disorders

Several autoantibody-associated and autoimmune disorders can lead to DC (Table 3).[16] We put emphasis on two autoantibody-associated disorders, as early recognition and timely therapy can improve the outcome significantly in these conditions.[16]

Anti-N-Methyl-D-Aspartate Receptor (NMDAR) encephalitis in children is characterized by a combination of seizures, movement disorders, psychiatric symptoms and encephalopathy.[16] The first symptom is often non-psychiatric.[17] In addition to dystonia, multiple movement disorders can be seen in the same patient,[16] the most characteristic being orofacial dyskinesias.[17] Young children often present with temper tantrums, hyperactivity or irritability, whereas in older patients anxiety, psychosis and altered personality are the main psychiatric features observed.[17] Recognition of the combination of symptoms should prompt testing for anti-NMDARs antibodies, both in serum and cerebrospinal fluid (CSF).[17] Brain MRI, EEG and CSF may all show non-specific abnormalities. [17, 18] An underlying neoplasm is found in approximately 6% of girls younger than 12 years but rarely in boys, whereas the association with an ovarian teratoma increases in adolescent girls.[18] Treatment consists of immunotherapy and oncological treatment in those patients with a clinically detectable tumor.[18] Outcome is good in the majority of patients treated early enough.[18]

Autoimmune basal ganglia encephalitis is a syndrome characterized by extrapyramidal movement disorders including dystonia and parkinsonism, sleep disturbance, dysautonomia and psychiatric symptoms.[16] Approximately 70% of cases have serum antidopamine-2 receptor antibodies.[16] Many patients have MRI T2 hyperintense basal ganglia abnormalities and show signs of CSF inflammation including oligoclonal bands.[16] Immune therapy is the mainstay of treatment.[16] In the past, encephalitis with dominant involvement of the basal ganglia was given a variety of names, including encephalitis lethargica and (infantile) bilateral striatal necrosis.[16] These disorders and autoimmune basal ganglia encephalitis may all be part of the same clinical entity.[16]

Infections

DC caused by infection is relatively rare, but has been reported in children with viral infections, tuberculosis, mycoplasma or toxoplasmosis.[19] Infection by flaviviruses is an important cause of DC, the most common being Japanese encephalitis.[19] Other viruses associated with DC include influenza viruses, herpes viruses (including herpes simplex and herpes zoster) and measles viruses, which may lead to subacute sclerosing panencephalitis.[7, 8] The main bacterial infections are tuberculosis and infection by *Mycoplasma pneumoniae*.[8] Infection should be suspected in any child with dystonia and pre-existing immunodeficiency or signs of meningoencephalitis or encephalitis. Detecting the infectious agent may be important for the type of therapy chosen and therefore serum and CSF investigations are indicated in addition to neuroimaging.

Treatable IEMs

IEMs are highly heterogeneous. For most clinicians who do not work daily with IEMs, it will be virtually impossible to recognize all these often extremely rare conditions. Fortunately, since all IEMs can be detected with NGS diagnostics, early identification is only necessary for those IEMs where timely treatment can improve the outcome.[20]

In general, an important clue for an IEM is a complex clinical picture comprising both neurological and non-neurological features. An overview of treatable IEMs associated with DC is provided in Supplement 3. We defined 'treatable' as the availability of a therapy that might lead to the improvement or prevention of symptoms. We will highlight five significant subgroups of treatable IEMs that may cause DC.

Organic acidurias

Organic acidurias can present both acutely and intermittently and are associated with 'intoxication-like' non-specific symptoms, such as vomiting and anorexia, progressing towards encephalopathy. Episodes are frequently triggered by intercurrent illness, dietary changes or prolonged fasting.21 When the underlying enzymatic defect is severe, onset will be in the newborn period. Milder phenotypes may present later as a slowly progressive disorder or with an intermittent course. Examples of organic acidurias associated with DC are propionic aciduria, methylmalonic aciduria, cobalamin defects and glutaric aciduria type I.[22]

GLUT-1 deficiency

GLUT-1 deficiency, caused by mutations in the *SCL2A1* gene, can give rise to paroxysmal dystonia triggered by prolonged exercise.[23] This phenotype is also referred to as paroxysmal exertion-induced dystonia. The *SCL2A1* gene encodes for the glucose transport protein 1, and mutations in this gene compromise glucose transport to the brain. Paroxysmal dystonia can be the sole feature, but developmental delay, spasticity, ataxia and epilepsy can also be part of the phenotype. A ketogenic diet is the current gold standard for treatment and has proven to be beneficial in most cases.[23]

Metal storage

Wilson's disease (WD) and dystonia with brain manganese accumulation (DBMA), caused by *SLC30A10* mutations, are both metal storage disorders in which symptoms can be fully or partly prevented by timely treatment.[24, 25] In both disorders, a combination of neurological symptoms and hepatic involvement is usually present. Other manifestations are psychiatric symptoms and a corneal Kayser-Fleischer ring in WD and parkinsonism and polycythaemia in DBMA. Indicative biochemical findings include low serum copper and ceruloplasmin in WD and hypermanganesaemia in DBMA.

Lysosomal storage

Niemann Pick type C is a clinically heterogeneous disorder in which the presenting phenotype depends on the age of onset. Infants can present with ascites and liver or pulmonary disease. The classic presentation in mid to late childhood consists of ataxia, a supranuclear vertical gaze palsy,

psychiatric symptoms, dystonia and dementia, whereas the clinical picture in adults is dominated by psychiatric symptoms and cognitive decline.[26] Recently, treatment with miglustat has been shown to stabilise the progression of neurological symptoms, including in pediatric patients.[27]

Dopa responsive dystonias

Dopa-responsive dystonias (DRD) are a group of disorders with a more insidious onset, probably representing 5% of childhood dystonias.[28] The autosomal dominant form, GTP- cyclohydrolase deficiency, is most common. This form is also known as Segawa's disease and shows an excellent and sustained response to low doses of levodopa.[29] Typically, there is a diurnal fluctuation of symptoms, and associated parkinsonism. Furthermore, two autosomal recessive forms of DRD have been identified: tyrosine hydroxylase deficiency and sepiapterin reductase deficiency, both often accompanied by intellectual disability and ophthalmological problems like oculogyric crisis, upward gaze and ptosis.[30]

Since DRD features can be non-specific and can show considerable phenotypic variability, DRDs are frequently misdiagnosed as CP.[30] This may result in a considerable delay in diagnosis and adequate treatment.[29, 30]

In addition to biochemical and molecular studies, a levodopa trial can be used as a diagnostic procedure. However, it should be noted that a positive response on a levodopa trial is not specific for the classic DRDs, but can also be seen in other disorders such as ataxia telangiectasia and GLUT1-deficiency.[31, 32]

Classification of genetic dystonias

The genetic forms of dystonia including IEMs, may be categorized into two groups. The first group consists of the monogenetic forms of dystonia with assigned genetic loci identified as *DYT1-25*, formerly named 'primary dystonias' and 'dystonia plus syndromes'. These disorders are characterized by isolated dystonia, or dystonia combined with parkinsonism or myoclonus.[1] The second group consists of genetic disorders in which dystonia is an important feature among several other neurological and systemic features. On Axis I of the latest dystonia classification, these co-occurring neurological or systemic manifestations are classified as 'associated features'.[1] Important associated features in children include: ataxia, epilepsy, mental retardation, spasticity, hypotonia, abnormal eye movements, neuropathy, deafness, ophthalmological signs, hepatosplenomegaly, psychiatric and dysmorphic features. These features are decisive for accurate phenotyping and a prerequisite for correct interpretation of NGS results.

NGS methodology

Genetic techniques using massive parallel sequencing are called NGS. With these new techniques, sequencing the entire genome of a patient (whole-genome sequencing; WGS), the coding regions (exons) of every gene (whole-exome sequencing; WES) or targeting specific disease-causing genes (targeted resequencing; TRS) have all become a reality in DNA diagnostics. Technical details of the specific methods fall outside the scope of this review, but are described elsewhere.[33]

It is important to recognize that with WGS or WES approaches, information for all genes will become available, including those not relevant to the diagnostic question. These genes need to

be excluded to restrict the data analysis to a list of known genes that might explain the phenotype. If the phenotype is unique and no mutation is found in the selected genes, the information about the excluded genes may be used to hunt for new disease-causing genes. The drawbacks of WGS and WES are high costs, the risk of unsolicited findings, and coverage that is usually less than in TRS panels, compromising the diagnostic accuracy. In TRS panels, a preselected list of several known genes that cause dystonia are tested. By sequencing only preselected genes, the coverage significantly increases, contributing to diagnostic accuracy, and unsolicited findings are minimized, at significantly lower costs.

The important benefits of NGS diagnostics compared with regular biochemical procedures are that shipping DNA to referral centers is relatively cheap and straightforward, without stringent shipping conditions. In contrast, the costs and conditions of shipping samples, for instance, for (CSF) biochemical tests can be a serious hurdle in the present diagnostic process.

It is to be expected that in the near future the widespread use of NGS, both in research and in clinical diagnostics, will lead to many more reports of dystonia associated genes, and the list of associated genes will grow rapidly. However, it is important that independent confirmation of the causal relationship between gene variants and dystonia is performed, because in some of the recently annotated dystonia genes, variants in these genes also occur with high frequency in the general population.[34]

A NEW DIAGNOSTIC ALGORITHM

Owing to the extraordinarily broad range of possible causes of DC, several algorithms have been developed to assist clinicians in making diagnostic decisions.[2, 35, 36] These algorithms are not widely applicable as they mainly focus on (rare) neurometabolic causes and do not make use of the availability of NGS methodologies. On the basis of our systematic literature review and our own clinical experience, we propose a new diagnostic algorithm with five steps (Figure).

Step 1: Is it dystonia?

The first step in the algorithm is to record a careful history and perform a physical and neurological examination to determine that dystonia is an important feature.

Movement disorders that may be misdiagnosed as dystonia are listed in Table 1. In general, these 'pseudodystonias' have a known or presumed cause that is thought to differ from the causes of the broader dystonia group.[1] Applying the algorithm and using NGS testing is not advised in these conditions.

Step 2: Could the dystonia be medication-induced or caused by toxic agents?

The second step is to verify exposure to any medication or toxic agents that could be causing the dystonia (Table 2). Treatment consists of discontinuing medication or prevention of further toxic exposure, and, if possible, detoxification.

Step 3: Clinical clues suggesting acquired dystonia?

Step 3 is to consider whether the dystonia could be acquired. In Table 3 we indicate red flags for acquired disorders with the main subgroups. These red flags are only defined to guide clinicians to a limited number of disorders in which immediate diagnosis and treatment is necessary to identify treatable disorders, preventing insults to the brain during the diagnostic process.

Step 4: Biochemical investigations and levodopa trial

In any child with dystonia without obvious clues for an acquired cause, we recommend performing a laboratory workup (Table 4) aimed at identifying the treatable forms, before moving on to NGS testing. Of course this recommendation only applies for those centres where biochemical diagnostics will provide faster results than NGS testing, depending on the local facilities. CSF investigations are only recommended in selected patients (Table 4) because otherwise the diagnostic yield of CSF investigations is likely to be rather low.[37, 38]

Table 4. Biochemical investigations to identify treatable inborn errors of metabolism with dystonia as important feature

Laboratory test	In sample of	Disorder
Organic acids	Urine	glutaric aciduria type I, propionic aciduria, methylmalonic aciduria, cobalamin deficiencies
Lactate	Plasma	propionic aciduria, methylmalonic aciduria, biotin responsive basal ganglia disease
Pyruvate	Plasma	pyruvate dehydrogenase complex (PDC) deficiency
Acylcarnitines	Plasma	propionic aciduria, methylmalonic aciduria, glutaric aciduria type 1
Amino acids	Plasma	ornitine transcarbamylase deficiency, maple syrup urine disease, pterine defects
Homocysteine	Plasma	homocysteinuria
Copper, ceruloplasmin	Plasma, urine	Wilson's disease
Manganese	Plasma	dystonia with brain manganese accumulation
Biotinidase	Plasma	biotinidase deficiency
Creatine, guanidinoacetic acid	Plasma, urine	cerebral creatine deficiency syndrome 3 (AGAT deficiency), guanidinoacetate methyltransferase deficiency
Vitamin E (α-tocopherol)	Plasma	Ataxia with vitamin E deficiency (AVED)
Uric acid	Plasma	Lesch-Nyhan Syndrome
Cholestanol	Plasma	cerebrotendinous xanthomatosis
Glucose	CSF*, plasma	GLUT1 deficiency
Folate	CSF*	cerebral folate deficiency
HVA, 5-HIAA	CSF*	tyrosine hydroxylase deficiency
Pterines	CSF*, urine	GTP-cyclohydrolase 1 deficiency, 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency, aromatic l-amino acid decarboxylase (AADC) deficiency
Sepiapterin	CSF*	sepiapterin reductase deficiency

Note: performing this set of laboratory investigations is only recommended if obtaining the results of these tests will be faster than NGS testing.

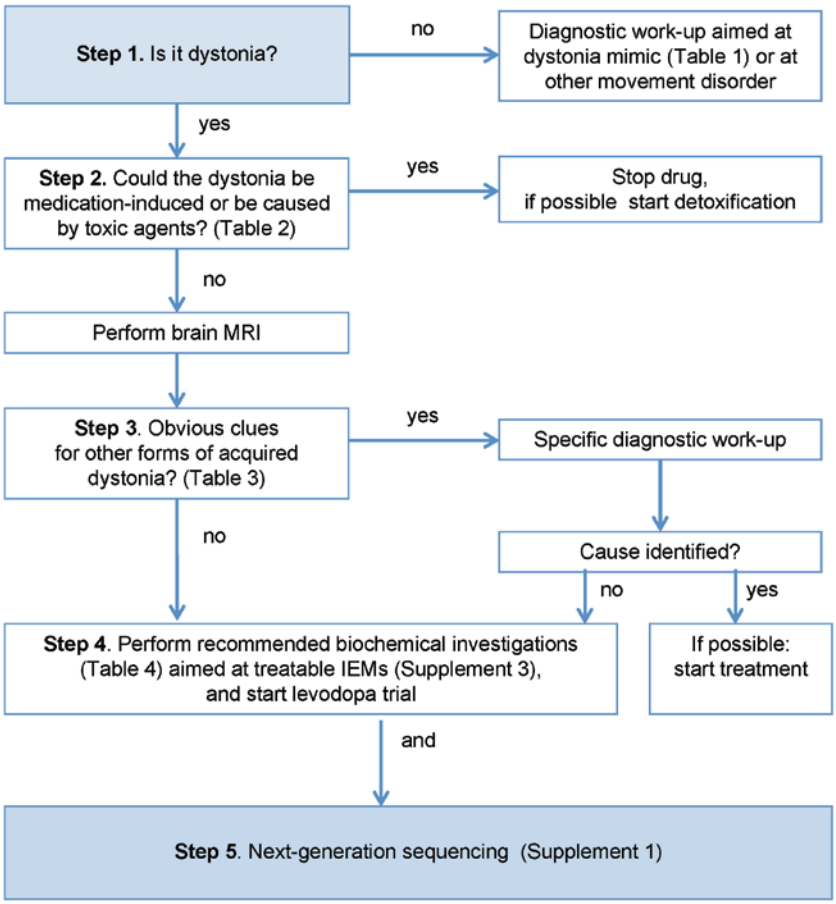
** CSF, cerebrospinal fluid. Lumbar puncture seems justified only in selected cases with a high clinical suspicion for these disorders.*

In addition to the laboratory investigations, we recommend that all patients receive a trial of levodopa with carbidopa.[30] The primary goal of the trial is diagnostic. However, an additional advantage is that levodopa can also give symptom relief in non-DRD dystonia.[39] The recommended starting dose of levodopa is 1 mg/kg/day, to be gradually increased until complete benefit or until dose-limiting side effects occur.[7] Most individuals respond to 4-5 mg/kg/day in divided doses.[40] Levodopa should be given for 3 months before considering the trial a failure.[39]

Step 5: NGS

Simultaneously with the biochemical investigations and the initiation of the levodopa trial, all possible genetic causes can be approached by using NGS diagnostic technologies. To facilitate this, we provide a list of DC associated genes (Supplement 1). For those cases that remain unsolved after NGS testing, referral to a tertiary referral center is recommended to further explore the possibilities to obtain an etiological diagnosis.

Figure 1. Diagnostic algorithm of dystonia in children and adolescents.



Discussion

We provide a comprehensive overview of DC and propose a new diagnostic algorithm (Figure 1). This five-step approach provides guidance for clinicians to determine which patients may benefit from innovative genetic tests and those for whom other investigations are required first, while taking into account the importance of early recognition of acquired and treatable causes of DC.

Our proposed flowchart (Figure 1) differs from existing algorithms in that certain commonly used processing steps have been omitted, such as age at onset, temporal pattern (eg, persistent or paroxysmal), associated features, and mode of inheritance.[2, 35, 36] Indeed, 'pattern recognition' based on these features has been important in the delineation of dystonia disorders and can still be successful in identifying classical phenotypes, especially by experts in the field.[1, 8] However, these features were not included in our algorithm because many clinicians will have limited experience with these rare disorders and specific clinical patterns will easily remain unrecognized. In addition, recent insights from more widely applied NGS testing demonstrate that the clinical heterogeneity of many disorders is much larger than expected,[23, 31] so clinical pattern recognition of milder, intermediate and unusual phenotypes remains problematic.

Nevertheless, careful clinical phenotyping still remains indispensable for two reasons. First, clinicians need to define, on the basis of these clinical parameters, the *a priori* risk that the patient is indeed suffering from a genetic disorder. NGS methodology should not be used when the *a priori* risk is low, because the numerous genes being tested increase the chance that variants will be misinterpreted as disease-causing, in genes that are unlikely to explain the clinical phenotype. Second, closely related to the first reason, detailed phenotyping is key when the results of NGS diagnostic strategies are available and need to be interpreted. As Hennekam and Biesecker[41] clearly stated, NGS and computers will not magically make patient diagnoses for us. Instead, there will be a shift from a pre-NGS-test differential diagnostic mode to a post-NGS-test diagnostic assessment mode.[41] Thus, the diagnostic skills of clinicians will be integrated into the evaluation of NGS test results, to make molecular diagnoses together with laboratory staff.

Notably, clinicians using NGS diagnostics should be aware that there are some technical pitfalls in the application of NGS diagnostics such as a limited ability to detect large structural rearrangements. In DC, this is particularly relevant if no causative mutation in a gene can be identified by NGS techniques, while at the same time the clinical picture is compatible with, for example, myoclonus dystonia or paroxysmal kinesigenic dyskinesia, both disorders that may be caused by deletions (in *SCGE* and *PRRT2*, respectively). In these cases, additional genetic tests detecting deletions are still required, such as multiplex ligation-dependent probe amplification or array comparative genomic hybridization (array-CGH).[42]

At present we live in a period of transition between emerging NGS diagnostic tests and changing costs, budgets and availability of diagnostic procedures. In the future, NGS tools will become increasingly available in many areas of clinical diagnostics and clinical decision-making, and will be incorporated in our daily work and change our daily routines. Although not a panacea, the advantages of this new strategy will be earlier diagnosis, avoidance of unnecessary investigations, and the possibility of genetic counselling for family members. It will crucially shorten the time DC patients and their families spend in uncertainty awaiting a definitive diagnosis.

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References

1 Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863-73.
2 Garcia-Cazorla A, Wolf NI, Serrano M, et al. Inborn errors of metabolism and motor disturbances in children. J Inherit Metab Dis. 2009;32(5):618-29.
3 Mink JW. Special concerns in defining, studying, and treating dystonia in children. Mov Disord. 2013;28(7):921-5.
4 Neveling K, Feenstra I, Gilissen C, et al. A post-hoc comparison of the utility of sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. Hum Mutat. 2013;34(12):1721-6.
5 de Ligt J, Willemsen MH, van Bon BW, et al. Diagnostic exome sequencing in persons with severe intellectual disability. N Engl J Med. 2012;367(20):1921-9.
6 Sanger TD, Chen D, Fehlings DL, et al. Definition and classification of hyperkinetic movements in childhood. Mov Disord. 2010;25(11):1538-49.
7 Jankovic HSSJMDGJ. Movement Disorders in Childhood. Philadelphia: Saunders: Elsevier 2010.
8 Donaldson I, Marsden CD, Schneider S, et al. Marsden's Book of Movement Disorders.
9 Defazio G, Hallett M, Jinnah HA, et al. Development and validation of a clinical guideline for diagnosing blepharospasm. Neurology. 2013;81(3):236-40.
10 Lin JP, Lumsden DE, Gimeno H, et al. The impact and prognosis for dystonia in childhood including dystonic cerebral palsy: a clinical and demographic tertiary cohort study. J Neurol Neurosurg Psychiatry. 2014;85(11):1239-44.
11 Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007;109:8-14.
12 Himmelmann K, McManus V, Hagberg G, et al. Dyskinetic cerebral palsy in Europe: trends in prevalence and severity. Arch Dis Child. 2009;94(12):921-6.
13 MacLennan A. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. (0959-8138 (Print)).
14 Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy: the European Cerebral Palsy Study. JAMA. 2006;296(13):1602-8.
15 Moreno-De-Luca A, Ledbetter Dh Fau - Martin CL, Martin CL. Genetic insights into the causes and classification of cerebral palsies. (1474-4465 (Electronic)).
16 Dale RC, Brilot F. Autoimmune basal ganglia disorders. J Child Neurol. 2012;27(11):1470-81.
17 Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10(1):63-74.
18 Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12(2):157-65.
19 Misra UK, Kalita J. Spectrum of movement disorders in encephalitis. J Neurol. 2010;257(12):2052-8.
20 van Karnebeek CD, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review. Mol Genet Metab. 2012;105(3):368-81.
21 Saudubray JM, Sedel F, Walter JH. Clinical approach to treatable inborn metabolic diseases: an introduction. J Inherit Metab Dis. 2006;29(2-3):261-74. 59
22 Deodato F, Boenzi S, Santorelli FM, et al. Methylmalonic and propionic aciduria. Am J Med Genet C Semin Med Genet. 2006;142C(2):104-12.
23 Pearson TS, Akman C, Hinton VJ, et al. Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS). Curr Neurol Neurosci Rep. 2013;13(4):342.

24 Taly AB, Meenakshi-Sundaram S, Sinha S, et al. Wilson disease: description of 282 patients evaluated over 3 decades. Medicine (Baltimore). 2007;86(2):112-21.
25 Stamelou M, Tuschl K, Chong WK, et al. Dystonia with brain manganese accumulation resulting from *SLC30A10* mutations: a new treatable disorder. Mov Disord. 2012;27(10):1317-22.
26 Patterson MC, Mengel E, Wijburg FA, et al. Disease and patient characteristics in NP- C patients: findings from an international disease registry. Orphanet J Rare Dis. 2013;8:12.
27 Lyseng-Williamson KA. Miglustat: a review of its use in Niemann-Pick disease type C. (1179-1950 (Electronic)).
28 Jankovic J. Treatment of dystonia. Lancet Neurol. 2006;5(10):864-72.
29 Tadic V, Kasten M, Bruggemann N, et al. Dopa-responsive dystonia revisited: diagnostic delay, residual signs, and nonmotor signs. Arch Neurol. 2012;69(12):1558-62.
30 Friedman J, Roze E, Abdenur JE, et al. Sepiapterin reductase deficiency: a treatable mimic of cerebral palsy. Ann Neurol. 2012;71(4):520-30.
31 Saunders-Pullman R, Raymond D, Stoessl AJ, et al. Variant ataxia-telangiectasia presenting as primary-appearing dystonia in Canadian Mennonites. Neurology. 2012;78(9):649.
32 Baschieri F, Batla A, Erro R, et al. Paroxysmal exercise-induced dystonia due to GLUT1 mutation can be responsive to levodopa: a case report. Journal of Neurology. 2014;261(3):615-6.
33 Keogh MJ, Daud D, Chinnery PF. Exome sequencing: how to understand it. Pract Neurol. 2013;13(6):399-407.
34 Zech M, Gross N, Jochim A, et al. Rare sequence variants in ANO3 and GNAL in a primary torsion dystonia series and controls. Mov Disord. 2014;29(1):143-7. 60
35 Assmann B, Surtees R, Hoffmann GF. Approach to the diagnosis of neurotransmitter diseases exemplified by the differential diagnosis of childhood-onset dystonia. Ann Neurol. 2003;54 Suppl 6:S18-24.
36 Gouider-Khouja N, Kraoua I, Benrhouma H, et al. Movement disorders in neuro- metabolic diseases. Eur J Paediatr Neurol. 2010;14(4):304-7.
37 Haliloglu G, Vezir E, Baydar L, et al. When do we need to perform a diagnostic lumbar puncture for neurometabolic diseases? Positive yield and retrospective analysis from a tertiary center. Turk J Pediatr. 2012;54(1):52-8.
38 Molero-Luis M, Serrano M, Ormazabal A, et al. Homovanillic acid in cerebrospinal fluid of 1388 children with neurological disorders. Dev Med Child Neurol. 2013;55(6):559-66.
39 Roubertie A, Mariani LL, Fernandez-Alvarez E, et al. Treatment for dystonia in childhood. Eur J Neurol. 2012;19(10):1292-9.
40 Thenganatt MA, Jankovic J. Treatment of dystonia. Neurotherapeutics. 2014;11(1):139-52.
41 Hennekam RC, Biesecker LG. Next-generation sequencing demands next-generation phenotyping. Hum Mutat. 2012;33(5):884-6.
42 Dale RC, Grattan-Smith P, Nicholson M, et al. Microdeletions detected using chromosome microarray in children with suspected genetic movement disorders: a single-centre study. Developmental Medicine & Child Neurology. 2012;54(7):618-23.

Supplement 1. *Overview of genes that may cause dystonia in children and adolescents*

Gene (OMIM)	Disease name/phenotype	Mode of inheritance
1: (Formerly called) Primary dystonias (DYTs):		
TOR1A (605204)	DYT1: Early-onset generalized primary torsion dystonia (PTD)	AD
TUBB4A (602662)	DYT4: Whispering dystonia	AD
GCH1 (600225)	DYT5: GTP-cyclohydrolase 1 deficiency	AD
THAP1 (609520)	DYT6: Adolescent onset torsion dystonia, mixed type	AD
PNKD/MR1 (609023)	DYT8: Paroxysmal nonkinesigenic dyskinesia	AD
SLC2A1 (138140)	DYT9/18: Paroxysmal choreoathetosis with episodic ataxia and spasticity/GLUT1 deficiency syndrome-1	AD
PRRT2 (614386)	DYT10: Paroxysmal kinesigenic dyskinesia	AD
SGCE (604149)	DYT11: Myoclonus-dystonia	AD
ATP1A3 (182350)	DYT12: Rapid-onset dystonia parkinsonism	AD
PRKRA (603424)	DYT16: Young-onset dystonia parkinsonism	AR
ANO3 (610110)	DYT24: Primary focal dystonia	AD
GNAL (139312)	DYT25: Primary torsion dystonia	AD
2: Inborn errors of metabolism:		
GCDH (608801)	Glutaric aciduria type 1	AR
PCCA (232000)	Propionic aciduria	AR
PCCB (232050)	Propionic aciduria	AR
MUT (609058)	Methylmalonic aciduria	AR
MMAA (607481)	Cobalamin A deficiency	AR
MMAB (607568)	Cobalamin B deficiency	AR
MMACHC (609831)	Cobalamin C deficiency	AR
C2orf25 (611935)	Cobalamin D deficiency	AR
MTRR (602568)	Cobalamin E deficiency	AR
LMBRD1 (612625)	Cobalamin F deficiency	AR
MTR (156570)	Cobalamin G deficiency	AR
CBS (613381)	Homocysteinuria	AR
PCBD (126090)	Hyperphelaninemia variant D	AR
TH (191290)	Tyrosine hydroxylase deficiency	AR
SPR (182125)	Sepiaterine reductase deficiency	AR
QDPR (612676)	Dihydropteridine reductase (DHPR) deficiency	AR
PTS (612719)	6-Pyruvoyltetra-hydropterin synthase (PTPS) deficiency	AR
DDC (107930)	Aromatic L-amino acid decarboxylase deficiency	AR
SLC19A3 (606152)	Thiamine transporter deficiency (formerly Biotin responsive basal ganglia disorder)	AR

GAMT (601240)	Guanidinoacetate methyltransferase deficiency	AR
GATM (602360)	Cerebral creatine deficiency syndrome 3 (AGAT deficiency)	AR
NPC1 (607623)	Niemann Pick type C	AR
NPC2 (601015)	Niemann Pick type C	AR
ATP7B (606882)	Wilson's disease	AR
SLC30A10 (611146)	Dystonia with brain manganese accumulation	AR
PDHA1 (300502)	Pyruvate dehydrogenase E1-alpha deficiency	XD
PDHX (608769)	Pyruvate dehydrogenase E3-binding protein deficiency	AR
PDHB (179060)	Pyruvate dehydrogenase E1-beta deficiency	AR
DLAT (608770)	Pyruvate dehydrogenase E2 deficiency	AR
PDP1 (605993)	Pyruvate dehydrogenase phosphatase deficiency	AR
LIAS (607031)	Pyruvate dehydrogenase lipoic acid synthetase deficiency	AR
BTD (609019)	Biotinidase deficiency	AR
GALT (606999)	Galactosemia	AR
ADCK3 (606980)	Coenzyme Q10 deficiency	AR
MTP (157147)	Abetalipoproteinemia (Bassen-Kornzweig syndrome)	AR
FOLR1 (136430)	Cerebral folate deficiency	AR
MOCS1 (603707)	Molybdenum cofactor (sulfite oxidase) deficiency type A	AR
OTC (300461)	Ornitine transcarbamylase deficiency	XR
HPRT2 (308000)	Lesch-Nyhan Syndrome	XR
ALDH5A1 (610045)	Succinic semialdehyde dehydrogenase deficiency	AR
SLC6A3 (126455)	Infantile parkinsonism-dystonia (Dopamine transporter deficiency)	AR
BCKDHA (608348)	Maple syrup urine disease type Ia	AR
BCKDHB (248611)	Maple syrup urine disease type Ib	AR
DBT (248610)	Maple syrup urine disease type II	AR
DLD (238331)	Dihydrolipoamide dehydrogenase deficiency (Maple syrup urine disease type III)	AR
ETHE1 (608451)	Ethylmalonic encephalopathy	AR
SLC6A8 (300036)	Cerebral creatinine deficiency syndrome 1	XR
SLC6A9 (608893)	Hartnup disorder	AR
SERAC1 (614725)	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome (MEGDEL)	AR
SUOX (606887)	Sulfocysteinuria	AR
FUCA1 (612280)	Fucosidosis	AR
GLB1 (611458)	GM1-gangliosidosis	AR
HEXA (606869)	Tay-Sachs disease (GM2-gangliosidosis type 1)	AR
HEXB (606873)	Sandhoff disease (GM2-gangliosidosis type 2)	AR
CLN3 (607042)	Neuronal ceroid lipofuscinosis 3 (Batten disease)	AR

TPP1 (607998)	Neuronal ceroid lipofuscinosis 2	AR
ARSA (6007574)	Metachromatic leukodystrophy (Arylsulfatase A deficiency)	AR
SLC16A2 (300095)	Allan-Herndon-Dudley syndrome (monocarboxylate transporter-8 (MCT8) deficiency)	XD
2.1 Mitochondrial disorders:		
POLG (174763)	Alpers/MNGIE/SANDO (Mitochondrial DNA depletion syndrome 4)	AR
SUCLA2 (603921)	Mitochondrial DNA depletion syndrome 5	AR
MPV17 (137960)	Mitochondrial DNA depletion syndrome 6 (hepatocerebral type)	AR
C2orf10 (606075)	Mitochondrial DNA depletion syndrome 7 (hepatocerebral type)	AR
NDUFS1 (157655)	Mitochondrial complex I deficiency	AR
NDUFS3 (603846)	Mitochondrial complex I deficiency	AR
NDUFS4 (602694)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFS7 (601825)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUSF8 (602141)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFA2 (602137)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFA9 (603834)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFA10 (603835)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFA12 (614530)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFAF2 (609653)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFAF5 (612360)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFAF6 (C8orf38) (612392)	Mitochondrial complex I deficiency/Leigh syndrome	AR
FOXRED1 (613622)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFV1 (161015)	Mitochondrial complex I deficiency/infantile bilateral striatal necrosis	AR
SDHA (600857)	Mitochondrial complex II deficiency (Succinate dehydrogenase deficiency)	AR
SDHAF1 (612848)	Mitochondrial complex II deficiency (Succinate dehydrogenase assembly factor 1 deficiency)	AR
BCS1L (603647)	Mitochondrial complex III deficiency/Leigh syndrome	AR
COX10 (602125)	Mitochondrial complex IV deficiency/Leigh syndrome	AR
COX15 (603646)	Mitochondrial complex IV deficiency/Leigh syndrome	AR
COX20 (614698)	Mitochondrial complex IV deficiency	AR
SURF1 (185620)	Mitochondrial complex IV deficiency/Leigh syndrome	AR
TACO1 (612958)	Mitochondrial complex IV deficiency/Leigh syndrome	AR
MTATP6 (516060)	Mitochondrial complex V deficiency/Leigh syndrome	Mitochondrial
MTND1 (516000)	Leber optic atrophy and dystonia	Mitochondrial
MTND3 (516002)	Leber optic atrophy and dystonia	Mitochondrial
MTND1 (516003)	Leber optic atrophy and dystonia	Mitochondrial
MTND1 (516006)	Leber optic atrophy and dystonia	Mitochondrial

MTATP6 (516060)	Mitochondrial infantile striatonigral degeneration	Mitochondrial
3 Other disorders, including neurodegenerative diseases:		
PANK2 (606157)	Neurodegeneration with brain iron accumulation (NBIA) 1/HARP	AR
PLA2G6 (603604)	Neurodegeneration with brain iron accumulation (NBIA) 2/PARK14	AR
FTL (134790)	Neurodegeneration with brain iron accumulation (NBIA) 3	AD
C19orf12 (614297)	Neurodegeneration with brain iron accumulation (NBIA) 4	AR
Wdr45 (300894)	Neurodegeneration with brain iron accumulation (NBIA) 5	XD
CYP27A1 (606530)	Cerebrotendinous xanthomatosis	AR
PLP1 (300401)	Pelizaeus-Merzbacher disease	XR
MTP (157147)	Abetalipoproteinemia (Bassen-Kornzweig syndrome)	AR
FA2H (611026)	Spastic paraplegia type 35	AR
ATP13A2 (610513)	Kufor-Rakeb syndrome (PARK9)	AR
PRKN (602544)	Juvenile Parkinson disease type 2 (PARK2)	AR
PINK1 (608309)	Early onset Parkinson disease type 6 (PARK6)	AR
DJ1 (602533)	Early onset Parkinson disease type 7 (PARK7)	AR
FBXO7 (605648)	Early onset Parkinson disease type 15 (PARK15)	AR
SYNJ1 (604297)	Early-onset atypical parkinsonism (PARK20)	AR
SPG11 (610844)	Spastic paraplegia type 11	AR
AP4B1 (607245)	Spastic paraplegia type 47	AR
TREX1 (606609)	Aicardi-Goutieres syndrome 1	AR,AD
RNASEH2B (610362)	Aicardi-Goutieres syndrome 2	AR
RNASEH2C (610330)	Aicardi-Goutieres syndrome 3	AR
RNASEH2A (606034)	Aicardi-Goutieres syndrome 4	AR
SAMHD1 (606754)	Aicardi-Goutieres syndrome 5	AR
ADAR1 (146920)	Aicardi-Goutieres syndrome 6	AR,AD
NUP62 (605815)	Infantile striatonigral degeneration	AR
NKX2-1/TITF1 (600635)	Benign hereditary chorea	AD
ATM (607585)	Ataxia-Telangiectasia	AR
VPS13A (605978)	Choreoacanthocytosis	AR
COL4A1 (120130)	Porencephaly 1	AD
SEPSECS (613009)	Pontocerebellar hypoplasia type 2D	AR
CTC1 (613129)	Cerebroretinal microangiopathy with calcifications and cysts (CRMCC) (Coats plus syndrome)	AR
ALSIN (606352)	Juvenile amyotrophic lateral sclerosis 2	AR
TIMM8A (300356	Mohr-Tranebjaerg syndrome (Dystonia deafness syndrome	XR
BTK (300300)	X-linked agammaglobulinemia with hearing impairment, dystonia-parkinsonism, and progressive neurodegeneration	XR
BCAP31(300398)	Deafness, dystonia and central hypomyelination	XR

OPA3 (606580)	Optic atrophy with early onset pyramidal tract signs and dystonia	AR
ACTB (102630)	Juvenile onset dystonia	AD
ARFGEF2 (605371)	Periventricular nodular heterotopia and dystonia	AR
GRIK2 (138244)	Intellectual disability, behavioral disorder, epilepsy and dystonia	AR
HTT (613004)	Huntington disease	AD
C2orf37/DCAF17 (612515)	Woodhouse Sakati syndrome	AR
MECP2 (300005)	Rett syndrome	XD
FOXG1 (164874)	Rett syndrome, congenital variant	de novo
ARX (300382)	Partington syndrome/X-linked mental retardation	XR
ATN1 (607462)	Dentatorubral-pallidoluysian atrophy	AD
CACNA1B (601012)	Myoclonus-Dystonia-like syndrome with cardiac arrhythmias	AD

Abbreviations: AR, Autosomal recessive, AD, Autosomal dominant, XR, X-linked recessive, XD, X-linked dominant

Supplement 2. *Search criteria systematic review*

We reviewed all papers regarding dystonia, both genetic and non-genetic, in three age groups (infancy, childhood and adolescence), which is from birth to 20 years of age.[1] The key terms we used were "dystonia" combined with (synonyms of) "children", "childhood", "adolescence" and "early onset", as well as (synonyms of) terms indicating possible etiologies including "genetic", "acquired", "primary", "secondary", "heredodegenerative", "hereditary", and "inborn errors of metabolism". All reviewed papers and abstracts were presented in English.

We considered using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for selecting papers, developed by Whiting and colleagues (see Supplemental references). However, this tool proved not to be applicable as disorders causing dystonia of childhood are rare and the available evidence consisted only of small clinical trials, case series and expert opinion. For the same reason, not all items of the PRISMA Checklist (Supplement 6) are applicable.

Study selection: included literature and associated references involved at least one adequate description of: symptoms, signs, laboratory investigations (including metabolic evaluation), neuroimaging or genetic analysis, with supporting evidence for the etiological diagnosis. Included literature concerned at least two patients with the same condition, presenting with dystonia as an isolated, prominent or presenting symptom. Further references were retrieved manually from reference lists. Text books, Online Mendelian Inheritance in Man (OMIM) and GeneReviews were used for overviews of possible causes of dystonia. The list of genes (Supplement 1) is based on a detailed literature search up to October 20th 2014). The final reference list was generated on the basis of originality and relevance to the topic.

Key electronic search strategy for PubMed:
(dyston* AND (child* OR pediatric OR adolescent* OR (early onset) OR (early-onset))) AND (genetic OR primary OR hereditary OR heredodegenerative OR acquired OR secondary OR (inborn errors of metabolism))
Filters activated: Humans, English.

Supplement 3. *Treatable inborn errors of metabolism with dystonia as important feature*

IEM	Gene (OMIM)	Characteristic features besides dystonia	Treatment
Glutaric aciduria type 1	*GCDH* (608801)	Macrocephaly, developmental retardation, cardiomyopathy, encephalopathic crisis	Lysine restriction, carnitine suppletion, emergency treatment during intercurrent illness
Propionic aciduria	*PCCA* (232000) / *PCCB* (232050)	Developmental retardation, encephalopathic crisis, optic nerve atrophy, cardiomyopathy, alopecia, pancytopenia, (pseudo-) diabetes	Dietary protein restriction, carnitine suppletion emergency treatment during intercurrent illness
Methylmalonic aciduria	*MUT* (609058)	Developmental retardation, encephalopathic crisis, renal insufficiency, alopecia, pancytopenia, (pseudo-) diabetes	Dietary protein restriction, carnitine suppletion emergency treatment during intercurrent illness
Cobalamin A deficiency	*MMAA* (607481)	Developmental delay, recurrent vomiting, ataxia, spasticity, pancytopenia	Hydroxocobalamin, protein restriction
Cobalamin B deficiency	*MMAB* (607568)	Developmental delay, recurrent vomiting, ataxia, spasticity, hepatomegaly, pancytopenia	Hydroxocobalamin, protein restriction
Cobalamin C deficiency	*MMACHC* (609831)	SGA, microcephaly, failure to thrive, anemia, developmental delay, abnormal retinal pigmentation, seizures, psychiatric disease	Hydroxocobalamin
Cobalamin D deficiency	*C2orf25*(611935)	Developmental delay, intellectual disability, anemia, ataxia, nystagmus, behavior problems	Hydroxo- / cyanocobalamin
Cobalamin E deficiency	*MTRR* (602568)	Developmental delay, intellectual disability, megaloblastic anemia, failure to thrive, ataxia, seizures, blindness	Hydroxo- / methylcobalamin, Betaine
Cobalamin F deficiency	*LMBRD1* (612625)	Developmental delay, intellectual disability, failure to thrive, frequent infections: stomatitis, ataxia, spasticity, pancytopenia	Hydroxocobalamin

Cobalamin G deficiency	*MTR* (156570)	Developmental delay, intellectual disability, megaloblastic anemia, failure to thrive, ataxia, seizures	Hydroxo- / methylcobalamin, Betaine
Homocysteinuria	*CBS* (613381)	Mental retardation, behavioral disturbances, marfan-like appearance, myopia, ectopia lentis, osteoporosis, thromboembolic events	Methionine restriction, Betaine in some cases Pyridoxine
GTPCH1-deficiency (Segawa disease)	*GCH1* (600225)	Diurnal fluctuation, hypokinetic-rigid syndrome, psychiatric disorders	Levodopa-carbidopa (marked response)
Tyrosine hydroxylase deficiency	*TH* (191290)	Developmental delay, hypokinetic-rigid syndrome, diurnal fluctuation, oculogyric crises, autonomic disturbance	Levodopa
Sepiapterin reductase deficiency	*SPR* (182125)	Developmental delay, intellectual disability, diurnal variation, oculogyric crises, hypotonia, autonomic disturbance	Levodopa-carbidopa, 5-hydroxytryptophan
Dihydropteridine reductase (DHPR) deficiency	*QDPR* (612676)	Progressive developmental delay, seizures, microcephaly, parkinsonism	Levodopa-carbidopa, 5-hydroxytryptophan Tetrahydrobiopterin, Folinic acid, Phe-restricted diet
6-Pyruvoyltetra-hydropterin synthase (PTPS) deficiency	*PTS* (612719)	Developmental delay, seizures, microcephaly, parkinsonism, hypersalivation	Tetrahydrobiopterin, Levodopa/carbidopa, 5-hydroxytryptophan
Aromatic L-amino acid decarboxylase deficiency	*DDC* (107930)	Developmental delay, oculogyric crises, hypotonia, autonomic symptoms	Levodopa / dopamine agonists, pyridoxine, MAO inhibitors (therapy only effective in a minority of patients)
GLUT-1 deficiency	*SLC2A1* (138140)	Paroxysmal dyskinesias, epilepsy, psychomotor retardation, spasticity, ataxia, microcephaly	Ketogenic diet
Galactosemia	*GALT* (606999)	Failure to thrive, food intolerance, hepatomegaly, jaundice, cataract	Lactose restricted diet
Thiamine transporter deficiency (formerly Biotin responsive basal ganglia disorder)	*SLC19A3* (606152)	Subacute encephalopathy, dysarthria, and dysphagia, severe rigidity, quadriparesis	Thiamine and Biotin

Guanidinoacetate methyltransferase deficiency	*GAMT* (601240)	Intellectual disability, seizures, autistic behavior, hypotonia	Creatine, Ornithine, dietary arginine restriction
Cerebral creatine deficiency syndrome 3 (AGAT deficiency)	*GATM* (602360)	Mental retardation with severe delay of speech, myopathy causing muscle weakness, failure to thrive	Oral creatine suppletion
Niemann Pick type C	*NPC1* (607623) / *NPC2* (601015)	Dementia, psychiatric symptoms, epilepsy, ataxia, supranuclear vertical gaze palsy, cholestatic icterus, liver failure	Miglustat
Wilson's disease	*ATP7B* (606882)	Chronic liver disease, Kayser-Fleischer rings, cardiomyopathy, hemolysis	Zinc, Tetrathiomolybdate
Dystonia with brain manganese accumulation	*SLC30A10* (611146)	Chronic liver disease, polycythemia, parkinsonism, hypermanganesaemia	Chelation with intravenous disodium calcium edentate, Ferro fumarate
Pyruvate dehydrogenase complex (PDC) deficiency *(Mostly X-linked)*	*PDHA1* (300502) *PDHX* (608769) *PDHB* (179060) *DLAT* (608770) *PDP1* (605993) *LIAS* (607031)	Mental retardation, hypotonia, hypertonia, seizures, microcephaly, ataxia	Thiamine, ketogenic diet, dichloroacetate (DCA)
Biotinidase deficiency	*BTD* (609019)	Developmental delay, seizures, hypotonia, ataxia, vision and hearing problems, cutaneous abnormalities	Biotin
Coenzyme Q10 deficiency	*ADCK3* (606980)	Ataxia, exercise intolerance, seizures.	Coenzyme Q10
Cerebrotendinous xanthomatosis	CYP27A1 (606530)	Diarrhea, cataract, tendon xanthomas, neuropsychiatric symptoms, spasticity	Chenodeoxycholic acid
Abetalipoproteinemia (Bassen-Kornzweig syndrome)	*MTP* (157147)	Fat malabsorbtion, retinitis pigmentosa, ataxia, acathocythosis	Vitamin E, fat reduced diet
Ataxia with Vitamin E Deficiency (AVED)	*TTPA* (600415)	Ataxia, areflexia, loss of proprioception, dysdiadochokinesiahead titubation, decreased visual acuity	Vitamin E (alpha-tocopherol)
Cerebral folate deficiency	*FOLR1* (136430)	Epileptic seizures, mental retardation,	Folinic acid

Molybdenum cofactor (sulfite oxidase) deficiency type A	*MOCS1* (603707)	Intractable neonatal seizures, developmental delay, feeding difficulties, lens dislocation	Cyclic PMP
Ornitine transcarbamylase deficiency *(X-linked)*	*OTC* (300461)	Mental retardation, episodic lethargy and irritability, coma, ataxia.	Protein restricted diet with arginine supplementation, sodium benzoate
Maple syrup urine disease (type I and II)	*BCKDHA* (608348) / *BCKDHB* (248611) / *DBT* (248610)	Neonatal encephalopathy, ataxia, intercurrent illness	Leucine restricted diet, in some patients thiamine suppletion

Supplement 4. *Supplemental references*

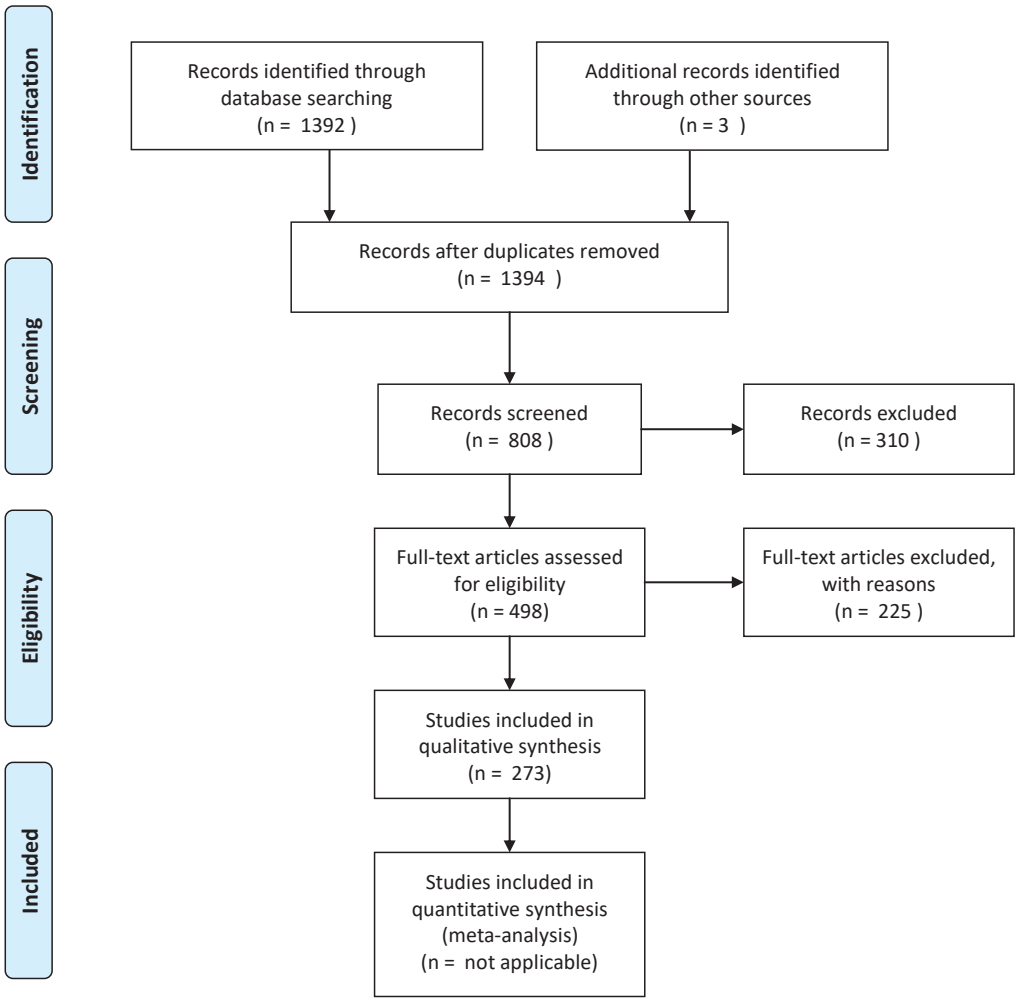
- Alarcon F, Maldonado JC, Rivera JW. Movement disorders identified in patients with intracranial tuberculomas. Neurologia. 2011;26(6):343-50.
- Alarcon F, Duenas G, Cevallos N, et al. Movement disorders in 30 patients with tuberculous meningitis. Mov Disord. 2000;15(3):561-9.
- Angelini L, Rumi V, Nardocci N, et al. Hemidystonia symptomatic of primary antiphospholipid syndrome in childhood. Mov Disord. 1993;8(3):383-6.
- Armangue T, Titulaer MJ, Malaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr. 2013;162(4):850-6 e2.
- Ashtekar CS, Jaspan T, Thomas D, et al. Acute bilateral thalamic necrosis in a child with Mycoplasma pneumoniae. Dev Med Child Neurol. 2003;45(9):634-7.
- Baizabal-Carvallo JF, Jankovic J. Movement disorders in autoimmune diseases. Mov Disord. 2012;27(8):935-46.
- Balint B, Bhatia KP. Dystonia: an update on phenomenology, classification, pathogenesis and treatment. Curr Opin Neurol. 2014;27(4):468-76.
- Bardon-Cancho EJ, Munoz-Jimenez L, Vazquez-Lopez M, et al. Periventricular nodular heterotopia and dystonia due to an *ARFGEF2* mutation. Pediatr Neurol. 2014;51(3):461-4.
- Basumatary LJ, Raja D, Bhuyan D, et al. Clinical and radiological spectrum of Japanese encephalitis. J Neurol Sci. 2013;325(1-2):15-21.
- Bax M, Goldstein M, Rosenbaum P, et al. Proposed definition and classification of cerebral palsy, April 2005. Dev Med Child Neurol. 2005;47(8):571-6.
- Bejot Y, Giroud M, Moreau T, et al. Clinical spectrum of movement disorders after stroke in childhood and adulthood. Eur Neurol. 2012;68(1):59-64.
- Bhatjiwale MG, Polkey C, Cox TC, - Dean A, et al. Rasmussen's encephalitis: neuroimaging findings in 21 patients with a closer look at the basal ganglia. (1016-2291 (Print)).
- Bressman SB, Saunders-Pullman R. Primary dystonia: moribund or viable. Mov Disord. 2013;28(7):906-13.
- Brockmann K. Episodic movement disorders: from phenotype to genotype and back. Curr Neurol Neurosci Rep. 2013;13(10):379.
- Burbaud P, Berge J, Lagueny A, et al. Delayed-onset hemidystonia secondary to herpes zoster ophthalmicus-related intracerebral arteritis in an adolescent. J Neurol. 1997;244(7):470-2.
- Cambonie G, Houdon L, Rivier F, et al. Infantile bilateral striatal necrosis following measles. Brain Dev. 2000;22(4):221-3.
- Cardoso F. Movement disorders in childhood. Parkinsonism Relat Disord. 2014;20 Suppl 1:S13-6.
- Carroll E, Sanchez-Ramos J. Hyperkinetic movement disorders associated with HIV and other viral infections. Handb Clin Neurol. 2011;100:323-34.
- Chakrabarti S, Chand PK. Lithium - induced tardive dystonia. Neurol India. 2002;50(4):473-5.
- Charlesworth G, Bhatia KP. Primary and secondary dystonic syndromes: an update. Curr Opin Neurol. 2013;26(4):406-12.
- Charlesworth G, Bhatia KP, Wood NW. The genetics of dystonia: new twists in an old tale. Brain. 2013;136(Pt 7):2017-37.
- Cheyette BN, Cheyette SN, Cusmano-Ozog K, et al. Dopa-responsive dystonia presenting as delayed and awkward gait. Pediatr Neurol. 2008;38(4):273-5.
- Choi IS, Cheon HY. Delayed movement disorders after carbon monoxide poisoning. Eur Neurol. 1999;42(3):141-4.
- Clardy SL, Lennon VA, Dalmau J, et al. Childhood onset of stiff-man syndrome. JAMA Neurol. 2013;70(12):1531-6.

- Cordoba M, Rodriguez S, Gonzalez Moron D, et al. Expanding the spectrum of Grik2 mutations: intellectual disability, behavioural disorder, epilepsy and dystonia. Clin Genet. 2015;87(3):293-5.
- Derinoz O, Caglar AA. Drug-induced movement disorders in children at paediatric emergency department: 'dystonia'. Emerg Med J. 2013;30(2):130-3.
- Dill P, Wagner M, Somerville A, et al. Child neurology: paroxysmal stiffening, upward gaze, and hypotonia: hallmarks of sepiapterin reductase deficiency. Neurology. 2012;78(5):e29-32.
- Domingo A, Schmidt TG, Barcelon E, et al. X-linked agammaglobulinemia with hearing impairment, dystonia-parkinsonism, and progressive neurodegeneration. J Neurol. 2014;261(11):2225-7.
- Fahn S, Bressman SB, Marsden CD. Classification of dystonia. Adv Neurol. 1998;78:1-10.
- Fell JM, Reynolds AP, Meadows N, et al. Manganese toxicity in children receiving long-term parenteral nutrition. Lancet. 1996;347(9010):1218-21.
- Fernandez-Alvarez E. Dystonia. The paediatric perspective. Eur J Neurol. 2010;17 Suppl 1:46- 51.
- Fletcher NA, Thompson PD, Scadding JW, et al. Successful treatment of childhood onset symptomatic dystonia with levodopa. J Neurol Neurosurg Psychiatry. 1993;56(8):865-7.
- Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol. 2009;66(1):11-8.
- Franquet E, Salvado-Figueres M, Lorenzo-Bosquet C, et al. Nigrostriatal pathway dysfunction in a methanol-induced delayed dystonia-parkinsonism. Mov Disord. 2012;27(10):1220-1.
- Frucht S. Dystonia, athetosis, and epilepsia partialis continua in a patient with late-onset Rasmussen's encephalitis. Mov Disord. 2002;17(3):609-12.
- Fuchs T, Ozelius LJ. Genetics of dystonia. Semin Neurol. 2011;31(5):441-8.
- Fung VS, Jinnah HA, Bhatia K, et al. Assessment of patients with isolated or combined dystonia: an update on dystonia syndromes. Mov Disord. 2013;28(7):889-98.
- Geller RJ, Barthold C, Saiers JA, et al. Pediatric cyanide poisoning: causes, manifestations, management, and unmet needs. Pediatrics. 2006;118(5):2146-58.
- Goenka A, Michael BD, Ledger E, et al. Neurological manifestations of influenza infection in children and adults: results of a National British Surveillance Study. Clin Infect Dis. 2014;58(6):775-84.
- Gollomp SM, Fahn S. Transient dystonia as a complication of varicella. J Neurol Neurosurg Psychiatry. 1987;50(9):1228-9.
- Groen JL, Andrade A, Ritz K, et al. CACNA1B mutation is linked to unique myoclonus-dystonia syndrome. Hum Mol Genet. 2015;24(4):987-93.
- Head RA, de Goede CG, Newton RW, et al. Pyruvate dehydrogenase deficiency presenting as dystonia in childhood. Dev Med Child Neurol. 2004;46(10):710-2.
- Hsieh BH, Deng JF, Ger J, et al. Acetylcholinesterase inhibition and the extrapyramidal syndrome: a review of the neurotoxicity of organophosphate. Neurotoxicology. 2001;22(4):423-7.
- Kirkham FJ, Haywood P, Kashyape P, et al. Movement disorder emergencies in childhood. Eur J Paediatr Neurol. 2011;15(5):390-404.
- Klein C. Genetics in dystonia. Parkinsonism Relat Disord. 2014;20 Suppl 1:S137-42.
- Krageloh-Mann I. Imaging of early brain injury and cortical plasticity. Exp Neurol. 2004;190 Suppl 1:S84-90.
- Lohmann K, Klein C. Genetics of dystonia: what's known? What's new? What's next? Mov Disord. 2013;28(7):899-905.
- Mahajan P, Lieh-Lai MW, Sarnaik A, et al. Basal ganglia infarction in a child with disulfiram poisoning. Pediatrics. 1997;99(4):605-8.
- Manoli I SJ, Venditti CP. Isolated Methylmalonic Acidemia. In: Adam MP AH, Pagon RA, ed. GeneReviews. Seattle 2005. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1231/

- Mariotti P, Nociti V, Stefanini MC, et al. Pneumonia's link with the head and heart. Lancet. 2010;376(9738):388.
- Mejia NI, Jankovic J. Tardive dyskinesia and withdrawal emergent syndrome in children. Expert Rev Neurother. 2010;10(6):893-901.
- Mengel E, Klunemann HH, Lourenco CM, et al. Niemann-Pick disease type C symptomatology: an expert-based clinical description. Orphanet J Rare Dis. 2013;8:166.
- Merskey H BN. Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 2 ed. Seattle,WA: IASP Press 1994.
- Micheli R, Perini A, Duse M. Hemidystonia secondary to acquired toxoplasmosis in a non- immunodeficient patient. Eur J Pediatr. 1994;153(10):731-3.
- Mink JW. Dopa-responsive Dystonia in Children. Curr Treat Options Neurol. 2003;5(4):279- 82.
- Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295-306.
- Moghimi N, Jabbari B, Szekely AM. Primary dystonias and genetic disorders with dystonia as clinical feature of the disease. Eur J Paediatr Neurol. 2014;18(1):79-105.
- Mohammad SS, Ramanathan S, Brilot F, et al. Autoantibody-associated movement disorders. Neuropediatrics. 2013;44(6):336-45.
- Murakami A, Morimoto M, Adachi S, et al. Infantile bilateral striatal necrosis associated with human herpes virus-6 (HHV-6) infection. Brain Dev. 2005;27(7):527-30.
- Nardocci N, Zorzi G, Grisoli M, et al. Acquired hemidystonia in childhood: a clinical and neuroradiological study of thirteen patients. Pediatr Neurol. 1996;15(2):108-13.
- Netravathi M, Pal PK, Indira Devi B. A clinical profile of 103 patients with secondary movement disorders: correlation of etiology with phenomenology. Eur J Neurol. 2012;19(2):226-33.
- Neville B. Congenital DOPA-responsive disorders: a diagnostic and therapeutic challenge to the cerebral palsies? Dev Med Child Neurol. 2007;49(2):85.
- Nygaard TG, Waran SP, Levine RA, et al. Dopa-responsive dystonia simulating cerebral palsy. Pediatr Neurol. 1994;11(3):236-40.
- Papapetropoulos S, Singer C, Sengun C, et al. Giant arteriovenous malformation presenting as pediatric
- task-specific dystonia. Neurology. 2008;70(15):1294.
- Przekop A, Sanger TD. Birth-related syndromes of athetosis and kernicterus. Handb Clin Neurol. 2011;100:387-Raut TP, Singh MK, Garg RK, et al. Evolution of certain typical and atypical features in a case of subacute sclerosing panencephalitis. BMJ Case Rep. 2012;2012.
- Ramos VF, Karp BI, Hallett M. Tricks in dystonia: ordering the complexity. J Neurol Neurosurg Psychiatry. 2014;85(9):987-93.
- Sazgar M, Robinson JL, Chan AK, et al. Influenza B acute necrotizing encephalopathy: a case report and literature review. Pediatr Neurol. 2003;28(5):396-9.
- Schneider SA, Bhatia KP. Secondary dystonia-clinical clues and syndromic associations. J Mov Disord. 2009;2(2):58-63.
- Scott BL, Jankovic J. Delayed-onset progressive movement disorders after static brain lesions. Neurology. 1996;46(1):68-74.
- Shiraishi K, Higuchi Y, Ozawa K. Dystonia in a 13-year-old boy with secondary progressive multiple sclerosis. Brain Dev. 2004;26(8):539-41.
- Smithers-Sheedy H, Badawi N, Blair E, et al. What constitutes cerebral palsy in the twenty- first century? Dev Med Child Neurol. 2014;56(4):323-8.
- Suarez-Lopez JR, Himes JH, Jacobs DR, Jr., et al. Acetylcholinesterase activity and neurodevelopment in boys and girls. Pediatrics. 2013;132(6):e1649-58.

- Sugimoto T, Woo M, Nishida N, et al. When do brain abnormalities in cerebral palsy occur? An MRI study. Dev Med Child Neurol. 1995;37(4):285-92.
- Surveillance of Cerebral Palsy in E. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). Dev Med Child Neurol. 2000;42(12):816-24.
- Tenembaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: a long-term follow-up study of 84 pediatric patients. Neurology. 2002;59(8):1224-31.
- Tse W, Cersosimo MG, Gracies JM, et al. Movement disorders and AIDS: a review. Parkinsonism Relat Disord. 2004;10(6):323-34.
- Uc EY, Rodnitzky RL. Childhood dystonia. Semin Pediatr Neurol. 2003;10(1):52-61.
- Usmani N, Bedi G, Lam BL, et al. Association between paroxysmal tonic spasms and neuromyelitis optica. Arch Neurol. 2012;69(1):121-4.
- Valenzuela R, Court J, Godoy J. Delayed cyanide induced dystonia. J Neurol Neurosurg Psychiatry. 1992;55(3):198-9.
- Willemsen MA, Verbeek MM, Kamsteeg EJ, et al. Tyrosine hydroxylase deficiency: a treatable disorder of brain catecholamine biosynthesis. Brain. 2010;133(Pt 6):1810-22.
- Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.
- Woolf AD, Wynshaw-Boris A, Rinaldo P, et al. Intentional infantile ethylene glycol poisoning presenting as an inherited metabolic disorder. J Pediatr. 1992;120(3):421-4.
- Woolf A, Wright R, Amarasiriwardena C, et al. A child with chronic manganese exposure from drinking water. Environ Health Perspect. 2002;110(6):613-6.
- Zuliani L, Graus F, Giometto B, et al. Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. J Neurol Neurosurg Psychiatry. 2012;83(6):638-45.

Supplement 5. *Prisma flow chart*



Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	NA*
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4, 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	NA
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Suppl 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Suppl 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Suppl 2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	NA
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	NA
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Suppl 5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	NA
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	NA
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23, 24, 25
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

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A post-hoc study on gene panel analysis for the diagnosis of dystonia

Chapter 4

M.E. van Egmond*, C.H.A. Lugtenberg*, O.F. Brouwer, M.F. Contarino, V.S.C. Fung, M.R. Heiner-Fokkema, J.J. van Hilten, A.H. van der Hout, K.J. Peall, R.J. Sinke, E. Roze, C.C. Verschuuren-Bemelmans, M.A. Willemsen, N.I. Wolf, M.A.J. Tijssen, T.J. de Koning

*Shared first authors

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Abstract

Background

Genetic disorders causing dystonia show great heterogeneity. Recent studies have suggested that next-generation sequencing techniques, such as gene panel analysis, can be effective in diagnosing heterogeneous conditions. The objective of this study was to investigate whether dystonia patients with a suspected genetic cause could benefit from the use of gene panel analysis.

Methods

In this post-hoc study, we describe gene panel analysis results of 61 dystonia patients (mean age 31 years, 72% young-onset) in our tertiary referral center. The panel covered 94 dystonia-associated genes. As comparison with a historic cohort was not possible because of the rapidly growing list of dystonia genes, we compared the diagnostic workup with and without gene panel analysis in the same patients. The workup without gene panel analysis (control group) included theoretical diagnostic strategies formulated by independent experts in the field, based on detailed case descriptions. The primary outcome measure was diagnostic yield, secondary measures were cost and duration of diagnostic workup.

Results

Workup with gene panel analysis led to a confirmed molecular diagnosis in 14.8%, versus 7.4% in the control group ($P = 0.096$). In the control group on average 3 genes/case were requested. The mean costs were lower in the gene panel analysis group (€1822/case) than in the controls (€2660/case). The duration of workup was considerably shorter with gene panel analysis (28 vs 102 days).

Conclusions

Gene panel analysis facilitates molecular diagnosis in complex cases of dystonia, with a good diagnostic yield (14.8%), a quicker diagnostic workup, and lower costs, representing a major improvement for patients and their families.

Introduction

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements or postures, or both. Dystonic movements are typically patterned and twisting, and may be tremulous. They are often initiated or worsened by voluntary action and associated with overflow muscle activation.[1] The clinical evaluation of a patient with dystonia is a stepwise process, beginning with classification of the dystonia characteristics according to the latest consensus criteria and recognition of the dystonia syndrome; this, in turn, may lead to a targeted etiological differential diagnosis.[2]

There is a long list of causes of dystonia,[3, 4] whereas clinical clues for a genetic form include a positive family history and young-onset in the absence of an acquired cause.[5] A complex clinical picture comprising both neurological and non-neurological features is considered an important clue for an inborn error of metabolism.[6] The genetic disorders associated with dystonia are often clinically heterogeneous, with milder or atypical phenotypes that may easily remain unrecognized. The diagnostic workup of dystonia can therefore be challenging and time-consuming, and poses a burden on patients and their families.

It has become possible to analyze thousands of genes simultaneously, because next generation sequencing (NGS) techniques have been introduced into clinical diagnostics.[6, 7] Several studies suggest that NGS diagnostic strategies can be particularly effective in diagnosing heterogeneous conditions, including movement disorders.[8-11] One of these NGS techniques is targeted gene panel analysis (GPA), which comprises testing a preselected list (or panel) of genes. Compared with other NGS techniques, such as whole genome- and whole exome sequencing, the cost of GPA is lower and it provides a higher coverage and fewer unsolicited findings. GPA is therefore a good strategy to scan panels of multiple candidate genes and it is especially suitable for diagnostic purposes.[11, 12]

Despite a strong tendency to advocate the advantages of NGS testing, there is no evidence as yet that NGS approaches perform better than conventional diagnostic strategies for dystonic patients in clinical practice. In cases with an easily recognizable, classical phenotype, NGS techniques have limited added value so single gene testing is recommended.[9] However, in many dystonia cases in which several potentially causal genes are being considered, it is hypothesized that NGS strategies hold advantages like an earlier diagnosis, a higher diagnostic yield and lower costs.[9, 11]

This study therefore aimed to determine the possible benefits of using GPA for dystonia patients with a suspected genetic cause compared with conventional diagnostic workup.

Materials and methods

Patients

All patients in this study were referred to the tertiary Movement Disorders outpatient clinic of the University Medical Center Groningen (the Netherlands) to establish the cause of their dystonia. In 2013 we introduced GPA of 94 dystonia-associated genes (Supplement 1) as part of routine clinical DNA diagnostic testing. Patients of all ages were consecutively enrolled in our study if they

had isolated dystonia or dystonia as a main symptom, a clinical suspicion of a genetic cause, and genetic testing using GPA that was performed between December 2013 and April 2015. Clinical suspicion of a genetic cause was defined as the absence of clinical clues suggesting an acquired cause of dystonia,[5] in combination with 1 or more of the following: onset of dystonia before the age of 40 years, a positive family history, dystonia combined with another movement disorder, co-occurrence of other unexplained neurological or systemic manifestations, paroxysmal dystonia and laryngeal dystonia (also known as spasmodic dysphonia). Exclusion criteria were an acquired form of dystonia, no clinical suspicion of a genetic cause and dystonia as a minor feature.

Of the 61 patients enrolled, 28 (46%) were male. Their mean age was 31.0 years (SD 21.8 years, range 1-73 years) on their first visit to our clinic. Forty-four of the patients (72%) had young-onset dystonia (starting before age 21 years). The patients' characteristics are summarized in Table 1 and an overview of the clinical characteristics of each individual patient is provided in Supplement 2.

Table 1. *Patients characteristics*

Age of onset of dystonia	Number (%)	Age on first visit (SD)	Academic referrals*
0-2 years	18 (29.5)	17.5 (±14.8)	6 (33.3)
3-12 years	17 (27.9)	18.9 (±13.6)	4 (23.5)
13-20 years	9 (14.7)	34.9 (±19.2)	0 (0.0)
21-40 years	8 (13.1)	46.4 (±12.2)	2 (25.0)
>40 years	9 (14.7)	63.3 (±8.8)	4 (44.4)
Overall	61 (100)	31.0 (±21.8)	16 (26.2%)

Gene panel analysis

The genes included in the dystonia GPA (Supplement 1) were selected based on a systematic literature review[5] From the list of all genes associated with dystonia, genes reported only in single families/cases were not put on the diagnostic panel to reduce the potential number of variants needed to be interpreted by genome staff. Therefore, the unconfirmed candidate genes *CACNA1B* and *CIZ1* were omitted from the list. Notably, the list of 94 genes of the gene panel excluded several dystonia-associated genes (for example the spinocerebellar ataxias genes) because GPA cannot detect repeat expansions and whole-exon duplications or deletions.

GPA was offered to patients as a clinical diagnostic test, validated by the standards of the Dutch Society for Clinical Genetic Laboratory Diagnostics.[13] Also the interpretation and letters reporting test results were based on these guidelines. All test results, including pathogenic variants and variants of unknown significance, were first discussed in a multidisciplinary meeting with neurologists, clinical geneticists and genome laboratory staff. When the clinicians stated that a variant of unknown significance in a gene could explain the clinical phenotype, additional diagnostics steps were undertaken, such as array-comparative genomic hybridization (array-

CGH), multiplex ligation-dependent probe amplification (MLPA) analysis for autosomal recessive disorders, or sequencing the DNA of the parents to detect de-novo variants for dominant disorders. In some cases biochemical testing was done to confirm a diagnosis.

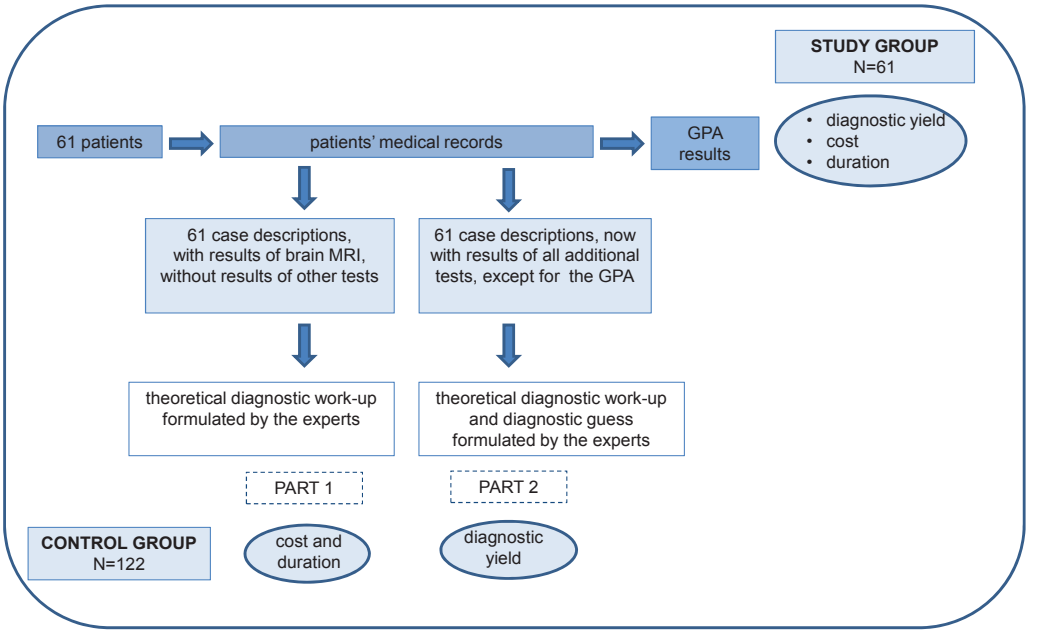
Study design

We conducted a post-hoc analysis by comparing the GPA study group with a theoretical control group without GPA. The primary outcome was the diagnostic yield and secondary outcomes were the cost and duration of diagnostic workup.

As comparison with a historic cohort was not possible because of the rapidly growing list of dystonia genes, we compared the diagnostic workup with and without GPA in the same patients. Each patient in our study therefore served as his/her own control. We built up a theoretical situation in which independent experts in the field were twice asked to formulate a diagnostic strategy: first, based only on the detailed clinical case description including the results of brain MRI (part 1), and second after we incorporated the results of further additional tests such as laboratory investigations and neuroimaging findings, except for the results of GPA (part 2).

The diagnostic yield obtained in the controls after part 2 was compared with the diagnostic yield obtained for the patients after GPA. The cost and duration of the diagnostic strategy for the controls in part 1 were compared with the cost and time required to perform the dystonia GPA. These study methods will be discussed in more detail below. Figure 1 gives an overview of the study design.

Figure 1. *Study design scheme*



Note: Study design scheme, 61 cases were included. Descriptions were made based on the patients' medical records. Two independent experts assessed the cases on their clinical features and developed a theoretical diagnostic strategy for each case (Part 1). They could request any extra tests deemed necessary, except for next-generation sequencing techniques. In Part 2 the cases were supplemented with the results of additional investigations and reassessed by the experts.

Diagnostic evaluation with GPA

For the diagnostic workup in the study group we followed our reported algorithm.[5] None of our 61 cases had any clinical clues of an acquired form of dystonia, neither in their clinical presentation nor on brain MRI. Biochemical diagnostics and a levodopa trial,[5] were not included in the diagnostic workup in the study group, as GPA is quicker in our center (28 days). Therefore, the diagnostic workup in the study group consisted exclusively of GPA.

Diagnostic evaluation without GPA

For each case, we had a description of the clinical phenotype (comprising the patient's medical history, history of present illness, family history, medication use, physical and neurological examination findings, and results of the brain MRI). All case descriptions were reviewed by the treating physician to ensure they presented an accurate reflection of the clinical picture. We asked 8 independent international experts to take part in our study (4 neurologists and 4 pediatric neurologists). Each case description was anonymized and randomly sent to 2 experts, who

independently assessed the cases. We took into account the ages of the patients at the time of examination when sending the cases to the pediatric or adult neurologists, using the age of 18 as cutoff point. Each case would be independently assessed by 2 experts, and inevitably, both experts would have differences in their assessments. Therefore, we decided to consider each assessment separately, resulting in a control group of 122 assessments.

In part 1 (control group), the experts formulated their theoretical diagnostic workup and diagnostic guesses. The experts could request any additional tests they deemed necessary, including a levodopa trial and single gene testing, but they were not allowed to use any NGS techniques in their diagnostic workup. In part 2 the case descriptions were again given to the same expert, but now with the results of all the additional tests (serum, urine, cerebrospinal fluid analysis, muscle and skin biopsies, consultations with other medical specialists, neuroimaging, neurophysiological tests, and the levodopa trial if available), all this information was retrieved from the patients' medical records. However, the results of the dystonia GPA were not provided. After part 2, the 2 experts reported their theoretical diagnostic strategies and diagnostic guesses, again independently. They could request any extra tests deemed necessary, except for NGS techniques.

Outcome measures

We defined the diagnostic yield as the percentage of cases with a genetically confirmed diagnosis. The diagnostic yield of the dystonia GPA in the 61 cases of the study group was compared with the diagnostic yield of the 122 theoretical diagnostic strategies in the control group. The diagnostic yield of the control group without GPA was established by assessing whether the single gene testing requested by the experts would have led to the etiological diagnosis according to the results of the dystonia GPA.

We investigated the cost of performing the dystonia GPA at our center (study group) and also the cost of performing the diagnostic tests requested by the experts for the controls in part 1 (see Supplement 3). To establish the duration of the diagnostic workup, we used standard reporting times for the diagnostic procedures in our clinic (see Supplement 3). In the study group, we defined the duration of a diagnostic workup as the time between requesting the dystonia GPA and receiving the results. In the control group (Part 1), we determined the theoretical cost and theoretical duration of diagnostic workup based on the experts' proposed strategies. To establish the duration, we considered the sequence of tests requested (simultaneous tests versus sequential tests).When an expert requested multiple simultaneous tests, only the test with the longest duration to generate a diagnostic report was taken into account. If the expert's strategy would have led to an etiological diagnosis halfway through the theoretical procedure the cost and time-frame of the remaining tests were not used in the analysis.

The use of brain MRI was not taken into account in analyzing both the study and control groups, because we considered the MRI to be an indispensable part of both the conventional diagnostic workup (control group) and of the workup with GPA (study group).[2, 5] Therefore, the results of the brain MRI were included in the clinical case descriptions in part 1.

Statistical analysis

We used SPSS (version 22, IBM SPSS Statistics) for our analysis and the 1-sided Fisher's exact tes for our primary outcome. For the secondary outcomes, we described the mean and range of the cost and duration of the diagnostic workup, with and without GPA. Comparison with Fisher's exact test was not possible for the secondary outcomes because of the fixed cost and fixed duration of GPA.

Results

Study group: diagnostic workup with GPA

In a multidisciplinary meeting with neurologists, clinical geneticists and genome laboratory staff all GPA results were discussed, including pathogenic variants and variants of unknown significance. Population frequencies and conflicting data regarding specific variants known in the literature were taken into consideration. In the series of patients included in this study, on average 0 to 2 variants of unknown significance were detected, and all were considered very unlikely to explain the phenotype. Therefore additional diagnostic steps, such as array-CGH or MLPA analysis, were felt unnecessary. A genetically confirmed cause of the dystonia was determined in 9 of 61 patients (14.8%) in the study group. The following diagnoses were made: DYT16 (*PRKRA* gene), Segawa syndrome (*TH* gene), glutaric aciduria type I (*GCDH* gene), Niemann-Pick type C (*NPC1* gene), paroxysmal kinesigenic dyskinesia (*PRRT2* gene) in 3 patients, and Rett syndrome (*MECP2* gene) in 2 patients (Table 2).

Control group: diagnostic workup without GPA

For the 122 control case descriptions, there were a total of 355 requests for gene tests on 66 different genes. On average, 3 single gene tests per case were requested by the experts. These led to identification of the genetic cause of the dystonia in 9 of 122 assessments (7.4%) see Table 2.

Diagnostic yield

The genetic diagnostic yield in the study group with GPA (14.8%) was higher than in the controls without GPA (7.4%), with statistical analysis tending toward, but not reaching significance (p=0.096).

Cost and duration of diagnostic workup

The cost of performing the dystonia GPA for one patient was €1,822 (study group). An overview of the requested diagnostic tests in the control group is shown in Supplement 3. The sum total of costs of the diagnostic strategies in the controls was € 324,482.93, which was divided by 122, resulting in a mean cost for the diagnostic tests in the controls of €2,660 per patient (SD 2747, range €0 to €18,688). For an overview of the requested tests in the control group, see Supplement 3.

Table 2. Identified genetic causes

Case no.	Child (< 19 years) or adult	Identified gene	Mode of inheritance	Mutation	Yield	Diagnosed by experts (control group)
1	Child	*PRKRA (DYT16)*	AR	c.558G>T p.(Glu186Asp)	Suggestive[a]	1 of 2
6	Adult	*MECP2*	XD	c.379C>A p.(Pro127Thr)	Solved	1 of 2
16	Adult	*GCDH*[b]	AR	c.482G>A p.(Arg161Gln) and c.1262C>T p.(Ala421Val)[c]	Solved	0 of 2
17	Child	*PRRT2*	AD	c.649dupC	Solved	2 of 2
19	Child	*TH*[b]	AR	c.1394C>G p.(Ser465Cys)	Suggestive[a]	0 of 2
27	Child	*MECP2*	XD	c.1178C>T p. (Pro393Leu)	Suggestive[a]	1 of 2
32	Adult	*PRRT2*	AD	c.649dupC	Solved	2 of 2
37	Adult	*PRRT2*	AD	c.649dupC	Solved	2 of 2
50	Adult	*NPC1*[b]	AR	c.2474A>G p.(Tyr825Cys) and c.3019C> G p.(Pro1007Ala)[c]	Solved	0 of 2

Identified genetic causes: causal gene mutations found in 9 of 61 patients and in 9 of 122 of the theoretical cases. Patients 17, 32, and 37 are not related.

[a] Suggestive yield means that our multidisciplinary team of clinicians and laboratory staff considered the results of genetic testing highly suggestive for a diagnosis, which often was confirmed afterwards by additional biochemical testing and/or molecular investigations of family members. With regard to case 1: the heterozygous mutation was considered causative based on reports of patients with heterozygous mutations in the PRKRA gene with a very similar phenotype,[14] and the patient had an excellent response on pallidal stimulation, which is in favor of an isolated dystonia such as DYT16. Concerning case 19: it was taken into account that more than 10% of TH mutations can be found in the promotor region of the TH gene[15]; these mutations will not be detected in a gene panel strategy. Therefore, in this patient a lumbar puncture was performed, which showed low homovanillic acid in the cerebrospinal fluid, confirming the diagnosis of TH deficiency.

[b] A treatable inborn error of metabolism.

[c] Compound heterozygosity.

AR, autosomal recessive; AD, autosomal dominant; XD, X-linked dominant.

We performed a subanalysis to compare the cost of the diagnostic workup using only single gene testing in the control group, with the cost of GPA. The cost of the workup with single gene testing alone was € 2,238 per patient (SD 2,444, range €0 to €16,918), which is higher than the cost of GPA (€1,822 per patient). For the study group, the time frame between requesting the dystonia GPA and receiving the results was 28 days. The mean duration of the diagnostic workup in the controls was 102 days (SD 66 days, range 0-301 days). The lower limit of the range of zero for cost and duration of the diagnostic workup in the control group was based on 1 case for whom one of the experts decided not to do any additional testing because of a presumed stationary encephalopathy.

Discussion

This study shows that GPA facilitates molecular diagnosis in complex cases of dystonia, with a good diagnostic yield (14.8%), a quicker diagnostic workup, and lower costs. In an ideal situation we would have set up a prospective cohort study, however, in such a study design it would not be ethically justified to withhold the use of NGS diagnostics to patients in the control group. We considered using a historic control group, but using a historic cohort of dystonia patients would not be relevant, as the list of known dystonia genes has expanded rapidly. Therefore, we compared the diagnostic workup with and without GPA in the same patients: each patient in our study served as his/her own control. The study design reflects a pragmatic approach: we evaluated how dystonia diagnostics are performed in clinical practice, with the aim of helping clinicians to make an informed choice between the conventional diagnostic workup and a workup with GPA.

The use of GPA in dystonia diagnostics in this study increased the yield compared with conventional workup, with statistical analysis tending toward, but not reaching significance. This may be because of the relatively small group of patients. Looking more closely at our results, we saw that particularly patients with an unusual or complex phenotype benefited from GPA, with disorders not considered in the initial differential diagnosis being identified. Below, we highlight 3 examples from our study. First, a patient presented at the age of 44 years in whom GPA analysis demonstrated a *GCDH* gene mutation (glutaric acidemia type I). Second, a patient with adult-onset myoclonus who later developed dystonia in his sixties and proved to have Niemann-Pick type C disease. And third, a patient with motor developmental delay as a child developed rapidly progressive parkinsonism and multifocal dystonia at age 13, and was then found to have a *TH* (tyrosine hydroxylase) gene mutation. Importantly, all 3 disorders are treatable forms of inborn errors of metabolism, with an accurate diagnosis allowing prompt initiation of therapy. Our findings are in line with other studies that suggest that particularly patients with a nonspecific or atypical clinical presentation will most likely benefit from NGS diagnostics.[9-11]

To our knowledge, this is the first study comparing the diagnostic yield of NGS techniques with conventional genetic techniques in diagnosing patients with dystonia, although other studies have compared NGS techniques with conventional genetic testing in other disorders, including movement disorders.[8, 9] Neveling and colleagues compared whole exome sequencing (WES) with Sanger sequencing in patients with heterogeneous diseases, including movement disorders.[8] The use of WES in 50 patients with movement disorders (29 hereditary spastic paraplegia, 12

cerebellar ataxia, 9 dystonia) compared with Sanger sequencing in 953 patients with movement disorders: WES had a diagnostic yield of 20% versus 5% in the Sanger sequencing group. The diagnostic yield of NGS in movement disorders in the study of Neveling et al. is higher (20%) than in our study (14.8%). This can be explained by differences in the patient population tested and a different study design, but another reason may lie in GPA is being restricted to preselected genes only, in contrast to WES. However, when we designed our study, we opted for GPA as the genetic coverage (sequencing depth) was higher than with other forms of NGS, at lower cost and with fewer variants to be interpreted and unsolicited findings.

Notably, the patients included in our study were all tertiary referrals and 16 of them (26%) were referred to us from other tertiary centers (Table 1). As a consequence, our study population comprised many complex cases, which is reflected in the proportion of cases who remained undiagnosed even after GPA. This is in line with other GPA studies with highly selective patient populations.12, 14 In heterogeneous disorders in which several potential genes are considered, the hypothesized advantages of NGS strategies are not only a higher diagnostic yield, but also an earlier diagnosis and lower costs. However, there is little published data relating to the cost-effectiveness of NGS technologies to date.[15, 16]

In our study, the mean costs were lower in the GPA group (€1822/case) than in the controls (€2660/case), and the cost incurred per expert varied greatly (range €0 to more than €18,988). This illustrates the very different diagnostic strategies used by individual experts. One possible explanation is the variability in costs, budgets and availability of diagnostic procedures between centers and countries, leading to different daily routines of clinicians. The cases with the highest costs were those with the most complex phenotypes, in which the cost-effectiveness of GPA can be highest. This is consistent with the cost- effectiveness of WES recently demonstrated in complex cases in a pediatric cohort with heterogeneous disorders.[16]

The duration of the diagnostic workup with GPA was considerably shorter than the mean duration of the conventional workup in the control group (28 vs 102 days). The duration in the control group is likely to be underestimated, as in clinical practice there is usually a delay between receiving the results of investigations, obtaining patient consent for the next diagnostic test, and requesting the next test. Furthermore, it has been shown in other studies that the diagnostic workup for dystonia patients may require many years.[5, 17] The reason for the relatively short duration of the diagnostic workup in the control group of our study is probably the involvement of highly experienced dystonia experts. A quicker diagnostic workup in the GPA group compared with conventional is a relevant finding, because the diagnostic odyssey is costly in terms of health care resources and poses a burden on the patient and his/her family.[18] In addition, diagnostic delays can have major implications with regard to potential therapies and avoiding unnecessary investigations.

In conclusion, our results show that GPA facilitates molecular diagnosis in complex cases of dystonia, with a good diagnostic yield, a quicker diagnostic workup, and lower costs, representing a major improvement for patients and their families. However, as Hennekam and Biesecker clearly stated, NGS and computers will not magically make diagnoses for us.[19] Careful clinical evaluation of the patient remains fundamental and NGS should not replace deep clinical phenotyping. As evident from our study, Sanger sequencing of the candidate gene will often lead to a diagnosis

in cases with a classical phenotype. In patients with complex and unusual phenotypes careful clinical evaluation remains as important as ever however, in these cases there will be a shift from a pre-NGS-test differential diagnostic mode to a post-NGS-test diagnostic assessment mode.[19] In line with this, a user-friendly and expandable online tool has been developed to help movement disorder clinicians to link NGS-test results to the clinical and phenotypic data of the individual patient.[20]

In the near future, NGS techniques will become increasingly incorporated into our daily clinical routines. Here we choose to use a targeted gene panel analysis, but WES coverage has improved significantly over time at much lower costs, making it more accessible for routine diagnostic purposes. With these advances in WES it will become easier to keep diagnostic tests up-to-date with the rapidly expanding lists of genes associated with dystonia, but also to have the possibility of unraveling novel dystonia-associated genes. For heterogeneous disorders such as dystonia, these developments will lead to earlier etiological diagnosis in a higher proportion of cases.

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References

1 Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863-73.
2 Fung VS, Jinnah HA, Bhatia K, et al. Assessment of patients with isolated or combined dystonia: an update on dystonia syndromes. Mov Disord. 2013;28(7):889-98.
3 Mink JW. Special Concerns in Defining, Studying, and Treating Dystonia in Children. Movement disorders : official journal of the Movement Disorder Society. 2013;28(7):921-5.
4 Garcia-Cazorla A, Wolf NI, Serrano M, et al. Inborn errors of metabolism and motor disturbances in children. J Inherit Metab Dis. 2009;32(5):618-29.
5 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(7):774-81.
6 de Ligt J, Willemsen MH, van Bon BW, et al. Diagnostic exome sequencing in persons with severe intellectual disability. N Engl J Med. 2012;367(20):1921-9.
7 Sikkema-Raddatz B, Johansson LF, de Boer EN, et al. Targeted next-generation sequencing can replace Sanger sequencing in clinical diagnostics. Hum Mutat. 2013;34(7):1035-42.
8 Neveling K, Feenstra I, Gilissen C, et al. A post-hoc comparison of the utility of sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. Hum Mutat. 2013;34(12):1721-6.
9 Shashi V, McConkie-Rosell A, Rosell B, et al. The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. Genet Med. 2014;16(2):176-82.
10 Tarailo-Graovac M, Shyr C, Ross CJ, et al. Exome Sequencing and the Management of Neurometabolic Disorders. N Engl J Med. 2016;374(23):2246-55.
11 Olgiati S, Quadri M, Bonifati V. Genetics of movement disorders in the next- generation sequencing era. Mov Disord. 2016;31(4):458-70.
12 Trump N, McTague A, Brittain H, et al. Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis. J Med Genet. 2016;53(5):310-7.
13 Weiss MM, Van der Zwaag B, Jongbloed JD, et al. Best practice guidelines for the use of next-generation sequencing applications in genome diagnostics: a national collaborative study of Dutch genome diagnostic laboratories. Hum Mutat. 2013;34(10):1313-21.
14 Pupavac M, Tian X, Chu J, et al. Added value of next generation gene panel analysis for patients with elevated methylmalonic acid and no clinical diagnosis following functional studies of vitamin B12 metabolism. Mol Genet Metab. 2016;117(3):363-8.
15 Beale S, Sanderson D, Sanniti A, et al. A scoping study to explore the cost- effectiveness of next-generation sequencing compared with traditional genetic testing for the diagnosis of learning disabilities in children. Health Technol Assess. 2015;19(46):1-90.
16 Valencia CA, Husami A, Holle J, et al. Clinical Impact and Cost-Effectiveness of Whole Exome Sequencing as a Diagnostic Tool: A Pediatric Center's Experience. Front Pediatr. 2015;3:67.
17 Bertram KL, Williams DR. Diagnosis of dystonic syndromes--a new eight-question approach. Nat Rev Neurol. 2012;8(5):275-83.
18 Warman Chardon J, Beaulieu C, Hartley T, et al. Axons to Exons: the Molecular Diagnosis of Rare Neurological Diseases by Next-Generation Sequencing. Curr Neurol Neurosci Rep. 2015;15(9):64.
19 Hennekam RC, Biesecker LG. Next-generation sequencing demands next-generation phenotyping. Hum Mutat. 2012;33(5):884-6.
20 Lill CM, Mashychev A, Hartmann C, et al. Launching the movement disorders society genetic mutation database (MDSGene). Mov Disord. 2016;31(5):607-9.

Supplement 1. *Dystonia gene panel (94 dystonia-related genes)*

Gene (OMIM)	Disease name/phenotype	Mode of inheritance
ADAR (146920)	Aicardi-Goutieres syndrome 6	AR, AD
ADCY5 (600293)	Familial dyskinesia with facial myokymia	AD
ALDH5A1 (610045)	Succinic semialdehyde dehydrogenase deficiency	AR
ANO3 (610110)	DYT24: isolated focal dystonia	AD
ARX (300382)	Partington syndrome/X-linked mental retardation	XR
ATP13A2 (610513)	Kufor-Rakeb syndrome (PARK9)	AR
ATP1A3 (182350)	DYT12: Rapid-onset dystonia parkinsonism	AD
ATP7B (606882)	Wilson's disease	AR
BCS1L (603647)	Mitochondrial complex III deficiency/Leigh syndrome	AR
*C10ORF2 (*609286)	Progressive external ophtalmoplegia with mitochondrial DNA deletions	AD
C19orf12 (614297)	Neurodegeneration with brain iron accumulation (NBIA) 4	AR
CDKL5 (300203)	Early-onset epileptic encephalopathy / variant Rett syndrome	XD
COX10 (602125)	Mitochondrial complex IV deficiency/Leigh syndrome	AR
COX15 (603646)	Mitochondrial complex IV deficiency/Leigh syndrome	AR
COX20 (614698)	Mitochondrial complex IV deficiency	AR
CP (117700)	Aceruloplasminemia	AR
DDC (107930)	Aromatic L-amino acid decarboxylase deficiency	AR
DJ1 (602533)	Early onset Parkinson disease type 7 (PARK7)	AR
DLAT (608770)	Pyruvate dehydrogenase E2 deficiency	AR
DLD (238331)	Dihydrolipoamide dehydrogenase deficiency (Maple syrup urine disease type III)	AR
FA2H (611026)	Spastic paraplegia type 35	AR
FBXO7 (605648)	Early onset Parkinson disease type 15 (PARK15)	AR
FOLR1 (136430)	Cerebral folate deficiency	AR
FOXG1 (164874)	Rett syndrome, congenital variant	de novo
FTL (134790)	Neurodegeneration with brain iron accumulation (NBIA) 3	AD
FUS (137070)	Hereditary essential tremor (ETM4)	AD
GCDH (608801)	Glutaric aciduria type 1	AR
GCH1 (600225)	DYT5: GTP-cyclohydrolase 1 deficiency	AD
GNAL (139312)	DYT25: isolated dystonia	AD
LRPPRC (607544)	Leigh syndrome, French-Canadian type	AR
MECP2 (300005)	Rett syndrome	XD
MTTP (157147)	Abetalipoproteinemia	AR
NDUFA10 (603835)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFA12 (614530)	Mitochondrial complex I deficiency/Leigh syndrome	AR

NDUFA2 (602137)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFA9 (603834)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFAF2 (609653)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFAF5 (612360)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFAF6 (*C8orf38*) (612392)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFS1 (157655)	Mitochondrial complex I deficiency	AR
NDUFS3 (603846)	Mitochondrial complex I deficiency	AR
NDUFS4 (602694)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFS7 (601825)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFS8 (602141)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NKX2-1/TITF1 (600635)	Benign hereditary chorea	AD
NPC1 (607623)	Niemann Pick type C	AR
NPC2 (601015)	Niemann Pick type C	AR
NUP62 (605815)	Infantile striatonigral degeneration	AR
PAH (612349)	Phenylketonuria/hyperphenylalaninemia	AR
PANK2 (606157)	Neurodegeneration with brain iron accumulation (NBIA) 1/HARP	AR
PRKN (602544)	Juvenile Parkinson disease type 2 (PARK2)	AR
PCBD1 (126090)	Hyperphenylalaninemia variant D	AR
PDHA1 (300502)	Pyruvate dehydrogenase E1-alpha deficiency	XD
PDHB (179060)	Pyruvate dehydrogenase E1-beta deficiency	AR
PDHX (608769)	Pyruvate dehydrogenase E3-binding protein deficiency	AR
PINK1 (608309)	Early onset Parkinson disease type 6 (PARK6)	AR
PLA2G6 (603604)	Neurodegeneration with brain iron accumulation (NBIA) 2/PARK14	AR
PLP1 (300401)	Pelizaeus-Merzbacher disease	XR
PNKD/MR1 (609023)	DYT8: Paroxysmal non-kinesigenic dyskinesia	AD
POLG (174763)	Alpers/MNGIE/SANDO (Mitochondrial DNA depletion syndrome 4)	AR
PRKRA (603424)	DYT16: Young-onset dystonia parkinsonism	AR
PRRT2 (614386)	DYT10: Paroxysmal kinesigenic dyskinesia	AD
PTS (612719)	6-Pyruvoyltetra-hydropterin synthase (PTPS) deficiency	AR
QDPR (612676)	Dihydropteridine reductase (DHPR) deficiency	AR
RNASEH2A (606034)	Aicardi-Goutieres syndrome 4	AR
RNASEH2B (610362)	Aicardi-Goutieres syndrome 2	AR
RNASEH2C (610330)	Aicardi-Goutieres syndrome 3	AR
SAMHD1 (606754)	Aicardi-Goutieres syndrome 5	AR
SCO2 (604272)	Cardioencephalomyopathy due to cytochrome c oxidase deficiency 1	AR
SERAC1 (614725)	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome (MEGDEL)	AR

SGCE (604149)	DYT11: Myoclonus-dystonia	AD
SLC16A2 (300095)	Allan-Herndon-Dudley syndrome (monocarboxylate transporter-8 (MCT8) deficiency)	XD
SLC19A3 (606152)	Thiamine transporter deficiency (formerly Biotin responsive basal ganglia disorder)	AR
SLC20A1 (137570)	Familial idiopathic basal ganglia calcification	AD
SLC2A1 (138140)	DYT9/18: Paroxysmal choreoathetosis with episodic ataxia and spasticity/GLUT1 deficiency syndrome-1	AD
SLC30A10 (611146)	Dystonia with brain manganese accumulation	AR
SLC6A19 (608893)	Hartnup disease	AR
SLC6A3 (126455)	Infantile parkinsonism-dystonia (Dopamine transporter deficiency)	AR
SPG11 (610844)	Spastic paraplegia type 11	AR
SPG7 (602783)	Spastic paraplegia type 7	AR
SPR (182125)	Sepiaterine reductase deficiency	AR
SUCLA2 (603921)	Mitochondrial DNA depletion syndrome 5	AR
SUCLG1 (611224)	Mitochondrial DNA depletion syndrome 9	AR
SURF1 (185620)	Mitochondrial complex IV deficiency/Leigh syndrome	AR
TACO1 (612958)	Mitochondrial complex IV deficiency/Leigh syndrome	AR
TAF1 (313650)	DYT3: X-linked dystonia-parkinsonism	XR
TH (191290)	Tyrosine hydroxylase deficiency	AR
THAP1 (609520)	DYT6: Adolescent onset torsion dystonia, mixed type	AD
TIMM8A (300356)	Mohr-Tranebjaerg syndrome (Dystonia deafness syndrome)	XR
TOR1A (605204)	DYT1: Early-onset generalized isolated dystonia (PTD)	AD
TREX1 (606609)	Aicardi-Goutieres syndrome 1	AR, AD
TUBB4A (602662)	DYT4: Whispering dystonia	AD
VPS13A (605978)	Choreoacanthocytosis	AR
Wdr45 (300894)	Neurodegeneration with brain iron accumulation (NBIA) 5	XD

Note: This list of genes excludes several dystonia-associated genes, for example the spinocerebellar ataxias genes, because gene panel analysis cannot detect repeat expansions, whole exon duplications or deletions. Furthermore, the ATM gene (ataxia telangiectasia) was omitted from the list, after much debate within our multidisciplinary team, given the fact that carriers of ATM have an increased risk for breast cancer. Finally, because a limited amount of genes that could be included in the panel, the HPRT1 gene (Lesch-Nyhan syndrome) was left out, because Lesch-Nyhan syndrome can be easily diagnosed by testing uric acid in plasma, saving space in the panel for other genes. However, both ATM and HPRT1 will be included in the updated version of the dystonia gene panel that currently is being implemented in our center. OMIM, Online Mendelian Inheritance in Man (www.omim.org); AR, autosomal recessive; AD, autosomal dominant; XR, X-linked recessive; XD, X-linked dominant.

Supplement 2. *Clinical charccteristics of the individual patients*

Case	Age*	Main clinical features at last examination	Age at onset of dystonia	Origin	FH#
1	6	isolated dystonia	5	Dutch	neg
2	13	isolated dystonia	11	Dutch/Asian	pos
3	21	dystonia with deafness	17	Dutch	pos
4	69	isolated dystonia	22	Dutch	pos
5	8	dystonia with myoclonus	6	Dutch	neg
6	21	dystonia with mild mental retardation	18	Dutch	neg
7	54	isolated dystonia	14	Dutch	pos
8	5	dystonia with psychomotor retardation	3 months	Dutch/British	neg
9	5	dystonia with psychomotor retardation, spasticity, hearing impairment	3	Dutch	neg
10	14	dystonia with myoclonus	3	Dutch	pos
11	11	dystonia with myoclonus	2	Dutch	pos
12	10	dystonia with myoclonus, psychomotor retardation, abnormal eye movements	4	Asian	neg
13	5	dystonia with myoclonus and ataxia	2	Dutch	neg
14	16	dystonia with tics	6	Dutch	neg
15	16	dystonia with myoclonus	since early childhood	Dutch	pos
16	44	dystonia with chorea	since early childhood	Dutch	neg
17	8	paroxysmal dystonia / dyskinesia	7	Dutch	pos
18	19	isolated dystonia	34	Dutch	neg
19	15	dystonia with bradykinesia and areflexia	since early childhood	Dutch	Neg
20	26	dystonia with myoclonus and epilepsy	since early childhood	Dutch	neg
21	14	dystonia with bradykinesia, psychiatric features, excessive growth	11	Dutch	neg
22	12	dystonia with parkinsonism, abnormal eye movements	4	Dutch	neg
23	21	dystonia with myoclonus	15	Dutch	pos
24	11	isolated dystonia	8	Dutch	pos
25	5	dystonia with psychomotor retardation and hearing impairment	since early childhood	Dutch	pos
26	31	paroxysmal dystonia / dyskinesia	21	Dutch	neg
27	6	dystonia with chorea, psychomotor retardation, microcephalus, epilepsy	since early childhood	Dutch	pos
28	66	dystonia with ataxia	63	Dutch	pos
29	39	dystonia with bradykinesia	38	Dutch	pos
30	45	dystonia with myoclonus	20	Dutch	pos

31	55	dystonia with chorea	20	Dutch	pos
32	46	isolated dystonia	since childhood	Asian	pos
33	16	dystonia with myoclonus	2	Dutch	pos
34	47	dystonia with myoclonus	since childhood	from former Yugoslavia	neg
35	7	dystonia with chorea	2	Dutch	neg
36	19	isolated dystonia	12	Dutch	pos
37	25	paroxysmal dystonia / dyskinesia	16	Dutch	neg
38	62	isolated dystonia	20	Dutch	neg
39	15	dystonia with myoclonus	since childhood	Dutch	pos
40	34	dystonia with abnormal eye movements	2	Dutch	neg
41	63	dystonic jerks	14	Dutch	pos
42	31	paroxysmal dystonia / dyskinesia	20	Dutch	neg
43	51	isolated dystonia	47	Dutch	pos
44	39	paroxysmal dystonia / dyskinesia	since childhood	Dutch	neg
45	19	dystonia with myoclonus	since early childhood	Dutch	pos
46	73	dystonic tremor	61	Dutch	pos
47	1.5	paroxysmal dystonia / dyskinesia and seizures	since early childhood	Dutch	pos
48	14	dystonia with myoclonus	4	Dutch	pos
49	7	dystonia with psychomotor delay	since childhood	Dutch	pos
50	58	dystonia with myoclonus	52	Dutch	pos
51	50	dystonia with myoclonus and psychiatric features	20	Dutch	pos
52	60	dystonia with myoclonus	since childhood	Dutch	pos
53	51	isolated dystonia	49	Dutch	pos
54	66	isolated dystonia	45	Dutch	pos
55	72	dystonia and mild rigidity	70	Dutch	pos
56	73	isolated dystonia (including laryngeal dystonia)	71	Dutch	pos
57	50	isolated dystonia	20	Dutch	neg
58	21	dystonia with myoclonus	4	Dutch	pos
59	43	dystonia with psychomotor retardation	35	Dutch	pos
60	16	dystonia with myoclonus	since childhood	Dutch	pos
61	35	dystonia with mild bradykinesia	since childhood	Dutch	pos

Supplement 3. *Cost and timeframe of diagnostic tests*

Diagnostic test	Source	Cost (€)	Duration (days)	No. of times requested
Levodopa trial	Pharmacotherapeutic compass[#]	30.40	90	76
Dystonia gene panel	Genetic Laboratory Management[#*]	1,821.90	28	NA
Brain MRI	Financial Management, UMCG	259.90	28	NA
Metabolic investigation plasma*	Mutual Services[##]	164.18	14	32
Metabolic investigation urine**	Mutual Services	255.45	21	40
CSF: general screening***	Mutual Services. Laboratory Management[###]	75.63	14	36
CSF: neurotransmitters*#	Laboratory Management	40.00	21	23
CSF/Plasma glucose ratio	Mutual Services	3.39	1	35
Sanger sequencing	Genetic Laboratory Management[#*]	769.00	42	355
Mitochondrial DNA	Genetic Laboratory Management	400.00	60	8
Consultation with pediatrician	Financial Management UMCG	170.93	60	1
Consultation with ophthalmologist	Financial Management, UMCG	55.34	60	16
Skin biopsy	Mutual Services	variable§	120	3
Muscle biopsy	Mutual Services	variable§	150	3
Abdominal CT	Financial Management, UMCG	160.78	21	1
CT cerebrum	Financial Management, UMCG	120.13	45	3
Abdominal ultrasound	Financial Management, UMCG	76.24	7	1
SPECT	Financial Management, UMCG	1,746.09	21	1
DOPA-PET	Financial Management, UMCG	543.91	30	1
FDG-PET	Financial Management, UMCG	543.91	21	1
EMG	Financial Management, UMCG	166.11	21	14
EEG	Financial Management, UMCG	113.54	14	16
SSEP	Financial Management, UMCG	113.54	28	8
EEG-EMG/Coherence analysis with back averaging	Financial Management, UMCG	147.60	28	1
Tremor registration	Financial Management, UMCG	147.60	28	7
SNP array	Mutual Services	210.29	70	1
CGH array	Mutual Services	210.29	70	8

Notes: We requested a list of the direct costs of these diagnostic tests (both material and personnel costs) from the management team of our hospital. If the cost of a diagnostic test was not on this list. we used the costs of the Mutual Services of the Dutch Healthcare Authorities (Onderlinge Dienstverlening). For the levodopa trial we used the cost of levodopa/carbidopa 100/25 CT for twice a day during 90 days, according to the Healthcare Institute of the Netherlands.

The estimation of the financial costs of several investigations for this study proved to be difficult. Especially the direct costs of the genetic tests were hard to determine Since the costs of genetic tests are constantly changing because these techniques are continually being developed. The genetic tests therefore cover the cost of development of the techniques, the training costs of staff, and the actual diagnostic test costs.

** Metabolic investigation of plasma consists out of amino acids and acylcarnitines.*

*** Metabolic investigation of urine consists out of mucopolysacharides, organic acids, creatines, sialic acid, saccharides and pterines.*

****General screening of CSF consists out of amino acids, lactate and pyruvate.*

**# Neurotransmitter investigation of CSF consists of 5-methylteleachopholate, pterines, vanillylmandelic acid and 5-hydroxyindoleacetic acid*

 # Pharmacotherapeutic compass of the Healthcare Institute of the Netherlands (Farmacotherapeutisch Kompas of the Zorginstituut Nederland)

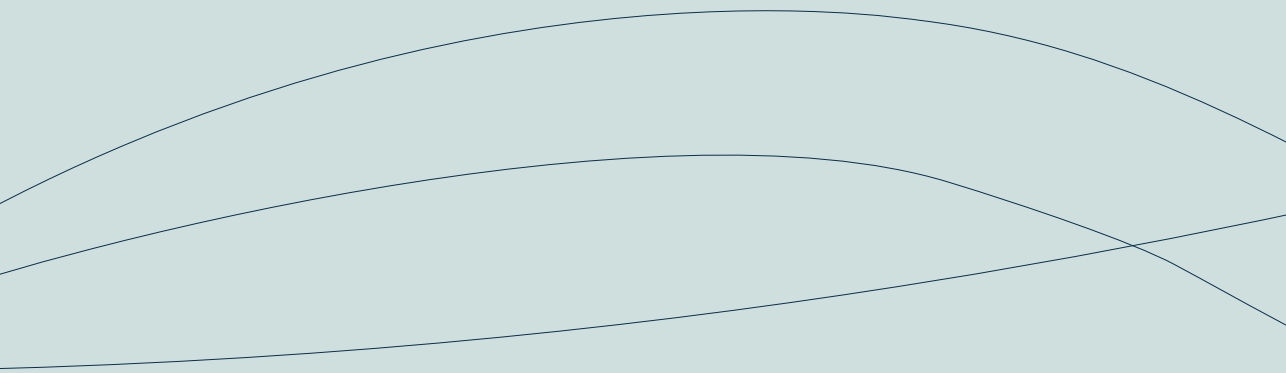
Mutual Services of the Dutch Healthcare Authorities (Onderlinge Dienstverlening of the Nederlandse Zorgautoriteit)

Costs estimated in consultation with the Laboratory Management, UMCG.

Costs estimated in consultation with the Genetic Laboratory Management, UMCG*

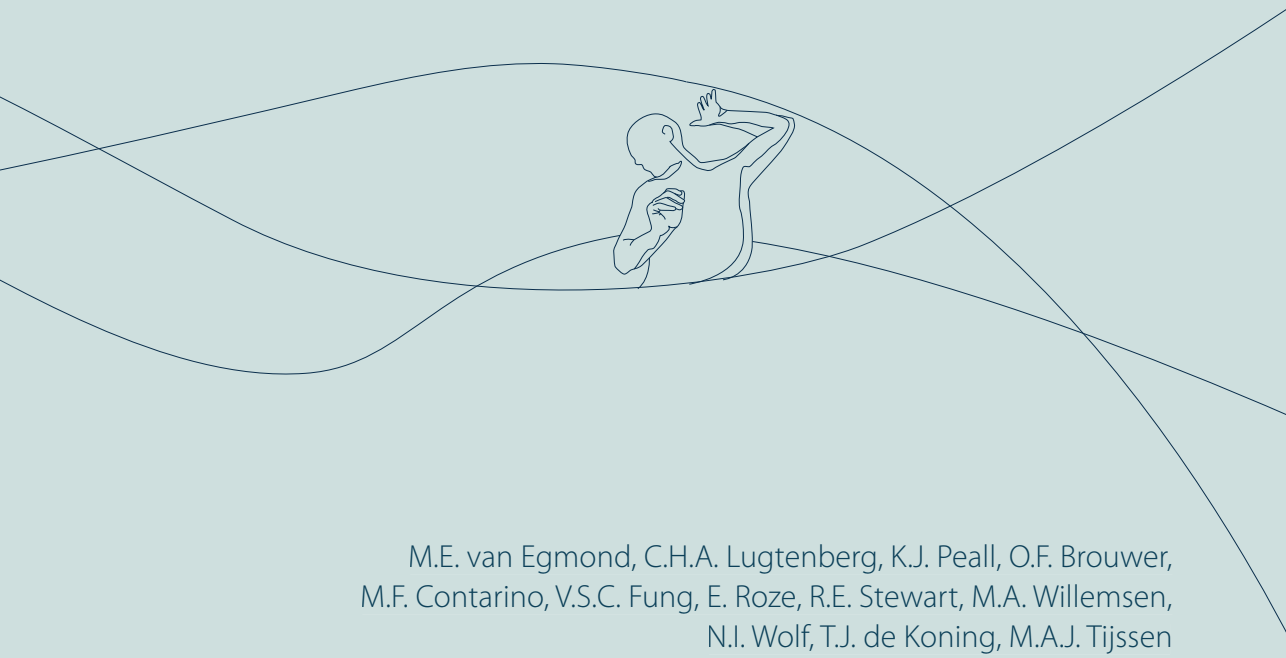
§ costs of skin biopsy (culturing the cells in combination with enzymatic and molecular testing) varied between €1510.07 and €3730.21, costs of muscle biopsy varied between €972 en €2082.07, depending on nature and amount of tests

Abbreviations: NA, not applicable; CT, computed tomography; SPECT, Single Photon Emission Computed Tomography; PET, Positron Emission Tomography; EEG, electroencephalography; EMG, electromyography; SEP, somatosensory evoked potentials; EMG-EEG, simultaneous electroencephalography/electromyography with coherence analysis. Tremor registration comprised EMG with accelerometry.



Dystonia classification and syndrome definition: moderate agreement among experienced clinicians

Chapter 5



M.E. van Egmond, C.H.A. Lugtenberg, K.J. Peall, O.F. Brouwer, M.F. Contarino, V.S.C. Fung, E. Roze, R.E. Stewart, M.A. Willemsen, N.I. Wolf, T.J. de Koning, M.A.J. Tijssen

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Abstract

Background
The dystonia classification system introduced in 2013 aimed to facilitate diagnosis and treatment, and to help in the development of research strategies. This classification enabled specific dystonia syndrome to be defined. The aim of this 'syndromic approach' is to assist diagnostic testing towards reaching an etiological diagnosis.

Objectives
To assess the concordance of experienced clinicians in their interpretation of written clinical information on the phenomenological and syndrome classifications of dystonia.

Methods
Detailed clinical case descriptions were written up for 56 dystonia patients (mean age 31 years), who visited our movement disorder outpatient clinic in a tertiary referral center. Eight experienced clinicians from four countries participated in an online exercise: for each vignette two clinicians independently classified the phenomenological features according to the dystonia classification (Axis I) and defined the patient's dystonia syndrome. The primary outcome measure was the interrater agreement.

Results
For Axis I items, there was moderate to substantial interrater agreement (kappa 0.45-0.8), while there was moderate agreement on the dystonia syndrome (kappa 0.5). Full agreement on all axis I items and on the syndrome was reached in only 7/56 cases (12.5%).

Conclusions
The results of this study reflect how clinicians vary in their use of clinical information and demonstrate how classification terms can be ambiguous. Optimal disease classification methodologies require reasonable consensus to be useful for clinical and research purposes, particularly in this next-generation sequencing era. We would therefore advocate starting a discussion on how we can improve the diagnostic accuracy of the dystonia classification system.

Introduction

In recent years, our knowledge on the variability of the clinical manifestations and causes of dystonia has grown dramatically. This is mainly due to the wider use of next-generation sequencing (NGS) techniques, which has led to the identification of many new dystonia- associated genes and distinct phenotypes.[1, 2] Dystonias may emerge at any age, involve nearly any body region, have a static or progressive course, and may co-occur with other neurological or systemic features.[2] Such heterogeneity means an accurate diagnosis can be challenging, particularly for the less common or unusual forms.[3] Consequently, there is a wide range of diagnostic approaches, even among experienced movement disorder specialists.[4]

The increasing information on various clinical manifestations of dystonia led to the revision of its definition and classification, which was published in 2013.[2, 5, 6] This consensus-based classification aimed to facilitate diagnosis, diagnostic testing and treatment, and to assist in the development of research strategies.[5]

The classification system includes two axes: the first Axis focuses on the clinical manifestations of dystonia, the second Axis on etiology.[5] Once a patient has been phenomenologically classified according to the first Axis (items include 'age at onset', 'body distribution', 'temporal pattern' and 'associated features') a dystonia syndrome can be defined.[5] To assist clinicians in defining a specific dystonia syndrome, Fung and colleagues listed 27 dystonia syndromes, supplemented with lists of potential etiologies for 16 of them.[4]

The absence of a diagnostic test or biomarker that can serve as a gold standard for dystonia means the clinical classification and syndromic approach[4,5] rely on the assumption that clinicians or researchers can organize the many dystonias into meaningful subgroups by clinical assessments.[7] Interrater agreement studies are important to clarify any discrepancies in the interpretation of the diagnostic criteria, as these discrepancies may lead to diagnostic and therapeutic disagreement and hinder the search for phenotype-genotype correlations. Our main aim in this study was to assess the concordance of interpretation of written clinical information amongst experienced clinicians on the phenomenological and syndrome classification of dystonia. For this study, we used detailed clinical case descriptions of 56 dystonia patients with a suspected genetic cause.[8] We also explored which factors influenced the perceived differences in dystonia classification and syndrome diagnoses.

Materials and methods

Patients and study design

All patients in this study were referred to the tertiary outpatient clinic for Movement Disorders of the University Medical Centre Groningen (the Netherlands) to establish the cause of their dystonia. Patients of all ages were consecutively enrolled in our study if they had isolated dystonia or dystonia as a main symptom, and if there was a clinical suspicion of a genetic cause, as described elsewhere.[8]

Based on 61 patients' medical records, we made detailed clinical case descriptions. Each description contained the key features of the clinical phenotype and comprised the patient's

medical history, history of present illness, family history, medication use, the physical and neurological examination findings, and the results of the brain MRI. All case descriptions were reviewed by the treating physician to ensure they presented an accurate reflection of the clinical picture. Later, all the case descriptions were read critically (by MvE) to ensure that all the parameters were described in sufficient detail; this led to the exclusion of six cases (#13, 38, 49, 50, 58 and 61), because the information in these vignettes did not permit a complete Axis I classification and dystonia syndrome definition.

Of the remaining 56 patients, 26 (46%) were male. Their mean age was 31 years (SD 21.7, range 1-73 years) on their first visit to our clinic. The clinical characteristics of the individual patients are described elsewhere in more detail.8

We asked eight international clinicians with experience in the field of movement disorders to take part in our study (four adult neurologists and four pediatric neurologists). Each case description was anonymized and randomly sent to two clinicians, who independently assessed the cases. We took into account the age of the patient at the time of examination when sending the cases to the pediatric or adult neurologists, using the age of 18 years as a cut-off point. On average, each clinician assessed 14 vignettes.

First, they were asked to classify the clinical characteristics of the cases according to the six items of Axis I of the current dystonia classification: 'age at onset' (age when symptoms were first noticed), 'body distribution', temporal pattern ('disease course' and 'variability') and associated features (isolated dystonia or combined with another movement disorder, and the list of other neurological or systemic manifestations occurring).[5]

If the clinicians reported that the patient in the case description had 'dystonia combined with another movement disorder', they were asked to specify which other movement disorder was present. Although this question is not part of the dystonia classification,[5] this information was required to understand the differences in the syndrome diagnoses.

Second, we asked the clinicians to formulate a dystonia syndrome for each case,[4] and we added the option 'None of the above'. The papers of Fung et al.[4] and Albanese et al.[5] were added to the instructions for the clinicians, with the request to classify the dystonia and dystonia syndromes according to the definitions described in them.

Statistical Analysis

All case descriptions were assessed by two independent clinicians with regard to the 6 items of Axis I of the dystonia classification and to the dystonia syndrome. After receiving the results of their assessments, we analyzed the interrater agreement for these items and for the dystonia syndromes. For five of the six items in the classification ('age at onset', 'body distribution', 'temporal pattern', 'variability', 'isolated or combined') and for the dystonia syndromes, we assessed the interrater agreement using the Fleiss' kappa.[9] Kappa values and their 95% confidence intervals (95% CI) were calculated and evaluated according to the Landis & Koch classification (<0.0 poor, 0.0–0.2 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1.0 excellent).[9] For the five items, we also calculated the percentage of agreement, i.e. the percentage of cases in which the clinicians gave the same answer.

In contrast to the first five items of the classification, the sixth item, 'occurrence of other neurological or systemic manifestations', is an open question instead of a multiple choice question. This also applies to the question on which other movement disorder besides dystonia was present in the case of a combined movement disorder. In theory, it would be possible to calculate a kappa value by categorizing the given answers, however, the kappa value would have been greatly influenced by the number of chosen categories. We therefore decided to use descriptive statistics instead of kappa calculations to describe the responses to these two questions. Here we will explain how we analyzed the responses.

First, we categorized the answers for 'occurrence of other neurological or systemic manifestations' (Supplement 1). For another question, 'other movement disorders', the answers did not need to be categorized because only eight different movement disorders were reported (see Results). If clinicians reported more than one feature, we considered they agreed if they reported features in the same category, regardless of what order the feature was mentioned in (first to fourth feature). Second, we calculated the percentage of agreement, which we defined as the percentage of cases for which both clinicians gave an answer in the same category, plus the percentage of cases for which they both agreed upon the absence of other neurological or systemic manifestations. Clinicians were allowed to mention as many neurological or systemic manifestations as they considered relevant, there was no predetermined maximum number. We only calculated the percentage of agreement for the first two reported features, because third and fourth features were rarely mentioned.

Results

An absolute (100%) agreement between clinicians for all items of Axis I of the dystonia classification was observed in 9/56 cases (16.1%), and for both the Axis I classification and the dystonia syndrome in 7/56 cases (12.5%) (Supplement 2). Five of the six Axis I items were multiple choice questions, and if we excluded the open question on co-occurring manifestations, we would have reached full Axis I agreement in 14/56 (25%) cases. The interrater agreement and percentage of agreement among clinicians for the first five Axis I items and for the dystonia syndrome is shown in Table 1. For these Axis I items, kappa values ranged from 0.45–0.8, and the mean kappa with regard to which dystonia syndrome was 0.5 (moderate agreement). In Supplement 3 we summarize some illustrative cases, highlighting elements that might explain the non-agreement seen among the clinicians for each of the five Axis I items.

Table 1. Inter-rater agreement for the first five Axis I items of the dystonia classification and for the dystonia syndrome

	agreement	agreement %	inter-rater agreement, kappa	95% confidence interval
Items dystonia classification (Axis I)				
Age at onset	46/56	75.0	0.80*	0.69 - 0.91
Body distribution	34/56	60.7	0.45	0.27 - 0.63
Temporal pattern, disease course	44/56	78.6	0.52	0.29 - 0.76
Temporal pattern, variability	47/56	83.9	0.62	0.41 - 0.83
Isolated or combined	44/56	78.6	0.50	0.27 - 0.73
Dystonia syndromes				
Dystonia syndrome	31/56	55.3	0.5	0.40 – 0.59

** weighted kappa. Kappa categories: <0.0 poor, 0.0 to 0.2 slight, 0.21 to 0.40 fair, 0.41 to 0.60 moderate, 0.61 to 0.80 substantial, and 0.81 to 1.0 excellent.*

The results with regard to the 'co-occurring manifestations' are summarized in Supplement 4. In the case of a combined movement disorder, we asked the clinicians which other movement disorder might have been present. Eight different answers were given to this question: ataxia, myoclonus, spasticity, chorea, tics, paroxysmal dyskinesia, parkinsonism, and tremor. There was a high percentage of agreement for both the first and second features mentioned by the clinicians (75% and 84%, respectively). For those cases in which both clinicians gave an answer, there was only case in which the clinicians responded differently. This was a patient with dystonia and tremor, interpreted as dysmetria/ataxia by one rater and as parkinsonism by the other. We have summarized the answers for those cases in which only one clinician gave an answer (Supplement 4).

For the item on 'co-occurring neurological or systemic manifestations', the agreement was 73% for feature 1 and 70% for feature 2 (Supplement 4). In the cases when both clinicians gave an answer, there were two cases in which they answered differently. In the first case one rater mentioned psychiatric problems and the other eye movement disorders, in the second case one rater mentioned ocular apraxia, the other premature birth. For those cases in which only one clinician gave an answer, the answers are summarized in Supplement 4.

With regard to the dystonia syndromes, both clinicians agreed on which syndrome it was in 31/56 cases (55%) (Table 1). The two syndromes with the highest agreement between both raters were: 'dystonia with myoclonus' (9 cases) and 'dystonia as part of a paroxysmal dyskinesia ' (6 cases) (Supplement 2). The cases of non-agreement on the dystonia syndrome are summarized in Table 2. For 17/56 (30%) case descriptions, one or more of the clinicians noted 'none of the above'.

Discussion

Our study demonstrates that experienced clinicians reached moderate to substantial interrater agreement on the dystonia classification Axis I items (kappa range 0.45–0.8) and moderate agreement on the dystonia syndrome (kappa 0.5), with absolute agreement (100%) for both the classification and the syndrome in 12.5% of cases. These results reflect how much clinicians can vary in their use of clinical information and demonstrate how ambiguous classification terms can be.

Table 2. Cases with non-agreement on the dystonia syndrome (N=25)

	Dystonia with cerebellar ataxia	Dystonia as part of paroxysmal dyskinesia	Dystonia with chorea	Dystonia with tics	Dystonia with deafness	Dystonia with ophthalmological abnorm.	Dystonia with peripheral neuropathy	Dystonia with progressive dementia	Dystonia with basal ganglia lesions	Dystonia with leucoencephalopathy	None of the above
Isolated dystonia syndromes											
Cranial dystonia in young adults and children	1										1
Adult-onset generalized dystonia											2
Combined dystonia syndromes											
Dystonia with or without parkinsonism of infantile or childhood onset			1						1	1	3
Dystonia with or without parkinsonism of adolescent and young adult onset											1
Dystonia with spasticity (with or without parkinsonism)					1						
Dystonia with cerebellar ataxia							1				1
Dystonia with myoclonus		2	1			1		1			1
Dystonia as part of paroxysmal dyskinesia											1
Dystonia with chorea				1							
Dystonia with tics											
Dystonia with other neurological involvement											
Dystonia with deafness											
Dystonia with ophthalmological abnormalities											1
Dystonia with peripheral neuropathy											
Dystonia with progressive dementia											
Dystonia with systemic disease											
Dystonia with endocrine abnormalities											1
Dystonia with hematological abnormalities											
Dystonia with solid organ involvement											
Syndromes according to brain imaging											
Dystonia with MRI evidence of neuronal brain iron accumulation											1

Dystonia classification

Moderate interrater agreement was reached on the items 'body distribution', 'disease course' and 'isolated or combined' dystonia, while there was substantial agreement on 'age at onset' and 'variability'. The differences in interpretation are interesting, particularly because these five Axis I items seem to be relatively straightforward, and each clinician was sent the same written information.

The summary of illustrative cases in Supplement 3 reveals several factors that could lead to ambiguity. Here, we will discuss five of them. First, one important issue seemed to be different interpretations of co-occurrent jerky movements, which reflects a common dilemma in clinical practice. Looking in more detail, it appears that some clinicians made their own interpretation of co-occurring jerky movements, based on the complete clinical picture and pattern recognition, despite the fact that the phenomenology of the movement disorders was described in the vignette (see examples in Supplement 3). Second, dystonic posturing combined with dystonic jerks may lead to divergent answers regarding 'age at onset' and 'disease course', because posturing and jerks do not always start simultaneously and can show different temporal patterns. Similarly, in multifocal or generalized dystonia, the item 'variability' led to different interpretations, for example, dystonic movements could be action-specific in one part of the body but persistent elsewhere. Third, for paroxysmal dystonia, the items 'body distribution' and 'isolated or combined' could be difficult to classify because, in most cases, the neurologic examination was normal. Therefore, specific clinical characteristics could only be deduced from non-specific descriptions in the case history, and there were often differences between the episodes described (see example in Supplement 3). Fourth, for young patients, the complexity of the developing brain was a factor that could explain the different answers. For example, several patients first had abnormal motor development and developed hyperkinetic involuntary movements several years later, which led to different answers for 'age at onset'. A fifth possible factor is that for some Axis I items, it is not clear whether the classification should be based on symptoms (history) or signs (neurologic examination), as there were discrepancies at this point in some cases.

Together, all the above factors might explain different aspects in the diversity of the final classifications and the overall ambiguity. It is noteworthy that the classification items are interconnected, for example, if jerky movements are interpreted by one rater as myoclonus and by the other as dystonic jerks, the answers will not only differ for the item 'isolated or combined', but often for other items too, such as 'body distribution', 'age at onset' and 'disease course'.

For specification of 'co-occurring neurological or systemic manifestations (Axis I, item 6), the raters' agreement was 73% for the first feature mentioned, and 70% for the second. In 23% of cases, the two raters assessed the co-occurring features differently (Supplement 4). It is important to note that if both clinicians reported a co-occurring feature, they rarely disagreed on which feature it was (Supplement 4), which suggests that the information given in the vignettes was clear and unambiguous.

To our knowledge, this is the first study to specifically investigate the interrater agreement of Axis I items in of the dystonia classification. However, from a broader perspective, our results are in line with another study addressing the interrater reliability for the diagnosis of various subtypes of dystonia.[10] In this recent study by Beghi and colleagues, 35 neurologists assessed

video recordings of 29 adults (18 with dystonia, 9 with other movement disorders, and 2 healthy controls). The raters were asked whether dystonia or another movement disorder was present, to establish the body distribution, and about the level of diagnostic certainty (definite, probable, or no dystonia). Their assessments were compared to those of the treating (movement disorder) neurologist.[10] The results showed low levels of agreement (kappa values ranged from 0.30–0.46). If experienced clinicians can reach a moderate to substantial interrater agreement on the Axis I items, as shown in our study, or low levels of agreement, as shown by Beghi and colleagues,[10] the interrater agreement may be even lower among less experienced clinicians. This may hinder the implementation of the classification system in clinical practice and raises the question of how diagnostic agreement can be improved.

Theoretically, more stringent criteria could improve some of the possible explaining factors, including the diagnostic agreement regarding to co-occurring jerky movements. For example, co-existent jerks and dystonia in the same body region may be defined as dystonic movements ('jerky dystonia') rather than as myoclonus.[11] Another option to enhance diagnostic agreement in challenging cases may be to organize team assessments and consensus meetings, as suggested for psychogenic jerky movement disorders.[12] In the field of epilepsy, the use of a panel of raters led to much increased interrater agreement compared to individual ratings for the diagnosis and classification of a first paroxysmal event in childhood.[13] A third possible option to improving diagnostic agreement would be to offer a training program or e-learning course to gain a certificate in the dystonia classification, analogous to the training and certification developed for the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS).[14]

In addition to these options, we advocate opening a discussion on whether the current dystonia classification could be simplified for those items for which it is difficult to formulate strict criteria, and also for items that may not be essential for assembling meaningful subgroups. Considering the options for each of the six independent items of Axis I, including the listing of associated neurological features, there are thousands of possible independent item combinations that could be generated.7 Given this number of possible combinations, it is not so surprising that we only observed absolute (100%) agreement between clinicians on all the items of Axis I in 9/56 (16.1%) of cases.

Dystonia syndromes

With regard to dystonia syndromes, the clinicians agreed on the syndrome diagnosis in 32/56 cases (57%), reaching moderate interrater agreement (kappa 0.5) (Table 1). The degree of concordance reached on the dystonia syndrome was probably influenced by the relatively low interrater agreement on Axis I items, as the syndrome diagnosis is determined by the phenomenological classification. In 17/56 cases (30%), one or more of the clinicians considered none of the 28 dystonia syndromes listed to be applicable (Table 2, Supplement 2), which emphasizes how challenging it can be to classify a dystonia syndrome, even for experienced clinicians.

Clearly, the formulation of the dystonia syndrome depends on what clinicians choose to emphasize and what they ignore in a vignette, as illustrated by the vignettes with non- agreement on the dystonia syndrome (Table 2). For the same vignette, one clinician may consider a co-occurring movement disorder the most distinctive feature (e.g. myoclonus, and consequently

define the syndrome as "dystonia with myoclonus"), whereas another clinician may consider a systemic feature as most distinctive (e.g. ocular abnormalities, leading to the syndrome diagnosis of "dystonia with ophthalmological abnormalities").

Looking at those vignettes when both clinicians agreed on the syndrome (Supplement 2), it is interesting to see that the syndromes with the highest number of cases with agreement were 'dystonia with myoclonus' and 'dystonia as part of paroxysmal dyskinesia'. We assume that these phenotypes were the best recognizable as dystonia syndromes. One explanation is that these patients may typically have no other 'co-occurring neurological or systemic manifestations', leading to less diagnostic ambiguity.

Overall, our findings illustrate how the individual interpretation of the clinical picture seems to play an important role in the syndromic diagnosis, in line with our results on the phenomenological classification.

After publication of the revised definition and classification of dystonia and the list of dystonia syndromes,[4, 5] several articles were published on the rationale and clinical applications.[6, 7, 15, 16] Notably, the list of dystonia syndromes was meant to help clinicians guide diagnostic work-up rather than intended as a classification.[4] However, as Jinnah and colleagues recently pointed out, the many overlapping dystonia syndromes may limit the use of the syndromic approach in clinical practice.[17] Evidently, classification systems for disease entities and the way we use them evolve over time. In this NGS era, (syndromic) clinical classification of dystonia will remain as important as ever, also to guide interpretation of the genetic results.[18, 19] The process will be iterative, with syndromes and genetic results analyzed back and forth to improve the accuracy and comprehensiveness of both.

In a recent study, Lumsden et al. retrospectively applied the dystonia classification system to 145 patients with young-onset dystonia, using a two-step cluster analysis to identify groups of patients with similar characteristics, and detected four main clusters of patients.[7] In the future, similar software programs to cluster phenotypic features may be helpful for both clinical and research purposes, including the categorization of clinical data for biobanking,[20] and expandable online tools to link NGS test results to the clinical and phenotypic data of the individual patient.[21] However, a prerequisite for adequate use of these software programs, databases and online tools, is the consistent input of unequivocal phenotypic data. This cannot be done without good clinical characterization, requiring a phenomenological classification with clear definitions and well-trained raters.

Limitations

Our results need to be interpreted with caution. First, because each vignette was evaluated by only two clinicians, while in an ideal situation, the inter-rater agreement should be based on a larger number of raters. A second limitation of the study is that the patients were assessed only via written case descriptions instead of video assessments or live examinations. It is hard to verify if the results would have been markedly different if video assessments had been available. To our knowledge, there are no comparative studies for dystonia comparing the interrater agreement of professionals seeing videos and professionals reading vignettes. In 2012 Sellier and colleagues performed two studies on the interrater agreement for classifying children with CP, based either

on vignettes or on videos.[22] However, from these studies we cannot conclude that the interrater agreement improves with the use of videos, because the participants reading vignettes had different professional backgrounds than those assessing videos.[22] Other studies showed that videos might give rise to even more variability than written case reports, because with reports some choices regarding the clinical characterization have already been made by the author of the vignette.[12, 23] This may also apply to in-person evaluations and is underscored by the results of the interrater agreement study using video assessments of dystonia patients, which showed only slight to moderate interrater agreement.[10] Interestingly, in our study the interrater agreement was also suboptimal for Axis I items, such as 'age at onset', 'disease course' and 'variability', which are mostly based on written or spoken information instead of moving images (video assessments or live examinations). This underscores how individual interpretations by clinicians prevail.

Conclusion

For the majority of the dystonia cases in our study, the classification and syndrome definition of dystonia varied considerably among clinicians. These differences carry the risk of different diagnostic and treatment strategies being employed and may well hamper the search for phenotype-genotype correlations. Because the clinical characterization remains of great importance, also in this NGS era, we advocate starting a discussion on how to improve the diagnostic accuracy of the dystonia classification system and the definitions of dystonia syndromes. Future research should explore how to cluster phenotypic data into meaningful subgroups, both for clinical and research purposes.

Acknowledgments

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References

1 de Koning TJ, Tijssen MA. Movement disorders in 2014. Genetic advances spark a revolution in dystonia phenotyping. Nat Rev Neurol. 2015;11(2):78-9.
2 Jinnah HA, Teller JK, Galpern WR. Recent developments in dystonia. Curr Opin Neurol. 2015;28(4):400-5.
3 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(7):774-81.
4 Fung VS, Jinnah HA, Bhatia K, et al. Assessment of patients with isolated or combined dystonia: an update on dystonia syndromes. Mov Disord. 2013;28(7):889-98.
5 Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863-73.
6 Jinnah HA, Albanese A. The New Classification System for the Dystonias: Why Was it Needed and How was it Developed? Mov Disord Clin Pract. 2014;1(4):280-4.
7 Lumsden DE, Gimeno H, Lin JP. Classification of dystonia in childhood. Parkinsonism Relat Disord. 2016;33:138-41.
8 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(4):569-75.
9 L. Fleiss J. Measuring Nominal Scale Agreement Among Many Raters. Psychological Bulletin. 1971;76(5):378-82.
10 Beghi E, Regio V, Papantonio A, et al. Reliability of clinical diagnosis of dystonia. Neuroepidemiology. 2014;43(3-4):213-9.
11 Zutt R, Dijk JM, Peall KJ, et al. Distribution and Coexistence of Myoclonus and Dystonia as Clinical Predictors of *SGCE* Mutation Status: A Pilot Study. Front Neurol. 2016;7:72.
12 van der Salm SM, de Haan RJ, Cath DC, et al. The eye of the beholder: inter-rater agreement among experts on psychogenic jerky movement disorders. J Neurol Neurosurg Psychiatry. 2013;84(7):742-7.
13 Stroink H, van Donselaar CA, Geerts AT, et al. Interrater agreement of the diagnosis and classification of a first seizure in childhood. The Dutch Study of Epilepsy in Childhood. J Neurol Neurosurg Psychiatry. 2004;75(2):241-5.
14 www.movementdisorders.org/MDS/Education/Rating-Scales/Training-Programs.htm.
15 Balint B, Bhatia KP. Isolated and combined dystonia syndromes - an update on new genes and their phenotypes. Eur J Neurol. 2015;22(4):610-7.
16 Berman BD, Jinnah HA. Dystonia: Five new things. Neurol Clin Pract. 2015;5(3):232-40.
17 Jinnah HA, Albanese A, Bhatia KP, et al. Treatable inherited rare movement disorders. Mov Disord. 2018;33(1):21-35.
18 Hennekam RC, Biesecker LG. Next-generation sequencing demands next-generation phenotyping. Hum Mutat. 2012;33(5):884-6.
19 Foley AR, Donkervoort S, Bonnemann CG. Next-generation sequencing still needs our generation's clinicians. Neurol Genet. 2015;1(2):e13.
20 Lohmann E, Gasser T, Grundmann K. Needs and Requirements of Modern Biobanks on the Example of Dystonia Syndromes. Front Neurol. 2017;8:9.
21 Lill CM, Mashychev A, Hartmann C, et al. Launching the movement disorders society genetic mutation database (MDSGene). Mov Disord. 2016;31(5):607-9.
22 Sellier E, Horber V, Krageloh-Mann I, et al. Interrater reliability study of cerebral palsy diagnosis, neurological subtype, and gross motor function. Dev Med Child Neurol. 2012;54(9):815-21.
23 Eggink H, Kremer D, Brouwer OF, et al. Spasticity, dyskinesia and ataxia in cerebral palsy: Are we sure we can differentiate them? Eur J Paediatr Neurol. 2017;21(5):703-6.

Supplement 1. *Categorization of co-occurring neurological or systemic manifestations*

Category	**Reported features***
Psychiatric and behavioral problems	Depression, anxiety, panic attacks, ADHD, autism, PTSS
Static cognitive impairment	Mental retardation, psychomotor retardation
Cognitive decline	Dementia, late onset cognitive problems, frontal dysfunction
Cranial nerves and sensory input	(congenital) deafness, hearing loss, visual loss / visual disturbances, abnormal eye movements, nystagmus, ocular motor apraxia
Peripheral nerves and autonomic nervous system	Polyneuropathy, carpal tunnel syndrome, autonomic symptoms
Muscle symptoms	Myalgia, exercise intolerance, muscle weakness, myopathy
Paroxysmal disorders	Epilepsy, transient loss of consciousness, non-cardiac syncope, hemiplegic migraine
Dysmorphisms and skeletal abnormalities	Short stature, congenital deformity of toes, facial dysmorphisms, pes cavus, hammer toes
Systemic disorders	Congenital heart disease, asthma, endocrine disorders (including diabetes mellitus, hypothyroidism, adrenal insufficiency), cutaneous hyperpigmentation
Miscellaneous#	Delayed motor development, perinatal asphyxia, axial hypotonia, hydromyelia, sleep apnea

* Answers given by the clinicians for the sixth item of Axis 1 of the dystonia classification: "occurrence of other neurological or systemic manifestations".

If clinicians reported features in the same category, this was always considered as 'agreement', except for the category 'Miscellaneous'. The five features of 'Miscellaneous' were only considered as 'agreement' if both clinicians reported the same feature within this category.

Note: Features mentioned by clinicians as 'co-occurring neurological or systemic manifestations' that were excluded from our descriptive analyses were: pain, worsening with anxiety and stress, worsening with writing and dystonic jerks (because we considered these as part of the dystonia); chorea, myoclonus and ataxia (because these are co-occurring movement disorders, which were covered by a separate question); positive family history and alcohol responsiveness (because we did not consider these aspects as co-occurring neurological or systemic manifestations); and brain imaging abnormalities (which is an Axis II item).

Supplement 2. *Number of cases with agreement upon the dystonia syndrome*

	Agreement upon all Axis I items and upon dystonia syndrome*	Agreement upon dystonia syndrome
Isolated dystonia syndromes		
Adult-onset generalized dystonia	1	1
Hemidystonia		1
Combined dystonia syndromes		
Dystonia with or without parkinsonism of infantile or childhood onset	1	2
Dystonia with or without parkinsonism of adolescent and young adult onset	1	1
Dystonia with myoclonus		9
Dystonia as part of paroxysmal dyskinesia	2	6
Dystonia with chorea		3
Dystonia syndromes with other neurological involvement		
Dystonia with deafness		2
Syndromes according to brain imaging		
Dystonia with MRI evidence of neuronal brain iron accumulation	1	1
Other		
Progressive dystonia with normal brain MRI or generalized atrophy		1
'None of the above'	1	4
Total	**7**	**31**

** Note: an absolute (100%) observed agreement between clinicians for all items of Axis I of the dystonia classification was reached in 9/56 cases (16.1%) (vignettes 2, 7, 24, 29, 32, 34, 37, 54, 59), and for both the Axis I classification and the dystonia syndrome in 7/56 cases (12.5%) (vignettes 2, 24, 29, 32, 37, 54, 59).*

Supplement 3. *Examples of non-agreement with regard to the first five Axis I items*

Age at onset

Several patients first had an abnormal motor development or an abnormal walking pattern, and several years later they developed involuntary movements (vignettes 12, 19, 21), which led to divergent answers for 'age at onset'. In other cases, different interpretations of the age at onset could be explained by dystonic jerks and dystonic posturing which started at different ages (vignettes 23, 30). Another case in which clinicians gave different answers concerned a patient who had had paroxysmal attacks with abnormal movements since the age of 1 year and who developed persistent dystonia (abnormal walking) from the age 4 years (vignette 5).

Body distribution

In 4/9 cases in which both clinicians agreed upon the presence of paroxysmal dystonia, they did not agree upon body distribution (vignettes 17, 26, 42, 47). In these four cases the findings of the neurological examination were normal, so the classification of body distribution was solely based on the history. For example, one patient described episodes with involuntary posturing and jerky movements of his left leg and right arm, and he once had an episode with involuntary movements in his whole body (vignette 42). This was interpreted by one clinician as multifocal isolated dystonia and by the other as generalized dystonia with myoclonus.
Another example of divergent answers on the item 'body distribution' was a patient with dystonia and parkinsonism with an abnormal truncal posture, interpreted by one clinician as multifocal dystonia combined with parkinsonism of the trunk, and by the other as generalized dystonia with truncal involvement (vignette 22). Jerky movements could also lead to different interpretations of body distribution, as described below (see item 'isolated or combined').

Disease course

One patient had progressive dystonic jerks and stable dystonic posturing, which was interpreted by one clinician as a progressive and by the other clinician as a static disease course (vignette 10, a similar example is vignette 15). Another illustrative case concerned a young patient who had an abnormal muscle tone as an infant, with delayed motor milestones, and later developed progressive hyperkinetic movements (vignette 12). In this case, one clinician rated a static disease course, while the other considered it progressive.

Variability

Noteworthy with regard to the item 'variability' was a patient with multifocal dystonia who had action-specific dystonia in one body part (writers' cramp) and persistent dystonic symptoms in other body parts (e.g. neck, legs), which led to divergent answers by the two clinicians (action-specific dystonia and persistent dystonia) (vignette 33, similar examples are vignettes 14 and 46). Another example comprised a patient who complained about symptoms that could fit with action-specific dystonia, however, the neurological examination only showed persistent dystonia (vignette 46). And in this case too, the two clinicians gave different answers for the item 'variability' (action-specific dystonia and persistent dystonia).

Isolated or combined

Several patients had jerky movements which were interpreted by one clinician as dystonic jerks without any co-occurring movement disorder, and by the other clinician as myoclonus or chorea (vignettes 10, 15, 18, 30, 52), as shown in Supplement 4. Different ratings of 'isolated or combined' may also influence the interpretation of body distribution; this is illustrated by a patient with cervical dystonia and jerky movements in both arms, rated as isolated dystonia involving multiple body parts by one clinician, and by the other as dystonia combined with myoclonus with a more limited body distribution (vignette 18, similar examples are vignettes 30 and 46). A final example is a patient with cervical dystonia and dystonic jerks, who mentioned in the case history that she was able to suppress the involuntary movements to a certain extent (vignette 18). For this vignette, one of the raters noted tics as a co-occurring movement disorder, despite the fact that only dystonic posturing and dystonic jerks were listed in the neurological examination report of the vignette.

Supplement 4. *Agreement with regard to co-occurring manifestations*

	Feature 1	**Feature 2**	**Feature 3**	**Feature 4**
Co-occurring movement disorders *				
Both clinicians gave an answer	**24**	**4**	**0**	NA
Agreement	23	4	0	
Non-agreement	1	0	0	
One of the clinicians gave an answer	**13**	**9**	**1**	NA
Ataxia	1		1	
Myoclonus	5	2		
Spasticity	1			
Chorea	2	5		
Tics		1		
Paroxysmal dyskinesia	2			
Parkinsonism	1	1		
Tremor	1			
Neither clinician gave an answer	**19**	**43**	**55**	NA
Agreement #	75%	84%		
Co-occurring neurological or systemic manifestations				
Both clinicians gave an answer	**20**	**5**	**2**	**2**
Agreement	20	3	2	2
Non-agreement	0	2	0	0
One of the clinicians gave an answer	**15**	**15**	**5**	**1**
Psychiatric and behavioral problems	5	1		
Static cognitive impairment	2	3		
Cognitive decline		1	1	
Cranial nerves and sensory input	1	1		
Peripheral nerves		2	1	
Muscle symptoms	2	1		
Paroxysmal disorders	2	1		
Dysmorphisms/skeletal abnormalities	1	1	1	
Systemic disorders	1	3		
Miscellaneous	1	1	2	1
Neither clinician gave an answer	**21**	**36**	**49**	**53**
Agreement#	**73%**	**70%**		

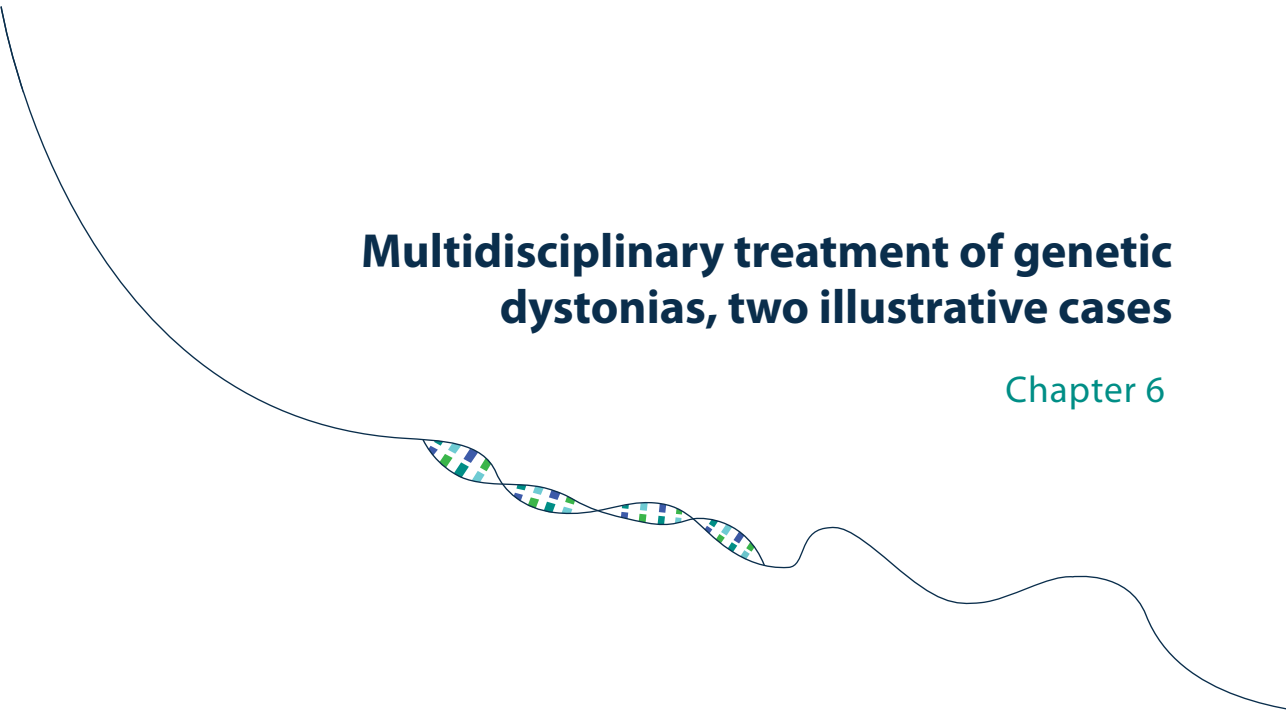
* specification of co-occurring movement disorders is not part of the Axis I classification

percentage of agreement was defined as the percentage of cases in which both clinicians gave an answer in the same category, plus the percentage of cases in which both clinicians agreed upon the absence of other neurological or systemic manifestations. We only calculated the percentage of agreement for those cases with one or two features mentioned, as these were considered the most relevant (see Methods).

NA, not applicable

Multidisciplinary treatment of genetic dystonias, two illustrative cases

Chapter 6



Dystonia-deafness syndrome caused by a β-actin gene mutation and response to deep brain stimulation

Chapter 6.1

H. Eggink, M.E. van Egmond, C.C. Verschuuren-Bemelmans,
M.C. Schönherr, T.J. de Koning, D.L.M. Oterdoom,J.M.C. van Dijk, M.A.J. Tijssen

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Supplementary videos related to this chapter can be found at
http://onlinelibrary.wiley.com/doi/10.1002/mds.26842/abstract

Abstract

Introduction
Dystonia-deafness syndrome is a distinct clinical presentation within the dystonia-spectrum. Although several genetic and acquired causes have been reported, etiology remains unknown in the majority of patients.

Objectives
To describe 2 patients with dystonia deafness syndrome due to a beta-actin gene mutation.

Methods
We report on disease course, genetic testing and management of 2 patients, mother and daughter, presenting with dystonia-deafness syndrome.

Results
After exclusion of known dystonia-deafness syndrome causes, whole exome sequencing revealed an beta-actin gene mutation (p.Arg183Trp) in both patients. Although beta-actin gene mutations are generally associated with developmental Baraitser-Winter syndrome, dystonia-deafness syndrome has been reported once in identical twin brothers. Bilateral GPi-DBS led to a significant decrease of dystonia and regain of independency in our patients.

Conclusion
The p.Arg183Trp mutation in the beta-actin gene is associated with the clinical presentation of dystonia-deafness syndrome, even with only minimal or no developmental abnormalities of Baraitser-Winter syndrome. GPi-DBS should be considered to ameliorate the invalidating dystonia in these patients.

Introduction

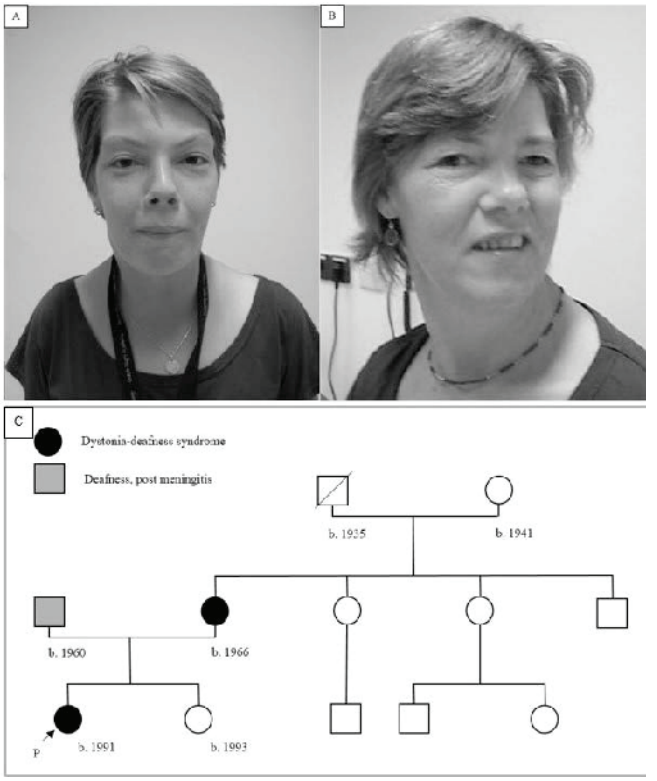
Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often patterned movements and/or postures. A combination of dystonia and sensory-neural deafness, referred to as dystonia-deafness syndrome (DDS), is a distinct clinical presentation within the dystonia-spectrum. Several genetic and acquired causes are associated with DDS, but the etiology remains undetermined in most patients.[1]

Patients and methods

We describe 2 patients, mother and daughter, presenting with DDS. The index patient was a 22 year old woman with congenital sensory-neural deafness, generalized dystonia and remarkably high-arched eyebrows (figure 1A). At the age of 19, dystonic symptoms started with writer's cramp and progressed to severe generalized dystonia within 8 months. Brain MRI, including suspectibility weighted imaging showed no abnormalities. Treatment with levodopa, trihexyphenidyl, clozapine, clonazepam and botulinum toxin injections were of limited effect. We performed bilateral DBS of the internal globus pallidus (GPi). Pallidal stimulation with continuation of botulinum toxin injections in her neck muscles led to a substantial improvement at 12-month follow-up (Burke Fahn Marsden Dystonia Rating Scale (BFMDRS) 78 vs. 24.5; stimulation parameters left/right GPi 0-/8-, amplitude 5.0V; pulse width 90 µsec, frequency 130 Hz). She regained her total independence, communication skills and ability to walk (see Video 1).

Patient 2, the 49-year-old mother of the index patient, was born with sensory-neural hearing loss leading to deafness at the age of 6. She had no other developmental abnormalities (figure 1B-C). Aged 16, her hands started trembling and 5 years later she developed writer's cramp. Her symptoms slowly progressed to dystonia of her trunk, neck, arms and legs and she became wheelchair dependent at 42. In addition, she suffered from a vital depression and auditory hallucinations. Because of increasing problems in daily functioning (BFMDRS 63.5) and stable psychiatric symptoms, she was recently treated with DBS and shows improvement of symptoms after 4 months (see Video 2, stimulation parameters left/right GPi 0-/8-, amplitude 2.5V, pulse width 90 µsec, frequency 135 Hz).

Figure 1.



Face of proband (A) with remarkably high-arched eyebrows and her mother (B) with no facial abnormalities. Pedigree of the family (C) showing proband (P) and mother as the only affected individuals.

Given that the positive family history pointed toward a genetic cause of the DDS, mutations in the DYT1 gene, DDP1 gene (Mohr-Tranebjærg syndrome) and mitochondrial DNA were screened and excluded.[2] Single nucleotide polymorphism array and targeted resequencing of 88 dystonia-associated genes associated did not lead to a causative gene.[2]

Whole exome sequencing (WES) was performed after using the Agilent SureSelectXT Human All Exon 50 Mb Kit for exome capture (Agilent Technologies, Santa Clara, CA) by an Illumina HiSeq2000TM machine at BGI-Europa in Denmark. After "read alignment" with BWA and 'variant calling' with GATK, variants were annotated by a program developed at the genetics department of the Radboud MC (Nijmegen, The Netherlands).[3] The gene variants that were present in the genes of the hearing impairment gene panel, DGD141114 were selected and ranked according to their predicted pathogenicity. Reported variants were confirmed by Sanger sequencing of the variant. The WES revealed a mutation in the beta-actin gene (*ACTB*) c.547C>T (p.Arg183Trp) in both mother and daughter.

Discussion

Known genetic causes of DDS include Mohr-Tranebjærg syndrome, organic acidurias, Woodhouse-Sakati syndrome and rare mitochondrial disorders. Here, we report 2 cases from one family with a p.Arg183Trp mutation in *ACTB* encoding for cytoplasmatic actin (OMIM *102630). *ACTB* mutations have been described with Baraitser-Winter syndrome. This is a developmental disorder recognized by congenital ptosis, hypertelorism, high-arched eyebrows and ocular colobomata and frequently associated with sensory-hearing deafness.[4] Verloes et al. advocated for a broader Baraitser-Winter cerebrofrontofacial syndrome (BWCFF)[5], a heterogeneous disorder with muscular, visceral and craniofacial involvement. Although definite diagnostic criteria are not established, facial anomalies with high-arched eyebrows appear to be the most consistent feature.

DDS has once been associated with *ACTB* mutation in 2 identical twin brothers with the exact same as our patients. The boys presented with DDS and developmental abnormalities (cleft palate, hypertelorism and achalasia) and normal brain imaging.[6] Dystonic symptoms started at the age of 12, generalized rapidly and both died of aspiration pneumonias in their twenties. Postmortem investigations suggested a neurodegenerative process with some iron accumulation in pallidal and nigral areas and aggregation of actin depolymerizing factor in eosinophilic rod-like structures in striatum and neocortex.6

Our index patient did have DDS but only showed minimal criteria (e.g. high-arched eyebrows) of BWCFF. Her mother suffered from isolated DDS. Taken together with the previously published twin brothers, the manifestation of DDS in all 4 patients carrying the p.Arg183Trp mutation makes the mutation highly suggestive of being causative. Interestingly, this is the first report of an autosomal-dominant inheritance, given that other *ACTB* mutations were reported as de novo.5 Procaccio and colleagues previously suggested an autosomal-dominant trait, but had no paternal DNA to support this theory.[6] DBS is the treatment of choice in medical refractory dystonia.[7] Our index patient showed an excellent response on pallidal stimulation, regaining her independency and communication abilities. This is in line with 2 previous case reports of DDS, 1 genetic confirmed and 1 unconfirmed Mohr-Tranebjærg syndrome patient, both leading to more than 70% reduction of dystonic symptoms.[8, 9]

In summary, the p.Arg183Trp mutation in the *ACTB* gene appears to be associated with an autosomal dominant syndrome of DDS, with minimal or no classic characteristics of the BWCFF syndrome. We hypothesize that DDS and BWCFF are part of the same phenotypic spectrum of *ACTB*-gene mutations. Pallidal stimulation is to be considered to ameliorate invalidating dystonia in these patients.

References

1 Kojovic M, Parees I, Lampreia T, et al. The syndrome of deafness-dystonia: clinical and genetic heterogeneity. Mov Disord. 2013;28(6):795-803.
2 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(7):774-81.
3 Neveling K, Feenstra I, Gilissen C, et al. A post-hoc comparison of the utility of sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. Hum Mutat. 2013;34(12):1721-6.
4 Baraitser M, Winter RM. Iris coloboma, ptosis, hypertelorism, and mental retardation: a new syndrome. J Med Genet. 1988;25(1):41-3.
5 Verloes A, Di Donato N, Masliah-Planchon J, et al. Baraitser-Winter cerebrofrontofacial syndrome: delineation of the spectrum in 42 cases. Eur J Hum Genet. 2015;23(3):292-301.
6 Procaccio V, Salazar G Fau - Ono S, Ono S Fau - Styers ML, et al. A mutation of beta - actin that alters depolymerization dynamics is associated with autosomal dominant developmental malformations, deafness, and dystonia. (0002-9297 (Print)).
7 Vidailhet M, Jutras MF, Grabli D, et al. Deep brain stimulation for dystonia. J Neurol Neurosurg Psychiatry. 2013;84(9):1029-42.
8 Havrankova P, Jech R, Roth J, et al. Beneficial effect of deep brain stimulation of GPi in a patient with dystonia-deafness phenotype. Mov Disord. 2009;24(3):465-6.
9 Cif L, Gonzalez V, Garcia-Ptacek S, et al. Progressive dystonia in Mohr-Tranebjaerg syndrome with cochlear implant and deep brain stimulation. Mov Disord. 2013;28(6):737-8.

Video legends

Video 1

The video shows the index patient sitting, pronating her arms, walking and writing before (left) and twelve months after (right) bilateral deep brain stimulation of the globus pallidus internus. Before the operation, the patient was not able to sit in a chair, communicate via sign language or walk because of her mobile dystonia. She was fed by a nasogastric tube, because of her dysphagia and subsequent weight loss. Twelve months after the surgery her mobile dystonia was greatly reduced, leading to her ability to sit, walk and communicate again. She was still in need of botulinum toxin injections in her neck to reduce the tonic neck dystonia.

Video 2

This video shows patient 2, mother of patient 1, in sitting position, pronating her arms, finger tapping and walking before (left) and 4 months after (right) bilateral pallidal stimulation. On this relatively short term, the stimulation led to reduction in her torticollis and a better ability to walk.

Reversal of status dystonicus after relocation of pallidal electrodes in DYT6 positive generalized dystonia

Chapter 6.2

D.L.M. Oterdoom*, M.E. van Egmond*, L.C. Ascencao, J.M.C. van Dijk, A. Saryyeva, M. Beudel, J. Runge, T.J. de Koning, M. Abdallat, H. Eggink, M.A.J. Tijssen, J.K. Krauss

**Shared first authors*

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Abstract

Background

DYT6 dystonia can have an unpredictable clinical course and the result of Deep Brain Stimulation (DBS) of the internal part of the Globus Pallidus (GPi) is known to be less robust than in other forms of autosomal dominant dystonia. Patients who had previous stereotactic surgery with insufficient clinical benefit form a particular challenge with very limited other treatment options available.

Case report

A pediatric DYT6 patient unexpectedly deteriorated to status dystonicus 1 year after GPi DBS implantation with good initial clinical response. After repositioning the DBS electrodes the status dystonicus resolved.

Discussion

This case study demonstrates that medication-resistant status dystonicus in DYT6 dystonia can be reversed by relocation of pallidal electrodes. This case highlights that repositioning of DBS electrodes may be considered in patients with status dystonicus, especially when the electrode position is not optimal, even after an initial clinical response to DBS.

Introduction

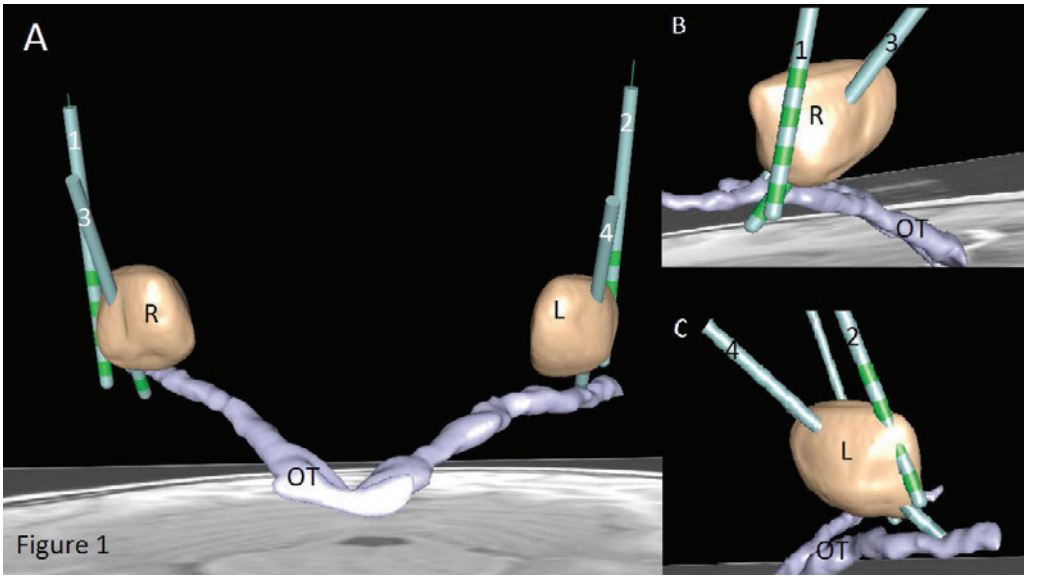
Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions, causing abnormal, often repetitive, movements, postures or both. Childhood dystonia is often genetic,[1] and DYT6 is one of the autosomal dominant forms, caused by mutations in the thanatos-associated domain-containing apoptosis-associated protein 1 (*THAP1*) gene.[2, 3] Clinically, DYT6 is characterized by an early age of onset, with symptoms that frequently start in the craniocervical region and spread to the extremities.[3, 4] Case series on deep brain stimulation (DBS) of the globus pallidus internus (GPi) for DYT6 suggest that improvement is to be expected, but less robust and less predictable than DYT1 dystonia.[4-6] One potential reason for this is that there is often prominent oromandibular dystonia, which is less responsive to DBS.[7] Furthermore, deterioration of dystonic symptoms 1-3 years after implantation has been reported in DYT6 patients.[4, 5]

Status dystonicus (SD) represents the severe end of a deteriorating spectrum of dystonia.8 Recently, SD has been defined as: "a movement disorder emergency characterized by severe episodes of generalized or focal hyperkinetic movement disorders that had necessitated urgent hospital admission because of life-threatening complications regardless of the patient's neurological condition at baseline."[9] To date, there is no consensus on the optimal treatment protocol for SD,[8, 10-12] but early surgical intervention may be a valuable addition to the medical armamentarium for its cessation.[8, 13] Here we report the case of an 11-year-old DYT6 patient with unexpected and rapid clinical deterioration to SD, after a 1- year period of good response to GPi DB. The SD was reversed by repositioning of the DBS electrodes.

Case report

After a normal birth and development, our patient developed a disturbed walking pattern at the age of 3.5 years. At age 5 he was diagnosed with dystonia and 1 year later a p.Arg29Pro mutation in the *THAP1* gene was found and the diagnosis DYT6 dystonia was made. His dystonia gradually progressed to the upper limbs at age 6 and at age 9 he developed generalized dystonia. Despite pharmacological treatment with different medications his symptoms further deteriorated and he was no longer able to attend school. He became wheelchair bound with hardly intelligible speech and developed a severely impaired hand function. The neurological assessment on the Burke-Fahn-Marsden Dystonia Rating Scale Movement (BFMDRS-M) at that time was 71 (range 0-120), and on the disability part of the scale (BFMDRS-D) the score was 21 (range 0-30), see Table 1. After multidisciplinary evaluation, DBS was performed with bilateral pallidal electrodes (model 3387; Medtronic, MN, USA) using direct magnetic resonance guided stereotactic targeting (Figure 1). A postoperative computed tomography scan showed that the actual electrode positions were more lateral than intended (Table 2). Nevertheless, the patient responded well to the DBS and 1 year after the implantation, he could walk without support, and had a clearly improved hand function and speech (BFMRSD-M 69 and BFMDRS-D 14). However, after the first year the effect of pallidal stimulation decreased and at 15 months postoperatively (age 11 years) his clinical status progressively deteriorated to SD, requiring hospital admission. Constipation was considered as a possible trigger and was treated by laxatives without success. No other possible triggers were identified.

Figure 1. Schematic depiction of the electrode positions



A) anterior coronal 3D view of initial electrode positions (right 1, left 2) and electrode positions after second surgery (right 3, left 4). Note position outside the right GPi (R) and barely inside the left GPi (L) of initial electrodes and the improved position after revision surgery. B) sagital view from the right. C) sagital view from the left. Note the improved position of 2 and 4 with at least two contacts within both GPi's. This is achieved by a more frontal burr hole facilitating a more oblique trajectory through the GPi. R, GPi right, L, GPi left, OT, optic tract, 1, initial electrode right, 2, revised electrode right, 3, nitial electrode left, 4, revised electrode left. Anatomical structures and DBS electrodes were drawn into the patients CT and MRI in SureTune2 software (Medtronic, MN, USA).

Table 1. BFMDSRS scores at different time points

BFMDRS scores	**May 2014**	**June 2015**	**December 2015**	**January 2016**	**February 2016**	**October 2017**
	Before 1st surgery	1 year after 1st surgery	Status dystonicus	Before 2nd surgery	After 2nd surgery	3 years after 1st surgery
Disability	26	14	29	30	27	15
Movement	71	69	90	108	73	64
Total	97	83	119	138	100	79

Note: The first DBS implantation was in May 2015, the second in February 2016. For privacy reasons, the patient and his parents did not give permission to provide supplemental videos.

Table 2. *Electrode positions relative to midcommisural point (in millimeters)*

	X left	Y left	Z left	X right	Y right	Z right
First surgery	22.4**	2.7	-2.9	22.6**	3.1	-2.8
Second surgery	20	3	-4	20	3	-4

*Target coordinates relative to AC-PC midpoint in mm. **Realized lateral coordinate left 23.1 mm and right 24.4 mm.*

Despite symptomatic treatment with trihexyphenidyl (6 mg/day, body weight 30 kg), gabapentin (300 mg/day) and clonazepam (1,0 mg/day) and reprogramming of the DBS settings, he developed severe episodes of generalized dystonic spasms, which progressed to continuous abnormal postures and sustained contractions. This was accompanied by metabolic derangements (creatine kinase levels up to 920 IU/L), exhaustion, pain, sleep disturbance, dysphagia and cachexia. Based on the criteria described by Allen et al.,[12] he was initially diagnosed with grade 3 SD, further deteriorating towards grade 4 SD.[12] Since this is a potentially life-threatening situation, the patient was admitted to an intensive care unit (ICU). On the ICU, pharmacological treatment with high doses of benzodiazepines (up until intravenous midazolam 1 mg/kg/hour and enteral clonazepam 3,6 mg/day, body weight 25 kg), clonidine (intravenous 105 ug/day), chloral hydrate (1250 mg/day), baclofen (12,5 mg/day), gabapentin (900 mg/day) and trihexyphenidyl (8 mg/day) had only limited effect. Nevertheless, he experienced less discomfort, less pain, and the metabolic derangements resolved. However, he suffered from severe adverse effects, especially drowsiness. When subsequently decreasing the dosages, the dystonic movements and the discomfort became more severe. After four weeks on the ICU, his condition deteriorated to a total BMFDRS score of 138 (Table 1).

After extensive multidisciplinary and multicenter deliberation it was decided to reposition the pallidal electrodes to a more dorsal and more medial position. Target coordinates of the old and new electrodes are shown in Table 2 and the new target was further refined by microelectrode recording. After the repositioning of the DBS electrodes the SD ameliorated to a BMFDRS score of 100 after 1 week, and medication dosages were drastically reduced. Six months after the second surgery he was able to walk short distances unaided and attend school without medication (BFMDRS-M 64, BFMDRS-D 15). At present, the duration after the repositioning of the electrodes is 24 months, and the clinical condition of the patient is still gradually improving.

During the first surgery the goal was to place electrodes in the posteroventrolateral GPi. However, Figure 1 shows that the electrodes were actually positioned within the external segment of the globus pallidus (GPe). The new electrodes were placed more medially in the posteroventrolateral GPi. The stimulation parameters after the initial implantation were: bilateral monopolar stimulation of the most ventral contacts (pulse width 90 µs frequency 130 Hz and voltage 2.5 V). In the first year after the initial implantation, voltages were bilaterally increased to 3.5 V. Nine months after the initial implantation stimulation parameters were switched to a big bipolar stimulation field (0-/3+ and 8-/11+), with pulse width of 90 µs, a stimulation frequency

of 130 Hz and a voltage of 4.0 V on both sides. During the SD, the stimulation frequency was changed into 180 Hz on both sides without clinical effect. After the repositioning the stimulation parameters were: contacts 1-/2+ and 8-/9+, pulse width 210 µs frequency 130 Hz, and a voltage of 5.4 V for both sites.

Discussion

This case study demonstrates that medication-resistant SD in DYT6 dystonia can be reversed by repositioning of pallidal electrodes. This is an important finding, particularly because status dystonicus (SD) can be life-threatening.[8]

The exact prevalence of SD in childhood is unknown.[8] Two comprehensive systematic literature studies describe a total of 133 episodes of SD in 109 patients, the majority of whom were under age 16 years.[8, 10] Clinically, SD is characterized by the development of increasingly frequent or continuous severe episodes of generalized dystonic spasms,[10, 12] often complicated by one or more of the following: bulbar weakness compromising upper airway patency; exhaustion, pain and metabolic imbalances.[12] In two-thirds of cases, a precipitating factor can be identified.[8, 10] Important triggers include infection, pain, constipation or a medication change.[8, 10, 11] Addressing these factors is the first step of a recently proposed multistaged approach to childhood SD.[10] Neurosurgical intervention for SD appears to have become more frequent in the management of SD, with reported percentages ranging from in 40 – 66 % of SD patients.[8, 10] In about 70% of these cases, return to the pre-SD baseline or further improvements have been reported.8, 10 However, prospective blinded studies on the treatment of SD with systematic follow-up are missing.

In our case, the initial DBS placement gave some clinical benefit, despite suboptimal electrode localisation. Fifteen months after surgery the patient developed severe SD and repositioning of DBS electrodes led to return to the pre-SD baseline condition. The initial response to the first DBS implantation despite the lateral position of the electrodes, might be explained by extension of the electrical field into the GPi. Alternatively, it could also be the effect of GPe inhibition. As proposed in the basal-ganglia-thalamic-circuit (BGTC) model for dystonia,[14] DBS induced increased GPe activity might disrupt the increased BGTC synchronized oscillations in dystonia.[8, 9, 15] However, the optimal DBS-target for dystonia is the posteroventrolateral GPi.[7] In the literature, target coordinates vary from 18 to 22 mm lateral from the midline.[16-18] In our patient, the electrodes were placed too lateral (left 23.1 mm / right 24.4 mm). The reversal of SD by repositioning of the electrodes highlights the importance of optimal electrode placement.

The case also illustrates the unpredictable clinical effect of DBS in DYT6. This is in line with previous studies focusing on the response of DYT6 patients to pallidal DBS .[4-6, 19] Two of these studies describe DYT6 patients who initially responded well to pallidal stimulation, but after 1-3 years of stimulation, regression occurred requiring lead reposition.[4, 5]

Noteworthy, in this case study, changes in clinical condition of the patient seem to be reflected better by the BFMDRS-D scores than by the BFMDRS-M scores. For example, the BFMDRS-M score 1 year after the first implementation (69), hardly differs from the preoperative BFMDRS-M score (71), while daily functioning was clearly improved, as is shown by a decrease in BFMDRS-D scores from

26 to 14. A possible explanation is that BFMDRS-M measures the intensity of dystonic movements, which usually fluctuate over minutes, hours or days,[8] while BFMDRS-D scores reflect disability for a longer period of time. This observation is paralleled by the results of a previous report showing that DBS may lead to a meaningful change across multiple domains of functioning and disability, even in the absence of a significant change in BFMDRS-M scores.[20]

In conclusion, this case study demonstrates that severe SD in DYT6 dystonia can be reversed by relocation of pallidal DBS electrodes, highlighting the importance of optimal electrode placement. Prospective multicenter studies with systematic follow-up are needed to investigate the optimal timing and patient selection for pallidal DBS in SD.

References

1 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(7):774-81.

2 Fuchs T, Gavarini S, Saunders-Pullman R, et al. Mutations in the THAP1 gene are responsible for DYT6 primary torsion dystonia. Nat Genet. 2009;41(3):286-8.

3 Djarmati A, Schneider SA, Lohmann K, et al. Mutations in THAP1 (DYT6) and generalised dystonia with prominent spasmodic dysphonia: a genetic screening study. Lancet Neurol. 2009;8(5):447-52.

4 Panov F, Tagliati M, Ozelius LJ, et al. Pallidal deep brain stimulation for DYT6 dystonia. J Neurol Neurosurg Psychiatry. 2012;83(2):182-7.

5 Groen JL, Ritz K, Contarino MF, et al. DYT6 dystonia: mutation screening, phenotype, and response to deep brain stimulation. Mov Disord. 2010;25(14):2420-7.

6 Zittel S, Moll CK, Bruggemann N, et al. Clinical neuroimaging and electrophysiological assessment of three DYT6 dystonia families. Mov Disord. 2010;25(14):2405-12.

7 Vidailhet M, Jutras MF, Grabli D, et al. Deep brain stimulation for dystonia. J Neurol Neurosurg Psychiatry. 2013;84(9):1029-42.

8 Lumsden DE, King MD, Allen NM. Status dystonicus in childhood. Curr Opin Pediatr. 2017;29(6):674-82.

9 Ruiz-Lopez M, Fasano A. Rethinking status dystonicus. Mov Disord. 2017;32(12):1667-76.

10 Fasano A, Ricciardi L, Bentivoglio AR, et al. Status dystonicus: predictors of outcome and progression patterns of underlying disease. Mov Disord. 2012;27(6):783-8.

11 Manji H, Howard RS, Miller DH, et al. Status dystonicus: the syndrome and its management. Brain. 1998;121 (Pt 2):243-52.

12 Allen NM, Lin JP, Lynch T, et al. Status dystonicus: a practice guide. Dev Med Child Neurol. 2014;56(2):105-12.

13 Ben-Haim S, Flatow V, Cheung T, et al. Deep Brain Stimulation for Status Dystonicus: A Case Series and Review of the Literature. Stereotact Funct Neurosurg. 2016;94(4):207-15.

14 Hendrix CM, Vitek JL. Toward a network model of dystonia. Ann N Y Acad Sci. 2012;1265:46-55.

15 Chiken S, Nambu A. Mechanism of Deep Brain Stimulation: Inhibition, Excitation, or Disruption? Neuroscientist. 2016;22(3):313-22.

16 Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J Neurosurg. 1992;76(1):53-61.

17 Starr PA, Vitek JL, DeLong M, et al. Magnetic resonance imaging-based stereotactic localization of the globus pallidus and subthalamic nucleus. Neurosurgery. 1999;44(2):303-13; discussion 13-4.

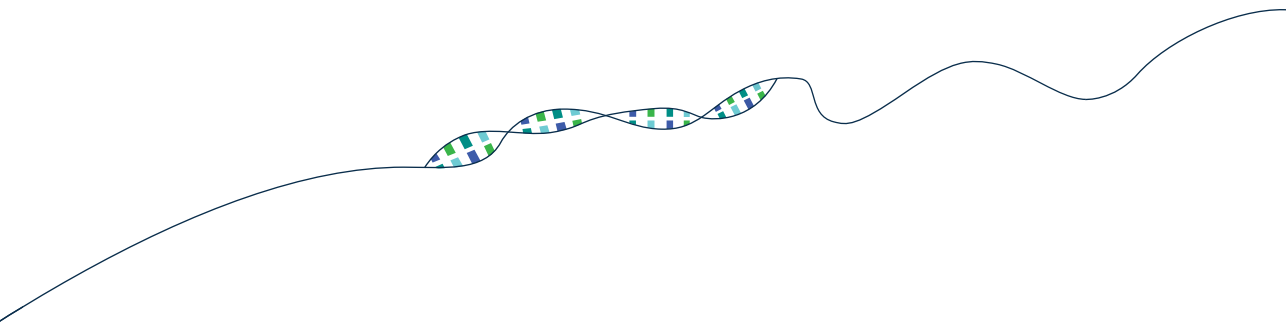
18 Krauss JK, Yianni J, Loher TJ, et al. Deep brain stimulation for dystonia. J Clin Neurophysiol. 2004;21(1):18-30.

19 Miyamoto R, Koizumi H, Morino H, et al. DYT6 in Japan-genetic screening and clinical characteristics of the patients. Mov Disord. 2014;29(2):278-80.

20 Gimeno H, Tustin K, Selway R, et al. Beyond the Burke-Fahn-Marsden Dystonia Rating Scale: deep brain stimulation in childhood secondary dystonia. Eur J Paediatr Neurol. 2012;16(5):501-8.

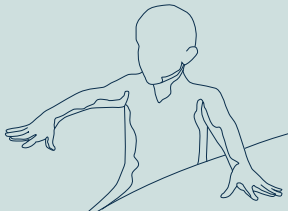
Myoclonus

Part III



A novel diagnostic approach to patients with myoclonus

Chapter 7



R. Zutt, M.E. van Egmond, J.W. Elting, P.J. van Laar, O.F. Brouwer, D.A. Sival, H.P. Kremer, T.J. de Koning, M.A.J. Tijssen

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Abstract

Myoclonus is a hyperkinetic movement disorder characterized by brief, involuntary muscular jerks. Recognition of myoclonus and determination of the underlying etiology remains challenging given that both acquired and genetically determined disorders have varied manifestations. The diagnostic work-up in myoclonus is often time-consuming and costly, and a definitive diagnosis is reached in only a minority of patients. On the basis of a systematic literature review up to June 2015, we propose a novel diagnostic eight-step algorithm to help clinicians accurately, efficiently and cost-effectively diagnose myoclonus. The large number of genes implicated in myoclonus and the wide clinical variation of these genetic disorders emphasize the need for novel diagnostic techniques. Therefore, and for the first time, we incorporate next-generation sequencing (NGS) in a diagnostic algorithm for myoclonus. The initial step of the algorithm is to confirm whether the movement disorder phenotype is consistent with, myoclonus, and to define its anatomical subtype. The next steps are aimed at identification of both treatable acquired causes and those genetic causes of myoclonus that require a diagnostic approach other than NGS. Finally, other genetic diseases that could cause myoclonus can be investigated simultaneously by NGS techniques. To facilitate NGS diagnostics, we provide a comprehensive list of genes associated with myoclonus.

Introduction

Myoclonus is a complex hyperkinetic movement disorder characterized by sudden, brief, involuntary jerks of a single muscle or a group of muscles. Diagnosis of jerky movement as myoclonus can be difficult, as was shown in a recent study by movement disorder specialists.[1] Little is known about the epidemiology of myoclonus, mainly because this disorder has a wide spectrum of clinical manifestations and numerous causes. The only available epidemiological study of myoclonus comprised a defined population recruited in Olmsted County from 1976 to 1990, and revealed a lifetime prevalence of persistent and pathological myoclonus of 8.6 cases per 100,000 people.[2]

Three approaches to the classification and diagnosis of myoclonus exist: clinical, aetiological and anatomical. The clinical classification is based on clinical signs, including the distribution and temporal pattern of jerks and their relationship to motor activity. The etiological classification is divided into four subgroups: physiological myoclonus, essential myoclonus, epileptic myoclonus, and symptomatic myoclonus.[3] In clinical practice, the initial approach is guided by the anatomical classification. Myoclonus can be generated in the cortex, in subcortical areas, in the spinal cord, or in the peripheral nerves. No epidemiological studies have been conducted on the anatomical subtypes of myoclonus. Cortical myoclonus is the most common type of myoclonus,[4, 5] whereas spinal myoclonus and peripheral myoclonus are rare.[6] The anatomical locus of myoclonus is associated with clinical and electrophysiological characteristics that can be linked to an aetiological differential diagnosis, thereby guiding the selection of treatment.[7]

The next challenge in myoclonus diagnostics is to determine the cause. A wide variety of acquired and genetic disorders can manifest as myoclonus. As some of these disorders are treatable, it is important to identify the etiology. For example, many commonly used drugs can cause myoclonus, and discontinuation of the drug often leads to immediate cessation of the condition. Other treatable causes include infections, systemic metabolic derangement, autoantibody disorders, and certain inborn metabolic abnormalities.

In cases where the myoclonus is likely to be of genetic origin, conventional Sanger sequencing and new molecular diagnostic techniques, including next-generation sequencing (NGS), can be used to identify the cause. NGS has enabled a shift from targeted single gene mutation analysis to massively parallel sequencing of hundreds of genes in a single assay.[8]

The types of NGS include whole-genome sequencing (WGS), whole-exome sequencing (WES), and targeted resequencing (TRS) panels which focus on a selection of genes.[9] Both established and potential genetic causes of myoclonus-associated diseases can be tested simultaneously with NGS. This approach has already proved effective in highly heterogeneous neurological disorders such as epilepsy.[10] In patients with movement disorders (hereditary spastic paraplegia, cerebellar ataxia and dystonia), NGS increased the diagnostic yield fourfold (from 5% to 20%) compared with Sanger sequencing.[11] The number of genes associated with myoclonus-inducing disease has grown substantially, and will continue to increase in the coming years. Moreover, costs and turnaround time of the various NGS techniques are decreasing rapidly. Thus, we expect that NGS will largely replace specific biochemical analyses and conventional Sanger sequencing in the diagnostic approach to myoclonus.

Here, we present a novel diagnostic algorithm for myoclonus. This algorithm is based on a systematic review (Supplementary Appendix 1) of all the causes of myoclonus, and includes—for the first time—the systematic use of targeted NGS. We also provide a comprehensive overview of genes reported to be associated with myoclonus, together with their key clinical features, to facilitate the use of targeted NGS.

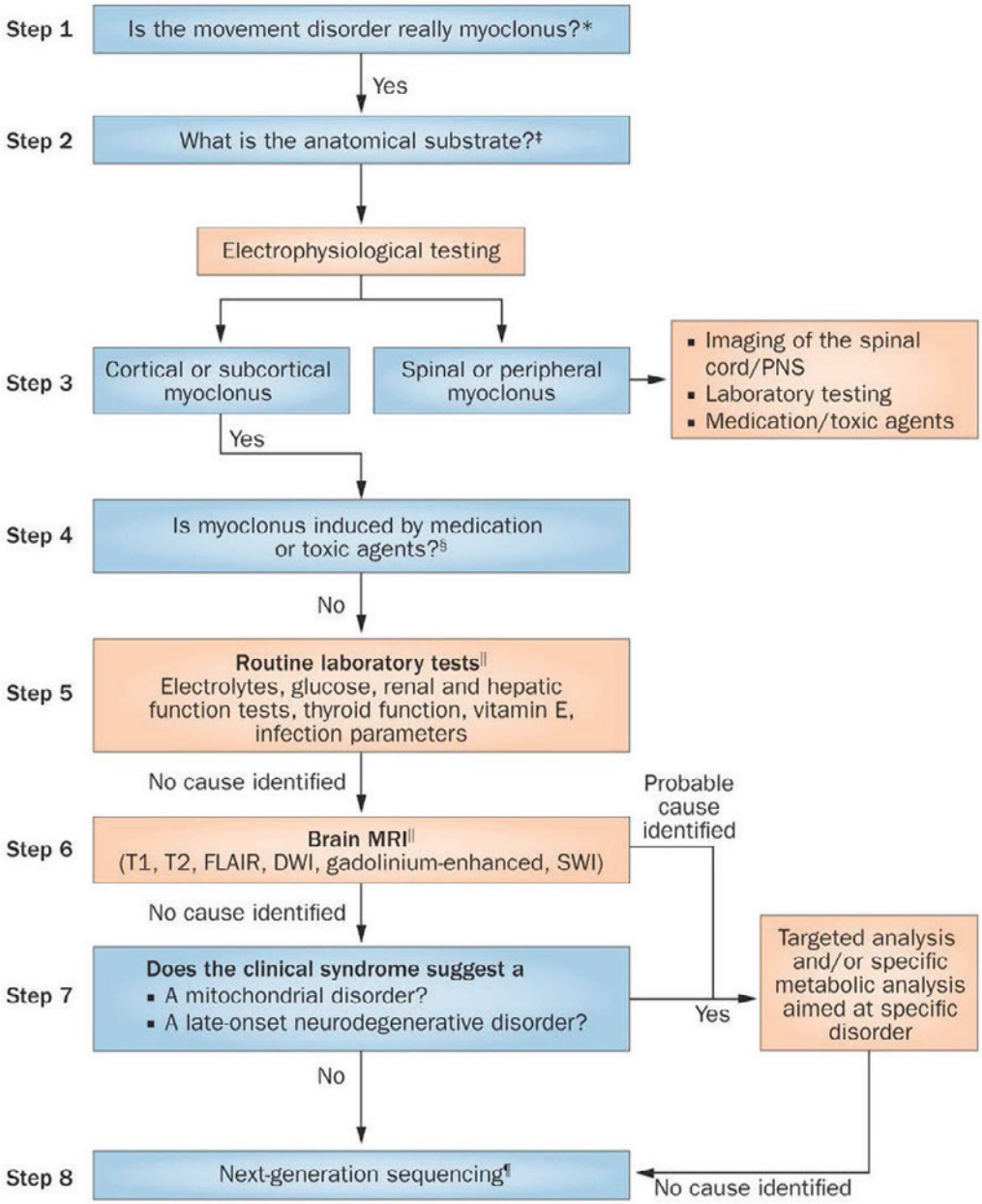
Clinical approach to myoclonus

In this section, we propose a new diagnostic algorithm for myoclonus consisting of eight consecutive steps (Figure 1).

Step 1: is the symptom really myoclonus?

Myoclonus is characterized by sudden, brief, involuntary jerks of a muscle or a group of muscles, caused by muscular contraction (positive myoclonus) or interruption of muscle activity (negative myoclonus).[12, 13] Three types of negative myoclonus have been described: asterixis (flapping tremor of the hands when the wrist is extended) in patients with a toxic– metabolic encephalopathy;[14] negative myoclonus involving the axial muscles and lower limbs, which results in a wobbling gait and sudden falls;[15] and epileptic negative myoclonus. Epileptic negative myoclonus is defined as an interruption of muscle activity time-locked to an epileptic EEG abnormality, without evidence of antecedent positive myoclonus. Epileptic negative myoclonus can be observed in a heterogeneous range of epileptic disorders.[16, 17] Myoclonus must be distinguished from other hyperkinetic movement disorders on the basis of a combination of clinical features and electrophysiological characteristics (Table 1). Alternative diagnoses include tremor, motor tics, chorea, dystonic jerks, and functional (psychogenic) jerks.

Figure 1. *A novel eight-step diagnostic algorithm for myoclonus*



*Note: We suggest a diagnostic algorithm consisting of eight consecutive steps (blue) and electrophysiological, imaging and laboratory tests (orange). *See Table 1. ‡See Table 2. §See Table 3. ||See Table 4. *See Supplementary Table 1. Abbreviations: DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility-weighted imaging.*

Table 1. Mimics of myoclonus

Hyperkinetic movement disorder	Clinical characteristics	Electrophysiological characteristics
Functional (psychogenic) jerks	• Inconsistent Reduces with distraction Entrainment	• Variation in muscle involvement Variation in muscle recruitment order • Variation in burst duration and/or amplitude Pre-movement potential on back-averaging
Chorea	• Dance-like movements • Non-patterned Integrated with normal movement	• Variation in burst duration Variation in muscle recruitment order
Motor tics	• Stereotypic or repetitive movements Onset in childhood Coexistence of other tics Can be voluntarily suppressed Premonitory sensations (urge) Relief after movement	• Burst duration >100 ms Pre-movement potential on back-averaging
Dystonic jerks	• Jerks together with dystonia Sensory tricks (geste antagoniste) can alleviate	• Co-contraction agonist and antagonist • Burst duration >100 ms Overflow(unintentional muscle contractions that accompany jerks, but is anatomically distinct from the primary dystonic movements)
Tremor	• Sinusoidal and rhythmic	• Alternating contractions of antagonistic muscles • Steady frequency on accelerometry

Step 2: anatomical substrates of myoclonus

Myoclonus can be classified into peripheral, spinal (segmental and propriospinal), subcortical and cortical forms. Table 2 provides an overview of the important clinical and electrophysiological features of these myoclonus subtypes.

Peripheral

Peripheral myoclonus has a focal distribution affecting the distal limbs, sometimes presenting as minipolymyoclonus owing to damage of the PNS.[18] Polymyography shows a short burst (<50 ms) duration, and electromyography (EMG) can help to detect and assess the severity of PNS damage.

Spinal

Spinal myoclonus can be divided into segmental myoclonus, in which adjacent body areas (for example, muscles in one arm, or muscles in the neck and proximal muscles in one arm) are involved, and propriospinal myoclonus, which is characterized by myoclonus of the trunk and abdominal muscles with a fixed up-and-down pattern of muscle activation. Though sometimes organic, propriospinal myoclonus often has a psychogenic origin.[19]

Table 2. Differentiating characteristics of anatomical subtypes of myoclonus[1,4]

Subtype of myoclonus	Clinical characteristics	Electrophysiological characteristics
Cortical	• (Multi)focal or generalized • Affects face, distal limbs • Spontaneous, action-induced or stimulus-sensitive • Negative myoclonus	• Burst duration <100 ms • Positive back-averaging • Positive coherence • Giant somatosensory evoked potentials • C reflex
Subcortical		
Brainstem	• Generalized or synchronous • Axial • Affects proximal limbs • Spontaneous or stimulus-sensitive	• Burst duration >100 ms • Simultaneous rostral and caudal muscle activation • Habituation
Basal ganglia	• (Multi)focal • Axial, affects proximal limbs • Spontaneous or action-induced	• Burst duration >100 ms
Spinal		
Segmental	• Focal or segmental • Spontaneous (sometimes action-induced)	• Burst duration >100 ms • Distribution of bursts depends on the affected segment
Propriospinal	• Fixed pattern • Affects axial muscles • Spontaneous or stimulus-sensitive (lying down can be a provoking factor)	• Burst duration >100 ms • Initiation in midthoracic segments followed by rostral and caudal activation • Slow propagation velocity (5–10 m/s)
Peripheral	• Focal • Affects distal limbs • Spontaneous or action-induced • Can be accompanied by weakness and/or atrophy	• Burst duration <50 ms • Large motor unit action potentials • Minipolymyoclonus • Fasciculations/myokymia

Subcortical

The electrophysiological characteristics of subcortical myoclonus are a burst duration of >100 ms, and absence of cortical excitability (see below). Important subgroups of subcortical myoclonus are myoclonus–dystonia and brainstem myoclonus. The exact pathophysiology of myoclonus–dystonia is unclear. The neurophysiological features are not consistent with cortical myclonus, as the giant somatosensory evoked potential is absent, and no EEG–EMG correlation can be detected.

A subcortical origin is suggested by improvement of myoclonus on deep brain stimulation of the globus pallidus internus.[20, 21] As deep brain stimulation interferes with a network, this finding does not directly imply that the origin of the myoclonus is in the basal ganglia. The cerebellum also seems to have an important role in myoclonus–dystonia.[22]

The myoclonus in myoclonus–dystonia is multifocal, mostly affects the upper limbs, and is exacerbated by posture and action. Brainstem myoclonus is characterized by abnormal activity starting in the brainstem and spreading in both rostral and caudal directions, resulting in generalized myoclonus that is often stimulus-sensitive.

Cortical

Cortical myoclonus is the most frequent form of myoclonus,[4, 5] and is characterized by multifocal myoclonus predominantly affecting the face and distal limbs (areas with large cortical representation). Cortical myoclonus is often exacerbated by voluntary movements, and is sometimes provoked by unexpected stimuli (referred to as reflex myoclonus or startle myoclonus). The clinical manifestations of cortical myoclonus include polyminimyoclonus, especially in parkinsonian syndromes, such as multiple system atrophy or corticobasal degeneration.

In cortical myoclonus, a short burst duration (<100 ms) is seen on polymyography. In terms of somatosensory evoked potentials, a giant potential often is detected.[23] No definitive criteria for electrophysiological diagnosis of cortical myclonus have been accepted, but it is generally assumed that the P27 peak has an amplitude >5 mV and N35 peak has a suitable shape or amplitude >10 mV. Back-averaging of simultaneous EMG and EEG recordings can reveal that cortical discharges on EEG precede the jerks seen on EMG.[24] In high-frequency myoclonus, coherence analysis demonstrates a correlation between cortical and muscle activity.[25] In cortical reflex myoclonus, a C reflex is often present, suggesting that the polysynaptic (long-loop) reflex mediated by the sensorimotor cortex is stronger than usual.[24, 26, 27] These electrophysiological features prove the existence of enhanced cortical excitability, but the exact pathogenesis of cortical myoclonic syndromes remains unclear. Although clinical symptoms arise from dysfunction of the cortex, neuropathological changes in the cerebellum have been detected in many patients with confirmed cortical myoclonus,[28, 29] suggesting an important role for this structure.

Defining the anatomical locus

Unfortunately, differentiation of subtypes of myoclonus can be difficult in clinical practice, for several reasons. Little is known about the sensitivity and specificity of clinical features and electrophysiological tests in the heterogeneous myoclonus disorders. Moreover, more than one anatomical subtype can coexist in a given patient.

Different types of myoclonus have different etiologies and, therefore, require different clinical approaches. Cortical and subcortical myoclonus can either be acquired or result from genetic disorders, warranting genetic testing in addition to MRI and laboratory tests, whereas spinal and peripheral myoclonus are usually acquired. The subsequent steps of the diagnostic algorithm aim at elucidating the underlying cause of the myoclonus by separating spinal and peripheral myoclonus (see step 3 in Figure 1) from cortical and subcortical myoclonus.

Step 3: defining the etiology

Spinal or peripheral myoclonus

If the anatomical locus of the myoclonus has been established as peripheral or spinal, signs of muscle denervation (clinical inspection and/or EMG) and structural lesions must be assessed by appropriate electrophysiological testing and/or imaging to narrow down the possible causes for myoclonus. For example, peripheral myoclonus usually results from damage to the PNS, typical causes for such damage include lesions of the brachial plexus lesions[30] or the spinal root,[31] which can be detected with EMG and sometimes with MRI, or amputation of a distal limb ('jumping stump').[32] Discussion of the various disorders that can cause damage to the PNS is outside the scope of this Review. Damage to the spinal cord can induce spinal myoclonus.[33-35] Segmental myoclonus is very rare, and is almost always caused by a structural spinal cord lesion.

Acute or subacute onset, fast progression, radiculopathy or polyradiculopathy, and systemic features (fever, skin rash, or joint involvement) suggest infectious or autoimmune cause, which should be confirmed with appropriate laboratory testing.

It is important to note that the vast majority of cases of propriospinal myoclonus are now considered to be functional movement disorders.[19] Furthermore, in rare cases, spinal myoclonus can be induced by medication[36-38] or infections,[39] underlining the need for careful evaluation of patients with this type of myoclonus.

Cortical and subcortical myoclonus

Cortical and subcortical myoclonus have a broad differential diagnosis. In general, acute or subacute onset and/or fast progression of myoclonus are important clues for an acquired cause, whereas an early-onset disease with a slower progression is more characteristic of a genetic disorder. Specific clinical features that coexist with myoclonus often provide important information regarding the underlying disease.

The next steps of the algorithm systematically evaluate the aetiological causes of cortical and subcortical myoclonus.

Step 4: are medications or toxic agents involved?

Drug-induced myoclonus usually begins more or less acutely at the start of treatment, but can also occur after chronic use, especially with intercurrent illness. Drug-induced myoclonus vanishes within a brief period after withdrawal of the drug.

Serotonin reuptake inhibitors and antiepileptic drugs that enhance GABAergic neurotransmitter systems are commonly involved in drug-induced myoclonus,[40] but other drugs, such as levodopa and tricyclic antidepressants, can also induce myoclonus.[41] Other toxic causes of myoclonus include chronic alcohol abuse as well as alcohol withdrawal, aluminum toxicity in patients with dialysis syndrome, and exposure to certain insecticides, such as methyl bromide.[41]

It is important to recognize these acquired causes of myoclonus, because cessation of the drug or detoxification will ameliorate the symptoms. An overview of medications and toxic agents associated with myoclonus[40-42] is provided in Table 3.

Step 5: routine laboratory tests

Homeostatic imbalance, organ failure or infection can cause cortical or subcortical myoclonus. Common examples include acute or chronic renal failure, acute or chronic hepatic failure, chronic respiratory failure with hypercapnia, disturbances of glucose homeostasis, hyperthyroidism, and metabolic alkalosis or acidosis. Treatment of the underlying organ dysfunction and restoration of homeostasis generally leads to the disappearance of myoclonus.

Careful evaluation of a potential infectious or immune-mediated cause for myoclonus is warranted. If systemic signs of infection are present, the next step is serum and/or cerebrospinal fluid (CSF) analysis to test for immune-mediated disorders and to identify infectious agents. Immune-mediated disorders, such as anti-*N*-methyl-d-aspartate receptor (anti-NMDAR) encephalitis, stiff-person syndrome (SPS), progressive encephalomyelitis with rigidity and myoclonus (PERM), and opsoclonus–myoclonus syndrome (OMS), can be accompanied by acute or subacute onset of myoclonus. Early recognition of these disorders is important, because treatment—particularly when started early after symptom onset—can suppress the autoimmune response effectively.

Anti-NMDAR encephalitis

Anti-NMDAR encephalitis is characterized by a combination of psychiatric symptoms, seizures, movement disorders, and encephalopathy.[43] EEG usually reveals slow and disorganized activity or the unique extreme delta-brush pattern.[44] In CSF, moderate pleiocytosis with CSF-specific oligoclonal bands and NMDAR antibodies can be detected. Patients with anti-NMDAR encephalitis should be carefully tested for solid tumours, in par- ticular, ovarian teratoma, which is present in over 50% of adult female patients with anti- NMDAR encephalitis.[45] In younger patients (<18 years), the occurrence of underlying tumours is less likely.[43, 46]

Other autoimmune causes

SPS and PERM usually have a subacute onset (weeks) and are characterized by limb and truncal rigidity, painful muscle spasms, hyperekplexia, and brainstem symptoms. A substantial number of SPS and PERM cases are associated with glutamic acid decarboxylase, amphiphysin, and glycine receptor subunit α-1 antibodies[47], and PERM can also be associated with dipeptidyl peptidase-like protein 6 antibodies.[48]

Opsoclonus–myoclonus syndrome

OMS is characterized by involuntary, arrhythmic, chaotic, multidirectional, fast eye movements, in combination with brainstem myoclonus involving the axial muscles and limbs. It is important to note that OMS is usually a manifestation of a paraneoplastic syndrome, and is associated with breast cancer or small-cell lung carcinoma in adults[49] and neuroblastoma in children.[50, 51]

Whipple disease

Of particular interest is Whipple disease, a rare but treatable bacterial multisystem infection characterized by systemic symptoms such as gastrointestinal complaints, fever, weight loss, and joint involvement in combination with CNS involvement. The triad of dementia, ophthalmoplegia (supranuclear gaze palsy and characteristic oculomasticatory myorrhythmia) and myoclonus

is highly suggestive of Whipple disease. The diagnosis is based on PCR-based detection of *Tropheryma whipplei* in a CSF or duodenal biopsy sample.

Table 3. *Overview of medication and toxic agents associated with myoclonus*

Drug/toxic agent group	Specific substances
Prescription drugs	
Anticonvulsants	Phenytoin, carbamazepine, sodium valproate, gabapentin, pregabalin, lamotrigine, phenobarbital, vigabatrin, oxcarbazepine, levetiracetam
Antipsychotics	Haloperidol, chlorpromazine, sulpiride, clozapine, olanzapine, metoclopramide
Antidepressants	Lithium, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, fluoxetine, imipramine
Antihypertensives	Verapamil, caverdilol, furosemide
Cardiovascular drugs	Propafenone, flecainide, diltiazem, nifedipine, buflomedil, veratramine, amiodarone
Antiparkinson drugs	Levodopa, bromocriptine, amantadine, entacopone, selegiline
Antibiotics	Quinolones, penicillin, cefepime, ceftazidime, moxalactam, ciprofloxacin, imipenem, carbenicillin, ticarcillin, piperacillin, cefuroxime, βlactam antibiotics, gentamicin
Other anti-infective drugs	Piperazine, isoniazid, acyclovir
Antineoplastic drugs	Chlorambucil, prednimustine, busulphan plus cyclophosphamide, ifosfamide
Opiates	Morphine, tramadol, fentanyl, methadone, pethidine, norpethidine, hydrocodone
Anxiolytics	Buspirone, lorazepam, midazolam, zolpidem, zopiclone, carisoprodol, benzodiazepine withdrawal
Antidementia drugs	Cholinesterase inhibitors
Anaesthetic agents	Enflurane, etomidate, propofol, choralose
Others	Bismuth salts, contrast media, domperidone, omeprazole, antihistamines, prednisolone, ketoprofene, physostigmine, tryptophan, diclofenac, cobalamine supplementation, cimetidine, salicylates, tetanus toxin, dextromethorphan, tacrolimus
Toxic agents	
Psychoactive substances	Alcohol, cannabis, amphetamine, cocaine, ecstasy, toluene, intoxicating inhalants (for example, gasoline), heroin
Heavy metals	Aluminium, manganese, bismuth, mercury, tetra-ethyl lead
Insecticides	Methyl bromide, dichlorodiphenyltrichloroethane
Others	Baking soda, carbon monoxide, chloralose, colloidal silver

Step 6: brain MRI

MRI can be helpful in identifying the acquired causes of myoclonus discussed in the previous step, and is probative in detecting structural lesions. Abnormalities seen on brain MRI can also indicate a genetic cause, such as neurodegeneration with brain iron accumulation (NBIA) disorders, leukodystrophy, or mitochondrial disorders. The recommended MRI protocol comprises T1-weighted and T2-weighted imaging, fluid-attenuated inversion recovery, and diffusion-weighted imaging (DWI), with administration of gadolinium contrast. Diagnosticians should also consider susceptibility-weighted imaging to assess iron accumulation. When detected, iron accumulation strongly raises a suspicion of pantothenate kinase-associated neurodegeneration[52, 53] or other forms of NBIA.[54]

Structural lesions can indicate posthypoxic, post-ischaemic or post-traumatic brain injury, tumours, demyelinating diseases, or spongiform encephalopathies. Abnormal T2 hyperintensity of the grey matter and/or white matter or the deep grey nuclei can indicate infection, autoimmune encephalopathy or a paraneoplastic disorder. DWI can detect lesions at an earlier stage than can T2-weighted imaging.

If white matter abnormalities are present, leukodystrophies should be considered. One example is Alexander disease, an autosomal dominant inherited leukodystrophy caused by mutations in the glial fibrillary acidic protein (*GFAP*) gene.[55] Palatal myoclonus is a common feature of Alexander disease. In typical infantile cases, brain MRI shows extensive white matter T2 hyperintensities that are especially marked in frontal regions; a rim of periventricular T2 hypointensity; T2 hyperintensity involving the basal ganglia, thalamus and brainstem; and contrast enhancement, particularly of periventricular regions and brainstem.[56] Brainstem and cerebellar lesions and ventricular garlands with contrast enhancement are seen in the juvenile form.[57] In the adult form, MRI shows progressive atrophy of the medulla oblongata and cervical spinal cord (the so-called 'tadpole sign'), accompanied by T2 hyperintensity in these areas.[55] An overview of the acquired causes of myoclonus, together with the recommended diagnostic investigations, is provided in Table 4.

Step 7: mitochondrial or neurodegenerative?

Although NGS is usually indicated in myoclonus, in two groups of patients —those with suspected mitochondrial disorders or late-onset neurodegenerative disorders— an initial approach other than NGS should be considered. Here, we will briefly discuss these two groups of disorders.

Table 4. Recommended investigations for acquired causes of myoclonus

Disorders and key features	Diseases causing myoclonus	MRI findings (the best diagnostic aid)	Recommended investigations
Metabolic			
(Sub)acute onset Negative myoclonus Encephalopathy Systemic involvement	Hyperthyroidism Hepatic failure Renal failure Dialysis syndrome Hyponatraemia Hypocalcaemia Hypomagnesaemia Hypoglycaemia Vitamin E deficiency Metabolic alkalosis or acidosis	No indication for neuroimaging	Basic laboratory tests, including electrolytes, glucose, renal and hepatic function tests, thyroid function, vitamin E (blood gas analysis)
Infectious or postinfectious			
(Sub)acute onset Fast progression Fever Encephalopathy Skin rash Joint or systemic involvement Radiculopathy Cranial nerve palsy	All infectious causes of myoclonus	T2-weighted imaging can detect abnormal hyperintensity of GM, WM or deep grey nuclei in the following structures:	Serum and/or CSF testing for infection parameters: specific antigens/ antibodies, PCR aimed at the specific agent, biopsy of the involved tissue
	Arbovirus	BG (bilaterally), thalamus and BS	
	Epstein–Barr virus	BG (symmetric pattern), thalamus, cortex, or BS	
	Enterovirus	Posterior medulla, pons, midbrain, DN, SC	
	Coxsackie virus	Midbrain, anterior SC	
	Herpes simplex virus	LS	
	Herpes zoster virus	Multifocal areas of cortex, BS, GM, CN	
	West Nile virus	BG, thalamus, BS, WM, SN, cerebellum, SC	
	HTLV-1	Deep WM	
	Miscellaneous bacteria (e.g. *Streptococcus, Clostridium)*	Meningitis, cerebritis, vasculitis, pus collections; T2-hyperintense BG	
	Shiga-toxin-producing Escherichia coli	BS, BG, deep WM	
	Whipple disease	(Multi)focal lesion(s) in the (fronto)temporal lobe, PV WM, BS (on contrast enhancement)	
	HIV	Atrophy and bilateral PV/ centrum semiovale WM, BG, cerebellum, BS	

	Malaria	Multiple cortical and thalamic infarcts with or without haemorrhages	
	Syphilis	Basilar meningitis	
	Cryptococcus	Dilated PVSs in deep grey nuclei, typically no contrast enhancement, miliary-enhancing or leptomeningeal-enhancing nodules or cryptococcomas	
	Borrelia burgdorferi	MS-like lesions + cranial neuritis and meningoradiculoneuritis (Bannwarth syndrome)	
	Progressive multifocal leucoencephalopathy (PML)	Asymmetrical T2 hyperintensity of SC areas	
	Subacute sclerosing panencephalitis	T2 hyperintensities in PV or SC WM (frontal>parietal>occipital lobes)	
Prion diseases			
Progressive (sub)acute dementia Psychiatric symptoms Vision loss	CJD	Progressive hyperintensity of BG, thalamus, and cerebral cortex seen on DWI/T2	RT-QuIC testing of nasal brushings;[58*] CSF 14-3-3 and tau proteins, EEG
	Variant CJD	'Pulvinar' sign: bilateral symmetrical hyperintensity of pulvinar (posterior) nuclei of thalamus relative to anterior putamen; 'hockey stick' sign: symmetric pulvinar and dorsomedial thalamic nuclear hyperintensity	
	Sporadic CJD	Cortical hyperintensity	
	Heidenhain variant CJD	Occipital lobe hyperintensity	
	Gerstmann–Straussler–Scheinker syndrome (GSS)	No abnormalities; DWI hyperintensities LS and atrophy	CSF 14-3-3 and tau proteins, EEG

Autoimmune or paraneoplastic			
(Sub)acute onset Fast progression Encephalopathy Epilepsy Psychiatric symptoms Other movement disorders	Hashimoto encephalitis (steroid-responsive autoimmune encephalopathy associated with autoimmune thyroiditis)	Diffuse/focal cortical, SC WM T2-hyperintensity with relative sparing of occipital lobes	Antithyroperoxidase and antithyroglobulin antibodies
	Anti-NMDA receptor encephalitis	T2 hyperintensities and atrophy in the LS	NMDA receptor antibodies
	Progressive encephalomyelitis with rigidity and myoclonus (PERM)	No abnormalities/T2 hyperintensity in MTLs and LS	Amphiphysin, LGI1, Caspr2, GAD, DPPX, and GLyR antibodies
	Stiff person syndrome	T2 hyperintensity in MTLs and LS	Paraneoplastic antibodies (anti-Hu, anti-Ri)
	Rasmussen encephalitis	Early unilateral swelling of gyri, followed by (predominantly frontal and parietal) progressive cortical atrophy	EEG
	Coeliac disease	WM T2 hyperintensities; cerebral and cerebellar atrophy	Anti-endomysial, anti-tissue transglutaminase, anti-reticulin and anti-gliadin antibodies; tissue biopsy of the small intestine
CNS lesions			
(Sub)acute onset Features depend on location of lesion	Neoplasia Ischaemia Amyloid angiopathy Demyelinating diseases Posthypoxic encephalopathy (Lance-Adams syndrome)	Variable	Variable

**RT-QuIC testing of nasal brushings is a promising diagnostic test in diagnosing CJD, but must be validated before the test can be used in clinical practice. Abbreviations: BG, basal ganglia; BS, brainstem; Caspr 2, contactin-associated protein-like 2; CJD, Creutzfeldt–Jakob disease; CN, cranial nerves; CSF, cerebrospinal fluid; DN, dentate nucleus; DPPX, dipeptidyl-peptidase-like protein-6; DWI, diffusion-weighted imaging; GAD, glutamic acid decarboxylase; GLyR, glycine receptor; GM, grey matter; HTLV-1, human T-lymphotropic virus 1; LGI1, leucine-rich glioma-inactivated 1; LS, limbic system; MTL, mesial temporal lobe; NMDA, N-methyl-d-aspartate; PV, periventricular; PVS, perivascular space; RT-QuIC, real-time quaking-induced conversion; SC, subcortical; SN, substantia nigra; WM, white matter.*

Mitochondrial disorders

In addition to genetic disorders caused by mutations in nuclear genes, one must be aware of mitochondrial disorders caused by mutations in mitochondrial DNA (mtDNA), which are associated with myoclonus including MERRF (myoclonic epilepsy with ragged red fibres) syndrome,[59, 60] Leigh syndrome,[59] and MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndrome.[59] Clinical clues for a mitochondrial disorder are multiorgan involvement, ophthalmoplegia, muscle involvement, neuropathy, ataxia, deafness, specific MRI brain findings, and maternal inheritance.

Targeted analysis of mtDNA is strongly advised if a mitochondrial disorder is suspected, because in many diagnostic laboratories, NGS analysis only reports mutations in nuclear genes (including mitochondrial DNA polymerase genes), and does not consider mtDNA mutations.

It is important to keep in mind that the mtDNA testing results obtained from peripheral blood samples can be falsely negative. Thus, testing of samples from different types of tissue, including cells isolated from urine, skin and muscle tissue, could be required.

Late-onset neurodegenerative disorders

Late-onset neurodegenerative disorders that are often accompanied by myoclonus include Alzheimer disease, Parkinson disease (PD), multiple system atrophy (MSA) and—less commonly—dementia with Lewy bodies, Huntington disease, and corticobasal degeneration.

Myoclonus in PD and MSA usually manifests as irregular, small-amplitude, often stimulus-sensitive myoclonic jerks of the fingers during muscle activation (cortical polyminimyoclonus).[61-64] Neurodegenerative disorders can also be accompanied by orthostatic myoclonus that contributes to gait problems.[65,66] Diagnosis of neurodegenerative disorders is based on clinical criteria together with, for example, neuroimaging or CSF biomarker diagnostics and, in rare cases, DNA analyses.

Step 8: next-generation sequencing

If the previous diagnostic steps have not revealed the cause of the myoclonus, the next step is NGS, which comprises several massively parallel sequencing techniques, including WGS and WES, and TRS, which focuses on known disease-associated genes. The technical details of these techniques are reviewed elsewhere.[9]

Strengths and limitations of NGS

WGS and WES are particularly useful for identification of new disease-causing genetic variants, and WES of patient–parents trios is a particularly good strategy to detect de novo mutations in affected patients.[67] However, NGS diagnostics have some limitations. One important disadvantage of WGS and WES is the ethical dilemma associated with detection of unsolicited findings.

Most of the current NGS techniques miss repeat expansions, large structural rearrangements, and mutations in noncoding regions (deep intronic mutations and mutations in promoter regions). In addition, mutations in mtDNA often escape detection. For this reason, and because of the difficulties in recognizing mitochondrial disorders, targeted mtDNA analysis should be considered in cases that remain unsolved after completion of the diagnostic algorithm.[59]

WGS and WES can involve extensive data processing and confirmation of the detected variants, hence conferring higher costs than TRS. Another advantage of TRS over WGS and WES is that it avoids the interpretation of genetic variants with no relationship to the patient's phenotype. One crucial step—adequate data filtering and assessment of pathogenicity of all variants observed in NGS analyses—remains a challenge. Indeed, the main drawback of TRS diagnostic panels compared with WGS and WES is the need to consistently monitor all variants reported, collect all relevant information on newly defined disease genes, and continuously update the list of genes associated with myoclonus.[9]

NGS in myoclonus diagnostics

NGS can be a highly efficient tool to diagnose the disease that underlies myoclonus, because the list of disorders—and, hence, individual genes to be considered—in an individual patient is long. NGS is cost-effective in this respect, and can shorten the diagnostic process and avoid unnecessary diagnostic evaluations. The costs of all NGS techniques are rapidly falling, and the cost of WES or TRS is currently comparable to that of sequencing three individual genes.[10, 12]

The advantage of all NGS techniques is that mutations associated with an unusual clinical phenotype will also be detected. Even in monogenic disorders, patients often do not present with the classic phenotype and, as in other genetic disorders of the CNS, mutations in myoclonus-associated genes can cause a whole spectrum of symptoms. NGS is the only technique that enables screening of all the genes known to be related to myoclonus; using this approach, both 'typical' and 'atypical' presentations of gene defects can be diagnosed.

The clinical presentation of myoclonus disorders is very heterogeneous, and clear genotype–phenotype correlations are often lacking. For example, in six patients from two unrelated families with late-onset cortical myoclonus owing to sialidase-1 (*NEU1*) mutations, neither the canonical clinical phenotype nor the typical laboratory findings were evident, that is, macular cherry-red spots were absent, and urinary sialic acid excretion was not increased.[68] The involvement of *NEU1* would never have been suspected on clinical grounds or on the basis of laboratory test results, illustrating the power of NGS diagnostics. In this case, the mutations were detected with WES, but other NGS approaches would also have been successful.

Myoclonus-linked genes and genetic syndromes

The genetic disorders associated with myoclonus include five treatable inborn errors of metabolism: Niemann–Pick type C,[69, 70] Wilson disease,[71, 72] glucose transporter type 1 (GLUT1) deficiency,[73, 74] cerebrotendinous xanthomatosis,[75, 76] and tyrosine hydroxylase deficiency.[77] Identification of these disorders is crucial, because early treatment can prevent, stabilize or even improve symptoms. In general, these syndromes have additional defining symptoms that can support the diagnosis, but they are all associated with myoclonus. In the event of clinical suspicion of one of these disorders, the choice of diagnostic work-up depends on the facilities for biochemical testing and NGS available in the medical centre concerned (Table 4). A comprehensive overview of genes associated with myoclonus is provided in Supplementary Table 1 online. For use in clinical practice, we have classified these genes according to the key clinical feature (dystonia, epilepsy, spasticity, ataxia, dementia or parkinsonism) that is present in addition to myoclonus.

At present, the most common genetic causes of myoclonus remain unknown, because genetic diagnosis in myoclonus is a new advance and, therefore, prevalence data are not yet available. Moreover, the prevalence of genetic causes of myoclonus is likely to vary depending on the population characteristics (for example, the ethnic background). At present, we encourage multicenter collaboration to collect genetic data, so that the genetic background of myoclonus can be fully elucidated.

From diagnosis to treatment

Ideally, the underlying cause of myoclonus should be treated. Treatment can include withdrawal of drugs or toxic agents, correction of homeostasis or organ failure, or treatment of infections or autoimmune disorders. We have also stressed the importance of early treatment of the five inborn errors of metabolism, in which progression of the disease is potentially preventable (Table 5). However, symptomatic treatment needs to be considered in all patients with myoclonus, and the choice of treatment should be guided by the anatomical classification of their myoclonus. Symptomatic treatment of myoclonus can be difficult because of adverse effects, and polytherapy is often required for effective treatment.[7, 78] Levetiracetam and valproic acid are generally considered to be the first choices of treatment in cortical myoclonus, whereas clonazepam is the first choice in subcortical, spinal and peripheral myoclonus.[78] Details of current treatment options for myoclonus have been reviewed elsewhere.[78] Future treatments might include gene therapy and enzyme replacement to modify and improve the prognosis in genetic disorders.

Table 5. Investigation and treatment of five treatable inborn errors of metabolism

Disorder	MRI findings	Recommended investigations	Treatment
Inborn errors of metabolism			
Tyrosine hydroxylase deficiency	None	CSF analysis (homovanillic acid, 3methoxy4-hydroxy-phenylglucol, and homovanillic acid/5-hydroxyindoleacetic acid ratio)	Levodopa (deep brain stimulation should be considered only in severe cases)
Cerebrotendinous xanthomatosis	Symmetrical abnormalities in dentate nucleus (T2 hyper/hypointensities) T2 hyperintensities in substantia nigra, globus pallidus, inferior olives and periaqueductal nuclei	Specialized laboratory analysis (plasma cholestanol concentration, bile acid and alcohol levels in serum and urine, plasma 5α-cholestanol concentration); CSF analysis (cholestanol and apolipoprotein B)	Chenodeoxycholic acid
Niemann–Pick type C disease	Brain atrophy with cerebellar predominance and diffuse white matter disease Delayed myelination in infants	Specialized laboratory analysis (thrombocytes, transaminases [ASAT/ALAT], LDL- and HDL cholesterol, plasma triglycerides, chitotriosidase, oxysterol profile)	Miglustat
GLUT1 deficiency	Wide opercula and symmetrical T2 hyperintense basal ganglia (caudate/putamen>globus pallidus)	CSF analysis (glucose and lactate levels, CSF:blood glucose ratio commonly <0.4)	Ketogenic diet
Metal storage disorders			
Wilson disease	Symmetrical T2 hyperintensity or mixed intensity in putamen, caudate nucleus, thalamus, and globus pallidus Characteristic 'face of giant panda' sign at midbrain level	Laboratory analysis (24 h urine copper test, ceruloplasmin) Consult ophtalmologist (Kayser–Fleischer ring)	Zinc acetate, copper chelators (penicillamine, trientine, and tetrathiomolybdate)

Conclusion

In this Review, we have proposed a novel diagnostic algorithm (Figure 1) to guide clinicians in detecting myoclonus, assessing its anatomical subtype and diagnosing its underlying cause. Moreover, we provide a comprehensive overview of the acquired and genetic causes of myoclonus.

The traditional clinical and anatomical classifications are included in this new algorithm. Careful clinical and electrophysiological phenotyping is important, because it provides clues to the anatomical subtype and facilitates diagnostic testing. Distinction of myoclonus subtypes (step 2) remains challenging, and further studies are necessary to establish the diagnostic value (in particular, the sensitivity) of electrophysiological features of myoclonus in clinical practice.

The formal etiological classification of myoclonus includes a long list of possible causes. In our eight-step algorithm, we define steps to rule out acquired causes, mitochondrial disorders and late-onset neurodegenerative disorders, so as to identify the subgroup of patients in whom NGS diagnostics are highly recommended for the simultaneous analysis of all potential myoclonus-associated genes.

We believe that our diagnostic algorithm is useful for all practising clinical neurologists and pediatricians, including experts in the fields of movement disorders and epilepsy. The interesting genetic borderland of myoclonus between movement disorders and epilepsy leads to an ensemble of genetic causes, some of which have been previously linked with either epilepsy or movement disorders.

We expect that the new approach presented in this article will increase the diagnostic yield in myoclonus. Moreover, in the coming years, the systematic use of NGS diagnostics will lead to further discoveries of new myoclonus-associated genes and uncommon myoclonus phenotypes.

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References

1 van der Salm SM, de Haan RJ, Cath DC, et al. The eye of the beholder: inter-rater agreement among experts on psychogenic jerky movement disorders. J Neurol Neurosurg Psychiatry. 2013;84(7):742-7.
2 Caviness JN, Alving LI, Maraganore DM, et al. The incidence and prevalence of myoclonus in Olmsted County, Minnesota. Mayo Clin Proc. 1999;74(6):565-9.
3 Marsden CD, Hallett M, Fahn S. The nosology and pathophysiology of myoclonus. Movement Disorders: Butterworth-Heinemann; 1981:196-248.
4 Kojovic M, Cordivari C, Bhatia K. Myoclonic disorders: a practical approach for diagnosis and treatment. Ther Adv Neurol Disord. 2011;4(1):47-62.
5 Caviness JN, Brown P. Myoclonus: current concepts and recent advances. Lancet Neurol. 2004;3(10):598-607.
6 van der Salm SM, Erro R, Cordivari C, et al. Propriospinal myoclonus: clinical reappraisal and review of literature. Neurology. 2014;83(20):1862-70.
7 Zutt R, Elting JW, Tijssen MA. In: Wolters E, Baumann, C, ed. Parkinson Disease and Other Movement Disorders VU Univ. Press; 2014:513–33
8 de Koning TJ, Jongbloed JD, Sikkema-Raddatz B, et al. Targeted next-generation sequencing panels for monogenetic disorders in clinical diagnostics: the opportunities and challenges. Expert Rev Mol Diagn. 2015;15(1):61-70.
9 Keogh MJ, Daud D, Chinnery PF. Exome sequencing: how to understand it. Pract Neurol. 2013;13(6):399-407.
10 Lemke JR, Riesch E, Scheurenbrand T, et al. Targeted next generation sequencing as a diagnostic tool in epileptic disorders. Epilepsia. 2012;53(8):1387-98.
11 Neveling K, Feenstra I, Gilissen C, et al. A post-hoc comparison of the utility of sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. Hum Mutat. 2013;34(12):1721-6.
12 Friedreich N. Paramyoclonus multiplex. Neuropathologische Beobachtungen [German]. Virchows Arch. Pathol. Anat. 1881(86):421–34
13 Lance JW, Adams RD. Negative myoclonus in posthypoxic patients: historical note. Mov Disord. 2001;16(1):162-3.
14 Fahn S, Marsden CD, Van Woert MH. Definition and classification of myoclonus. Adv Neurol. 1986;43:1-5.
15 Frucht S, Fahn S. The clinical spectrum of posthypoxic myoclonus. Mov Disord. 2000;15 Suppl 1:2-7.
16 Andermann F, Tenembaum S. Negative motor phenomena in generalized epilepsies. A study of atonic seizures. Adv Neurol. 1995;67:9-28.
17 Rubboli G, Tassinari CA. Negative myoclonus. An overview of its clinical features, pathophysiological mechanisms, and management. Neurophysiol Clin. 2006;36(5- 6):337-43.
18 Spiro AJ. Minipolymyoclonus: A neglected sign in childhood spinal muscular atrophy. Neurology. 1970;20(11):1124-6.
19 van der Salm SM, Koelman JH, Henneke S, et al. Axial jerks: a clinical spectrum ranging from propriospinal to psychogenic myoclonus. J Neurol. 2010;257(8):1349- 55.
20 Gruber D, Kuhn AA, Schoenecker T, et al. Pallidal and thalamic deep brain stimulation in myoclonus-dystonia. Mov Disord. 2010;25(11):1733-43.
21 Rughani AI, Lozano AM. Surgical treatment of myoclonus dystonia syndrome. Mov Disord. 2013;28(3):282-7.
22 Ritz K, van Schaik BD, Jakobs ME, et al. SGCE isoform characterization and expression in human brain: implications for myoclonus-dystonia pathogenesis? Eur J Hum Genet. 2011;19(4):438-44.
23 Shibasaki H, Yamashita Y, Neshige R, et al. Pathogenesis of giant somatosensory evoked potentials in progressive myoclonic epilepsy. Brain. 1985;108 (Pt 1):225-40.
24 Shibasaki H, Yamashita Y, Kuroiwa Y. Electroencephalographic studies myoclonus. Brain. 1978;101(3):447-60.

25 Brown P, Farmer SF, Halliday DM, et al. Coherent cortical and muscle discharge in cortical myoclonus. Brain. 1999;122 (Pt 3):461-72.
26 Sutton GG, Mayer RF. Focal reflex myoclonus. J Neurol Neurosurg Psychiatry. 1974;37(2):207-17.
27 Shibasaki H, Hallett M. Electrophysiological studies of myoclonus. Muscle Nerve. 2005;31(2):157-74.
28 Ganos C, Kassavetis P, Erro R, et al. The role of the cerebellum in the pathogenesis of cortical myoclonus. Mov Disord. 2014;29(4):437-43.
29 van Rootselaar AF, van der Salm SM, Bour LJ, et al. Decreased cortical inhibition and yet cerebellar pathology in 'familial cortical myoclonic tremor with epilepsy'. Mov Disord. 2007;22(16):2378-85.
30 Banks G, Nielsen VK, Short MP, et al. Brachial plexus myoclonus. J Neurol Neurosurg Psychiatry. 1985;48(6):582-4.
31 Seidel G, Vieregge P, Wessel K, et al. Peripheral myoclonus due to spinal root lesion. Muscle Nerve. 1997;20(12):1602-3.
32 Tyvaert L, Krystkowiak P, Cassim F, et al. Myoclonus of peripheral origin: two case reports. Mov Disord. 2009;24(2):274-7.
33 Calancie B. Spinal myoclonus after spinal cord injury. J Spinal Cord Med. 2006;29(4):413-24.
34 Nogues MA, Leiguarda RC, Rivero AD, et al. Involuntary movements and abnormal spontaneous EMG activity in syringomyelia and syringobulbia. Neurology. 1999;52(4):823-34.
35 Nogues MA. Spontaneous electromyographic activity in spinal cord lesions. Muscle Nerve Suppl. 2002;11:S77-82.
36 Benatru I, Thobois S, Andre-Obadia N, et al. Atypical propriospinal myoclonus with possible relationship to alpha interferon therapy. Mov Disord. 2003;18(12):1564-8.
37 Post B, Koelman JH, Tijssen MA. Propriospinal myoclonus after treatment with ciprofloxacin. Mov Disord. 2004;19(5):595-7.
38 Zamidei L, Bandini M, Michelagnoli G, et al. Propriospinal myoclonus following intrathecal bupivacaine in hip surgery: a case report. Minerva Anestesiol. 2010;76(4):290-3.
39 Estraneo A, Saltalamacchia AM, Loreto V. Spinal myoclonus following herpes zoster radiculitis. Neurology. 2007;68(5):E4.
40 Jimenez-Jimenez FJ, Puertas I, de Toledo-Heras M. Drug-induced myoclonus: frequency, mechanisms and management. CNS Drugs. 2004;18(2):93-104.
41 Gordon MF. Toxin and drug-induced myoclonus. Adv Neurol. 2002;89:49-76.
42 Brefel-Courbon C, Gardette V, Ory F, et al. Drug-induced myoclonus: a French pharmacovigilance database study. Neurophysiol Clin. 2006;36(5-6):333-6. 181
43 Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10(1):63-74.
44 Schmitt SE, Pargeon K, Frechette ES, et al. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology. 2012;79(11):1094-100.
45 Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7(12):1091-8.
46 Silveira-Moriyama L, Lin JP. A field guide to current advances in paediatric movement disorders. Curr Opin Neurol. 2015;28(4):437-46.
47 Shugaiv E, Leite MI, Sehitoglu E, et al. Progressive encephalomyelitis with rigidity and myoclonus: a syndrome with diverse clinical features and antibody responses. Eur Neurol. 2013;69(5):257-62.
48 Balint B, Jarius S, Nagel S, et al. Progressive encephalomyelitis with rigidity and myoclonus: a new variant with DPPX antibodies. Neurology. 2014;82(17):1521-8.
49 Borg M. Symptomatic myoclonus. Neurophysiol Clin. 2006;36(5-6):309-18.

50 Krug P, Schleiermacher G, Michon J, et al. Opsoclonus-myoclonus in children associated or not with neuroblastoma. Eur J Paediatr Neurol. 2010;14(5):400-9.
51 Hersh B, Dalmau J, Dangond F, et al. Paraneoplastic opsoclonus-myoclonus associated with anti-Hu antibody. Neurology. 1994;44(9):1754-5.
52 Gregory A, Polster BJ, Hayflick SJ. Clinical and genetic delineation of neurodegeneration with brain iron accumulation. J Med Genet. 2009;46(2):73-80.
53 Pellecchia MT, Valente EM, Cif L, et al. The diverse phenotype and genotype of pantothenate kinase-associated neurodegeneration. Neurology. 2005;64(10):1810-2.
54 Schneider SA, Hardy J, Bhatia KP. Syndromes of neurodegeneration with brain iron accumulation (NBIA): an update on clinical presentations, histological and genetic underpinnings, and treatment considerations. Mov Disord. 2012;27(1):42-53.
55 Pareyson D, Fancellu R, Mariotti C, et al. Adult-onset Alexander disease: a series of eleven unrelated cases with review of the literature. Brain. 2008;131(Pt 9):2321-31.
56 van der Knaap MS, Naidu S, Breiter SN, et al. Alexander disease: diagnosis with MRimaging. AJNR Am J Neuroradiol. 2001;22(3):541-52.
57 van der Knaap MS, Ramesh V, Schiffmann R, et al. Alexander disease: ventricular garlands and abnormalities of the medulla and spinal cord. Neurology. 2006;66(4):494-8.
58 Orru CD, Bongianni M, Tonoli G, et al. A test for Creutzfeldt-Jakob disease using nasal brushings. N Engl J Med. 2014;371(6):519-29.
59 Mancuso M, Orsucci D, Angelini C, et al. Myoclonus in mitochondrial disorders. Mov Disord. 2014;29(6):722-8.
60 DiMauro S, Hirano M, Kaufmann P, et al. Clinical features and genetics of myoclonic epilepsy with ragged red fibers. Adv Neurol. 2002;89:217-29.
61 Caviness JN, Adler CH, Caselli RJ, et al. Electrophysiology of the myoclonus in dementia with Lewy bodies. Neurology. 2003;60(3):523-4.
62 Caviness JN, Adler CH, Beach TG, et al. Myoclonus in Lewy body disorders. Adv Neurol. 2002;89:23-30.
63 Caviness JN, Adler CH, Beach TG, et al. Small-amplitude cortical myoclonus in Parkinson's disease: physiology and clinical observations. Mov Disord. 2002;17(4):657-62.
64 Salazar G, Valls-Sole J, Marti MJ, et al. Postural and action myoclonus in patients with parkinsonian type multiple system atrophy. Mov Disord. 2000;15(1):77-83.
65 Glass GA, Ahlskog JE, Matsumoto JY. Orthostatic myoclonus: a contributor to gait decline in selected elderly. Neurology. 2007;68(21):1826-30.
66 Leu-Semenescu S, Roze E, Vidailhet M, et al. Myoclonus or tremor in orthostatism: an under-recognized cause of unsteadiness in Parkinson's disease. Mov Disord. 2007;22(14):2063-9.
67 de Ligt J, Willemsen MH, van Bon BW, et al. Diagnostic exome sequencing in persons with severe intellectual disability. N Engl J Med. 2012;367(20):1921-9.
68 Canafoglia L, Robbiano A, Pareyson D, et al. Expanding sialidosis spectrum by genome-wide screening: NEU1 mutations in adult-onset myoclonus. Neurology. 2014;82(22):2003-6.
69 Patterson MC, Hendriksz CJ, Walterfang M, et al. Recommendations for the diagnosis and management of Niemann-Pick disease type C: an update. Mol Genet Metab. 2012;106(3):330-44.
70 Lyseng-Williamson KA. Miglustat: a review of its use in Niemann-Pick disease type C. Drugs. 2014;74(1):61-74.
71 Taly AB, Meenakshi-Sundaram S, Sinha S, et al. Wilson disease: description of 282 patients evaluated over 3 decades. Medicine (Baltimore). 2007;86(2):112-21.
72 Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. Lancet Neurol. 2015;14(1):103-13.

73 Pearson TS, Akman C, Hinton VJ, et al. Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS). Curr Neurol Neurosci Rep. 2013;13(4):342.
74 Leen WG, Wevers RA, Kamsteeg EJ, et al. Cerebrospinal fluid analysis in the workup of GLUT1 deficiency syndrome: a systematic review. JAMA Neurol. 2013;70(11):1440- 4.
75 Nie S, Chen G, Cao X, et al. Cerebrotendinous xanthomatosis: a comprehensive review of pathogenesis, clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2014;9:179.
76 Federico A, Dotti MT. Cerebrotendinous xanthomatosis: clinical manifestations, diagnostic criteria, pathogenesis, and therapy. J Child Neurol. 2003;18(9):633-8.
77 Willemsen MA, Verbeek MM, Kamsteeg EJ, et al. Tyrosine hydroxylase deficiency: a treatable disorder of brain catecholamine biosynthesis. Brain. 2010;133(Pt 6):1810- 22.
78 Dijk JM, Tijssen MA. Management of patients with myoclonus: available therapies and the need for an evidence-based approach. Lancet Neurol. 2010;9(10):1028-36.

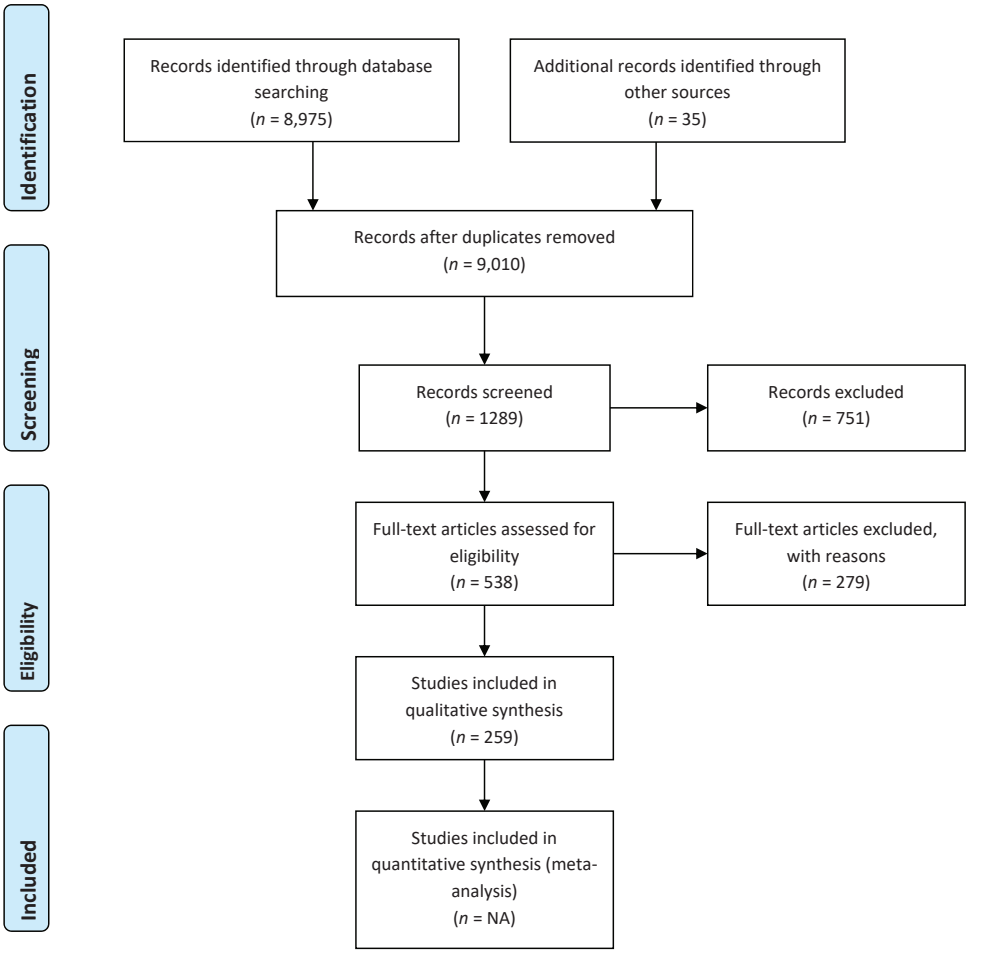
Supplement 1. *Full electronic search strategy for a systematic review of causes of myoclonus*

We systematically reviewed all papers regarding myoclonus and its acquired and genetic causes. References for this review were identified by PubMed, OMIM and Text book search up to June, 2015, as well as searching for the references cited in the relevant articles. The key search terms used were 'myoclonus' and 'myoclonic jerks' combined with terms indicating possible etiologies including: 'genetic causes', 'acquired causes', 'metabolic diseases', 'inborn errors metabolism', 'etiology', 'causality', 'drug', 'toxin', 'autoimmune', 'paraneoplastic', and 'epilepsy'. All the papers and abstracts we reviewed were published in English. The search strategy and details of the numbers of articles collected are visualized on the next page.

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool[1] could not be applied in selecting cases, because disorders causing myoclonus are rare and the available evidence consisted of small clinical trials, case series and expert opinion. For the same reason not all items of the PRISMA Statement checklist were applicable (see below).

Only causes presented in at least two patients with myoclonus were included in the review. Molecular defects had to be described in more than one family with myoclonus. The final reference list was generated on the basis of uniqueness and relevance to the topic.

Prisma 2009 flow diagram



Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	NA
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	NA
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	NA
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	9 / Suppl 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9 / Suppl 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9 / Suppl 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	NA
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	NA
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Prisma flow chart
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	NA
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	NA
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

1. Moher D., Liberati A., Tetzlaff J., Altman D. G. & The PRISMA Group Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. *PloS. Med.* **6**, e1000097 (2009).

Supplement 2. Comprehensive overview of genes associated with myoclonus

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
Startle response		Hyperekplexia	Autosomal dominant or autosomal recessive Autosomal recessive	Infancy	149400	*GLRA1*	Excessive startle responses Startle-induced stiff falls Generalized stiffness at birth
			Autosomal recessive X-linked		614618 614619 300429	*SCL6A5 /GlyT2* *GLRB ARHGEF9*	
Dystonia		Myoclonus dystonia	Autosomal dominant	First or second decade	604149	*SGCE*	Myoclonus predominantly of the upper body Dystonia (neck, writer's cramp) Psychiatric disorders
			Autosomal dominant		601012	*CACNA1B*	
			Autosomal dominant		600514	*RELN*	
			Autosomal dominant		616386	*KCDT17*	
			Autosomal dominant		610110	*ANO3*	Craniocervical dystonia Tremor
		'Russell-Silver syndrome'	Maternal uniparental disomy		180860	*mUPD7*	Myoclonus–dystonia Growth retardation Craniofacial dysmorphism
		Tyrosine hydroxylase deficiency	**Autosomal recessive**	**First or second decade**	**191290**	***TH***	**Levodopa-responsive myoclonu–dystonia**
		Benign hereditary chorea	Autosomal dominant	Childhood	600635	*NKX2-1/TITF1*	Myoclonus Dystonia presentation Chorea Hypothyroidism Pulmonary abnormalities
		Neurodegeneration with brain iron accumulation-1 (Hallervorden-Spatz)	Autosomal recessive	Childhood–adolescence	606157	*PANK2*	Dystonia Pyramidal syndrome Cognitive decline Psychiatric symptoms
		Familial dyskinesia with facial myokymia	Autosomal dominant	Childhood	600293	*ADCY5*	Periorbital and perioral facial dyskinesia Chorea Dystonia Axial hypotonia Movements worsened by anxiety
		Wilson disease	**Autosomal recessive**	**Early childhood–60 years**	**606882**	***ATP7B***	**Tremor** **Dystonia** **Parkinsonism** **Hepatic signs** **Psychiatric symptoms**

The diseases in bold are the five treatable inborn errors of metabolism mentioned in Step 8 of the manuscript, see Table V for an overview of the possibilities of diagnostic investigations other than NGS and information about the treatment

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
Epilepsy	***Generalized epilepsies***	Juvenile myoclonic epilepsy	Autosomal dominant	Onset around puberty	611136	*GABRA1*	Myoclonus mainly in arms, especially in the morning Tonic-clonic seizures especially at night. Absences
			Autosomal dominant		601949	*EJM6/CACNB4*	Juvenile myoclonic epilepsy Episodic ataxia
			Autosomal dominant		600570	*CLCN2*	
			Autosomal dominant		137163	*EJM7/GABRD EJM2/*	
			Autosomal recessive		604827	*CHRNA7*	
			Autosomal dominant		600235	*SCN1B*	Generalized epilepsy Febrile seizures Juvenile myoclonic epilepsy
			Autosomal dominant		254770	*EJM1/EFHC1*	
			X-linked		300817	*EFHC2*	
			Autosomal dominant		612899	*CASR*	
			Autosomal recessive		607058	*Cx-36*	
			Autosomal dominant		601540	*BRD2*	
			Autosomal dominant		154270	*ME2*	
			Autosomal recessive		190197	*CNTN2*	

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
	Epileptic encephalopathies	Doose syndrome (myoclonic astatic epilepsy)	unknown	7 months–6 years		Unknown *(SCN1A, SLCA1?)*	Seizures (myoclonic-astatic/atonic, absences, tonic–clonic, tonic seizures) Cognitive disability
		Dravet syndrome (severe myodonic epilepsy of infancy)	Autosomal dominant	First year of life (peak at 5 months)	607208	*SCN1A*	(Febrile) Seizures (focal, myoclonic seizures, atypical absences) Developmental delay
			X-linked		300088	*PCDH19*	
			Autosomal dominant		137164	*GABRG2*	
			Autosomal dominant		182390	*SCN2A*	
			Autosomal dominant		600235	*SCN1B*	
			Autosomal dominant		603415	*SCN9A*	
			Autosomal dominant		602926	*STXBP1*	
		SCN8A encephalopathy	Autosomal dominant	0–18 months	600702	*SCN8A*	Epilepsy Intellectual disability Hypotonia Dystonia
		Lennox-Gastaut syndrome	Autosomal recessive	1–7 years	600173	*JAK3*	Seizures (tonic–axial, atonic, absence seizures, myoclonic, generalized tonic-clonic, partial seizures) Mental retardation
			Autosomal dominant		602119	*CHD2*	
		Aicardi-Goutières syndrome	Autosomal dominant or autosomal recessive	Within first year of life	606609	*TREX1*	Severe developmental delay Seizures Progressive microcephaly Spasticity Dystonia
			Autosomal recessive		610326	*RNASEH2B*	
			Autosomal recessive		610330	*RNASEH2C*	
			Autosomal recessive		606034	*RNASEH2A*	
			Autosomal recessive		606754	*SAMHD1*	
		Infantile spasm syndrome	X-linked dominant	First months of life	300203	*CDKL5*	Epilepsy Mental retardation Lack of speech development Dysmorphic facial features

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
	Metabolic	Non-ketotic hyperglycinemia	Autosomal recessive	Neonatal period (milder form adult onset)	238300	GLDC	Lethargy Hypotonia Apnea Early myodonic epilepsy Mental retardation
			Autosomal recessive	First 2 years of life	238330	*GCSH*	
			Autosomal recessive		238310	*AMT*	
			X linked recessive		300011	*ATP7A*	Developmental delay Growth retardation Kinky hair Cerebral and cerebellar degeneration
				Early childhood			Seizures (infantile spasms) Myoclonus
		GLUT1 deficiency	**Autosomal dominant**	**First two years of life**	**138140**	***SLC2A1***	**Paroxysmal exertional dyskinesia** **Ataxia–epilepsy** **Developmental delay** **Spasticity**
		Menkes disease	X linked recessive	Childhood	300011	*ATP7A*	Developmental delay Growth retardation Kinky hair Cerebral and cerebellar degeneration Seizures (infantile spasms) Myoclonus
		Tay-Sachs disease Gangliosidosis (type 1)	Autosomal recessive	Childhood	606869	*HEXA*	Develepmental delay and/or regression Seizures Loss of vision (cherry red spot)
		Sandhoff's disease Gangliosidosis (type 2)	Autosomal recessive	Early childhood	606873	*HEXB*	Psychomotor retardation Seizures Visual loss (macular cherry-red spot) Ataxia
		Alpers-Huttenlocher syndrome	Mitochondrial		174763	*POLG*	Epilepsia partialis continua Developmental regression Refractory focal motor or myoclonic seizures Liver dysfunction

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
	Leigh syndrome		Mitochondrial	Birth–adolescence	*	*	Psychomotor retardation Retinitis pigmentosa Ataxia Neuropathy Seizures
	Neuropathy, ataxia, and retinitis pigmentosa (NARP syndrome)		Mitochondrial	Childhood	516060	*MTATP6*	Develepmental delay Retinitis pigmentosa Seizures Ataxia Sensory neuropathy
	Kearns-Sayre syndrome		Mitochondrial	Onset before age 20	590050	*MTTL1*/**	Progressive external ophthalmoplegia Pigmentary retinopathy Cardiac conduction block
	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome)		Mitochondrial	Childhood	***	***	Stroke-like episodes at a young age Encephalopathy Epilepsy Cognitive decline

* Unknown which gene mutations are accompanied by myoclonus. Genes causing Leigh syndrome: BCS1L (603647), NDUFA10 (603835), SDHA (600857), NDUFS4 (602694), NDUFS7 (601825), NDUFAF2 (609653), NDUFA2 (602137), NDUFAF5 (612360), NDUFAF6 (612392), SURF1 (185620), COX15 (603646), NDUFS3 (603846), NDUFS8 (602141), FOXRED1 (613622), NDUFA9 (603834), NDUFA12 (614530), COX10 (602125), SURF1 (185620), TACO1 (612958), MTATP6 (516060);
** Caused by deletion of multiple genes in the mitochondrial DNA;
*** Unknown which gene mutations are accompanied by myoclonus.

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
	Syndromic	Angelman syndrome	****	6–12 months	601623	*UBE3A*	Mental retardation Absent or lack of speech Behavioral problems Seizures Ataxia
		Multiple congenital Anomalies–hypotonia–seizures syndrome 2 (MCAHS2)	X-linked recessive	Early infancy	311770	*PIGA*	Facial dysmorphism Intellectual disability Seizures Neonatal hypotonia
		Rett syndrome	X-linked dominant	First year of life	300005	*MECP2*	Psychomotor retardation Impaired language development Hand stereotypies Seizures
		Coffin-Lowry syndrome	X-linked	Childhood	300075	*RPS6KA3*	Psychomotor and growth retardation Facial and digital abnormalities Skeletal anomalies Seizures

**** Loss of maternally derived *UBE3A* allel (*de novo* dominant, paternal uniparental disomy (UPD) or other rare causes).

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
	Progressive epilepsies (PME)	Myoclonic epilepsy with myoclonic ragged red fibers (MERRF syndrome)	Mitochondrial	5–42 years	590060	MTTK	Seizures (tonic–clonic) Dementia Neuropathy Myopathy
			Mitochondrial		590050	*MTTL1*	
			Mitochondrial		590040	*MTTH*	
			Mitochondrial		590080	*MTTS1*	
			Mitochondrial		590085	*MTTS2*	
			Mitochondrial		590070	*MTTF*	
		Sialidosis type I	Autosomal recessive	8–38 years	608272	*NEU1*	Gradual visual failure; cherry red spot Seizures (tonic clonic) Ataxia
		Sialidosis type II	Autosomal recessive	10–30 years	608272	*NEU1*	Dysmorphic features Seizures (tonic clonic) Hepatosplenomegaly Mental retardation
		Lafora disease	Autosomal recessive	11–18 years	607566	*EPM2A*	Progressive dementia Epilepsy Ataxia Visual hallucinations
			Autosomal recessive		608072	*EPM2B (NHLRC1)*	Less severe clinical course comparedwith the EPM2B variant
		Gaucher disease (mainly type III)	Autosomal recessive	5–15 years	606463	*GBA*	Hepatosplenomegaly Skeletal disorders Supranuclear gaze palsy (horizontal) Cognitive impairment Seizures Ataxia
			Autosomal recessive		610539	*Saposin C/PSAP*	
		Niemann-Pick type C Disease	**Autosomal recessive**	**Childhood–adolescence**	**607623**	***NPC1***	**Ataxia–dystonia** **Cognitive decline** **Supranuclear gaze palsy (vertical)** **Psychiatric symptoms** **Hepatosplenomegaly**
			Autosomal recessive		**601015**	***NPC2/HE1***	

The diseases in bold are the five treatable inborn errors of metabolism mentioned in Step 8 of the manuscript,
see Table V for an overview of the possibilities of diagnostic investigations other than NGS and information about the treatment.

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
	Neuronal ceroid-lipofuscinoses	Santavuori-Haltia	Autosomal recessive	Infantile onset (8–18 months)	256730	*CLN1/PPT1*	Progressive loss of motor milestones Dementia Visual loss Seizures
				Late infantile onset (2.5–4 years)			
		Jansky-Bielschowski	Homozygous or compound heterozygous mutation		204500	*CLN2/TPP1*	Seizures Intellectual deterioration Progressive visual loss (macula degeneration)
				Juvenile onset (4–10 years)			Ataxia Spasticity
		Batten disease (Spiel-meyer-Vogt-Sjogren-Batten disease)	Autosomal recessive	Adult onset (11–50 years)	607042	*CLN3*	Visual loss (pigmentary retinopathy) Dementia Seizures Myoclonus Behavioral disorders
		Parry disease	Autosomal dominant	Late infantile or adult onset (11–50 years)	611203	*CLN4/DNAJC5*	Dementia with motor disturbances Behavioural disorders Ataxia
		Kufs disease type A	Autosomal dominant or autosomal recessive	Late infantile	606725	*CLN6*	Myoclonus Ataxia Dementia Seizures
			Autosomal recessive	Late infantile	608102	*CLN5*	Hypotonia Seizures Visual loss Myoclonus
			Autosomal recessive		610951	*CLN7/MFSD8*	Epilepsy
			Autosomal recessive		607837	*CLN8*	Progressive mental retardation
			Autosomal recessive		614706	*CLN 11/GRN*	

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
	Progressive myoclonic ataxia (PMA) / Ramsay Hunt syndrome	North sea progressive myoclonus epilepsy	Autosomal recessive	Childhood	614018	*GOSR2*	Ataxia Areflexia Generalized seizures Cortical reflex myoclonus
		Action myoclonus renal failure syndrome (AMRS)	Autosomal recessive	9–30 years	602257	*SCARB2/LIMP2*	Ataxia Tremor Generalized tonic-clonic seizures Proteinuria and progressive renal failure (AMRS may occur without renal failure)
		Cerebrotendinous xanthomatosis	**Autosomal recessive**	**Childhood–adult onset**	**606530**	***CYP27A1***	**Tendinous/tuberous xanthomas** **Juvenile cataract** **Cerebellar ataxia** **Chronic diarrhoea** **Peripheral neuropathy** **Psychiatric disoders** **Mild mental retardation**
		Others in category of PME/PMA	Autosomal recessive		608500	*PRICKLE1*	
			Autosomal recessive		606919	*CERS1*	
			Autosomal recessive		613468	*ASAH1*	Spinal muscular atrophy Progressive myodonic epilepsy
			Autosomal recessive		611725	*KCTD7*	Progressive myodonic epilepsy Dystonia Ataxia
			Autosomal dominant		176258	*KCNC1*	
		Dentato-rubro-pallido-luysian atrophy (DRPLA)	Autosomal dominant	Mean age of onset 30 years (range first to seventh decade)	607462	*ATN1*	Seizures (tonic-clonic) Cerebellar ataxia Choreoathetosis Dementia
		Unverricht Lundborg Disease (Baltic myoclonus)	Autosomal recessive	Childhood–adolescence	601145	*EPM1 / CSTB*	Seizures Myoclonus Mild cognitive dysfunction Cerebellar signs

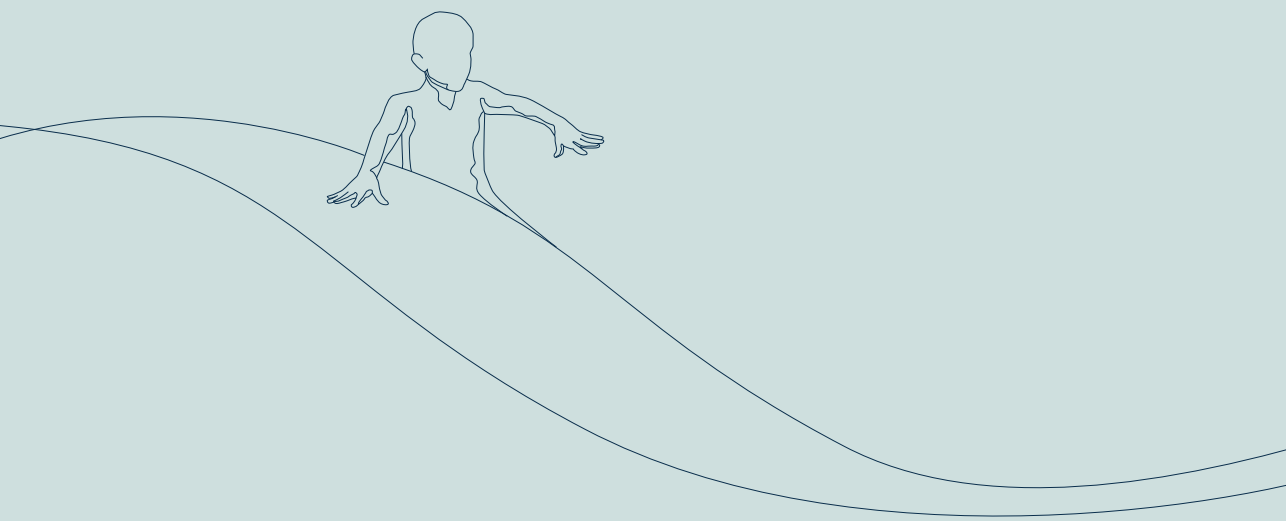
The diseases in bold are the five treatable inborn errors of metabolism mentioned in Step 8 of the manuscript, see Table V for an overview of the possibilities of diagnostic investigations other than NGS and information about the treatment.

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
Spasticity		Leucoencephalopathy with vanishing white matter	Autosomal recessive	Childhood	603945	EIF2B5	Cerebellar ataxia Spasticity (Myoclonic) Seizures
		Krabbe leucodystrophy	Autosomal recessive	Birth–adolescence	606890	GALC	Spasticity Seizures Loss of vision Dementia Peripheral neuropathy
		Alexander disease	Autosomal dominant	Infantile, juvenile, adult	137780	GFAP	Seizures Spasticity Cerebellar ataxia Bulbar or pseudobulbar symptoms Palatal myoclonus
		Kufor-Rakeb syndrome	Autosomal recessive	Average age of onset 13 years	610513	ATP13A2	Parkinsonism Supranuclear gaze palsy Spasticity Dementia

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
Ataxia		Friedreich ataxia	Autosomal recessive (GAA repeat)	First or second decade	606829	*FXN*	Progressive ataxia Limb muscle weakness Decreased vibratory perception & proprioception Scoliosis Cardiomyopathy and arrhythmias
		Ataxia telangiectasia	Autosomal recessive	Early childhood	607585	ATM	Cerebellar ataxia Oculocutaneous telangiectases Ataxia Immune defects Endocrinopathy Predisposition to malignancy
		SCA1	Autosomal dominant (CAG repeat)	Third or fourth decade	601556	ATXN1	Cerebellar ataxia Spastic paraplegia Supranuclear gaze palsy
		SCA2	Autosomal dominant (CAG repeat)	Mean age of onset in third decade	601517	ATXN2	Slowed ocular movements Tremor Myoclonus Parkinsonism Cognitive impairment
		SCA3 (Machado-Joseph disease)	Autosomal dominant (CAG repeat)	3–4th decade	607047	*ATXN3*	Ataxia Pyramidal signs Peripheral neuropathy Rigidity and bradykinesia

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
		SCA6	Autosomal dominant (CAG repeat)	20– 65 years	601011	*CACNA1A*	Ataxia Impaired smooth pursuit eyes, nystagmus (downbeat) Episodic exacerbations
		SCA 7	Autosomal dominant (CAG repeat)	Adult onset	607640	*ATXN7*	Ataxia Pigmental macular dystrophy Supranuclear ophthalmoplegia
		SCA8	Autosomal dominant (CAG repeat)	18–65 years	613289	*ATXN8*	Ataxia Nystagmus Mild pyramidal features
			Autosomal dominant (CTG repeat)	18–65 years	603680	*ATXN8OS*	
		SCA14	Autosomal dominant	Childhood–sixth decade	176980	*PRKCG*	Myoclonus Ataxia Gaze-evoked nystagmus Sensory loss
		SCA17	Autosomal dominant (CAG repeat)	Median age at onset 23 years	600075	*TBP*	Parkinsonism Psychiatric symptoms Cognitive impairment Ataxia
		SCA19 / SCA 22	Autosomal dominant	Variable age of onset	605411	*KCND3*	Ataxia (often pure)

Key feature (besides myoclonus)	Subcategory	Disease name	Inheritance	Common age of onset	OMIM	Locus / gene	Characteristic symptoms
Late onset dementia or parkinsonism		Creutzfeldt-Jakob disease	Autosomal dominant	Third to ninth decade	176640	PRNP	Progressive myoclonus Rapidly progressive dementia Behavioural disturbances Cortical visual disturbances
		Gerstmann-Straussler- Scheinker syndrome	Autosomal dominant	19–66 years	176640	*PRNP*	Rapidly progressive dementia Seizures Pyramidal and extrapyramidal features
		Fatal familial insomnia	Autosomal dominant	20–60 years	176640	*PRNP*	Insomnia Ataxia Rapidly progressive dementia
		Huntington disease	Autosomal dominant (CAG repeat)	Depends on number of CAG repeats	613004	*HTT*	Chorea Ataxia Dystonia Behavioural disturbances Cognitive decline
		Parkinson disease	Autosomal dominant	30–60 years	163890	*SNCA*	Parkinsonism Dystonia Cognitive decline
		Alzheimer disease					
		Pallido-ponto-nigral degeneration	Autosomal dominant	3th–4th decade	104311	*PSEN1*	Dementia
		Fronto- temporal Dementia	Autosomal dominant	Mean age of onset 45 years	157140	*MAPT*	Progressive parkinsonism Dementia Psychiatric symptoms
			Autosomal dominant	Mean age of onset 62 years	138945	*GRN*	Frontotemporal dementia Language deterioration Behavioural or psychiatric disturbances



Myoclonus in childhood-onset neurogenetic disorders: the importance of early identification and treatment

Chapter 8

M.E. van Egmond, J.W. Elting, A. Kuiper, R. Zutt, K.R. Heineman, O.F. Brouwer, D.A. Sival, M.A. Willemsen, M.A.J. Tijssen, T.J. de Koning

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Abstract

Background

In clinical practice, myoclonus in childhood-onset neurogenetic disorders frequently remains unrecognized, because it is often overshadowed by other neurological features. Since treatment can lead to significant functional improvement, accurate phenotyping is essential. To demonstrate the importance of early identification and treatment, we report on four patients with various childhood-onset neurogenetic disorders suffering from myoclonus.

Methods

We evaluated four patients with established childhood-onset neurogenetic disorders and involuntary jerky movements, who visited our young-onset movement disorder outpatient clinic.

Results

We present the clinical data of four patients (aged 8-21 years) with childhood-onset neurogenetic disorders, including ataxia-telangiectasia, Coffin-Lowry syndrome and epileptic encephalopathy due to *SCN1A* mutations. All four suffered from jerky movements that hampered normal daily activities and that had gone unrecognized for several years. The presence of multifocal myoclonus was confirmed by polymyography. In all patients, treatment resulted in marked improvement of both myoclonus and overall functioning.

Conclusion

These cases highlight the relevance of actively searching for myoclonus in childhood-onset neurogenetic disorders, even when a molecular diagnosis has already been established. To further improve the awareness and recognition of myoclonus in children, we provide a list of childhood-onset neurogenetic disorders with myoclonus as important associated feature.

Introduction

Myoclonus is defined as sudden, brief, shock-like involuntary movements caused by muscular contractions (positive myoclonus) or interruptions of tonic muscle activity (negative myoclonus).[1] A widely used approach is classification according to the anatomic origin, with the most common forms being CM (cortical myoclonus) and SM (subcortical myoclonus) (Table 1).[1]

Myoclonus in children and adolescents frequently remains unrecognized. However, it is an important feature in many childhood-onset conditions, especially in neurogenetic disorders (Supplemental Table), and identification is important because it is treatable. To illustrate this, we report on four patients with various childhood-onset neurogenetic disorders suffering from myoclonus, as confirmed by simultaneous electroencephalography/electromyography (EEG/EMG) recordings. Although myoclonus was not the main symptom in these patients, it had significant impact on their daily functioning. Treatment with clonazepam was effective in all patients.

Case study

Cases 1 and 2

Patient 1 and 2 are homozygote twin brothers, 21-years-old, with Dravet syndrome (DS) due to a C.3637C>T(p.Arg1213Stop) mutation of the *SCN1A* gene. They were referred to our young-onset movement disorders outpatient clinic because of involuntary jerky hand movements.

Since the age of 4 months both patients had suffered from intractable generalized tonic-clonic seizures, atypical absences and tonic seizures. During childhood, they had developmental delays with behavioral problems and autistic features. Their parents reported that the involuntary jerks had been present since birth and progressed during the last few years, limiting normal daily activities. Unexplained sudden falls had occurred since adolescence, with accidents and insecure gait.

Table 1. Clinical and neurophysiological features of different types of myoclonus in genetic disorders.

	Clinical presentation	Distribution	Temporal pattern	Electrophysiological examination		Treatment[a]
				EMG / Polymyography	Other	
Cortical myoclonus	Spontaneous Action induced Stimulus sensitive *also negative myoclonus*	(Multi) focal/ generalized: *Face, distal limbs*	Irregular (rhythmic)	• Short bursts (usually <50ms) • Back-averaging: time-locked contralateral cortical spike preceding myoclonus • Coherence analysis: cortico-muscular and inter-muscular coherence in alpha and beta band with a phase difference compatible with cortical drive	• SSEP: giant potential (P25/P30/N35) • Cortical reflex (C-reflex)	levetiracetam, piracetam, valproic acid, clonazepam, zonisamide, primidone, ethosuximide
Subcortical myoclonus	Spontaneous Action induced	Can be generalized *Axial/proximal limbs*	Irregular	• Burst duration variable (25-256 ms)	• SSEP: normal No C-reflex	clonazepam *Myoclonus dystonia:* clonazepam, trihexylphenidyl, levodopa[b], L-5-HTP[b] sodium oxybate *Hyperekplexia:* clonazepam
Brainstem myoclonus	Stimulus sensitive	Generalized/ synchronous *Axial/proximal limbs*	Irregular	• -Burst duration variable • Simultaneous rostral and caudal activation of muscles	• SSEP: normal • No C-reflex	clonazepam

This table is adapted from: Table 1 and Table 2 of Zutt et al. (Supplemental references).

[a] Drugs best to be avoided are phenytoin and carbamazepine (Cassim et al, Supplemental references).

[b] In combination with a decarboxylase inhibitor.

Neurological examination showed continuous multifocal stimulus-sensitive myoclonic jerks, most pronounced in their hands and faces, with exacerbation on action (Video 1A). EEG/EMG findings were supportive of CM: myoclonic jerks with burst duration of 30-60 ms and occasionally also negative myoclonus. Back-averaging and coherence analysis showed no cortical potential or increased coherence, most likely because not enough segments were available for analysis. Somatosensory evoked potentials (SEP) studies showed no giant potentials, possibly due to valproate use (Ikeda et al, Supplemental references). We classified the jerks as CM, with negative myoclonus leading to falls. As treatment with valproate and levetiracetam had not been beneficial, we initiated treatment with clonazepam (3 x 2 mg daily). This led to marked improvement of positive and negative myoclonus in both patients (Video 1B).

Case 3

A 20-year old patient with ataxia-telangiectasia (AT) visited the outpatient clinic because of involuntary jerky movements and a tremulous voice. Disease onset was at the age of 3 years with a gait disorder and delayed motor and language development. One year later, a cerebellar syndrome was reported with dysarthria, gait and limb ataxia. Sequential EMGs demonstrated progressive axonal sensorimotor polyneuropathy. The involuntary movements had been reported since he was 7 years old, with significant impact on his daily functioning.

Neurological examination showed limb ataxia, ocular apraxia, nystagmus, bilateral ptosis, dystonia of the fingers, areflexia, distal weakness and sensory loss. There was a marked cerebellar dysarthria and an irregular tremulous voice. Spontaneous multifocal myoclonic jerks were observed, mostly in both arms, worsening on action, without stimulus- sensitivity (Video 2). EEG/EMG demonstrated myoclonic jerks with burst duration of 30-80 ms, suggestive of CM. Back-averaging and coherence analysis showed no cortical correlate or increased coherence. SEP studies showed no potentials, due to the polyneuropathy. We classified the myoclonus as possibly cortical.

The patient was treated with clonazepam (2 x 0.5 mg daily), leading to a significant decrease in myoclonic jerks. The patient regained several fine motor skills such as eating without help and the ability to use his mobile phone. In addition, reduced voice tremor resulted in enhanced intelligibility. His overall functioning improved significantly.

Case 4

An 8-year old boy with Coffin-Lowry syndrome (CLS) due to exon 22 deletion in the *RPS6KA3* gene visited us because of invalidating stimulus-induced drop attacks since six months, and involuntary jerky hand movements since early childhood. The drop attacks had resulted in frequent and serious falling accidents, which had made him too insecure to walk without support. The episodes comprised sudden loss of motor tone in both legs during walking or standing with preserved consciousness, induced by unexpected touch or visual stimuli. The parents provided a video-fragment of one of the drop episodes, as recorded by the physiotherapist (Video 3A).

Neurological examination showed continuous myoclonic jerks in the face, limbs and trunk, stimulus-sensitive, worsening on voluntary movement. With support, he was able to walk a few steps, cautiously, with bended knees and a bobbing movement of the trunk (Video 3A), described

elsewhere as a 'bouncing' gait.[2] EEGs, including an EEG during a provoked drop episode, showed no epileptic abnormalities. SEP studies showed no giant potentials. EEG/EMG was not performed because his parents considered it to be too bothersome. We classified the positive and negative myoclonus as most likely to be CM. Treatment with clonazepam (0.06 mg/kg/day) led to a significant reduction in myoclonic jerks and falls, resulting in this patient regaining the ability to walk without support (Video 3B).

Discussion

Myoclonus is a diagnosis often missed in children and adolescents. One possible reason for this oversight is that myoclonus may be difficult to recognize because young-onset movement disorders are often mixed. In addition, reports on childhood myoclonus outside the context of childhood epilepsies, have been limited. Finally, in many neurogenetic disorders, the main focus is on the most dominant feature, such as the intractable seizures in DS. Therefore, the possibility of myoclonus needs to be actively investigated during history- taking and neurological examination.

Better diagnosis starts with clinical recognition. Myoclonus must be differentiated from other movement disorders such as tics, tremor, focal seizures and functional jerks. The following are important clinical clues for differentiation of myoclonus: simple, non- suppressible, jerky and generally arrhythmic movements, sometimes stimulus-sensitive, with absence of entrainment and not preceded by an urge to move. Positive myoclonus can be best observed by asking patients to stretch out their arms in front of them with extended and slightly spread fingers. To uncover the presence of negative myoclonus, it is necessary to test tonic muscle activity by wrist extension and to specifically ask for sudden unexpected falls. The repetitive loss of postural tone in axial and leg muscles may result in a typical 'bouncing' gait.[2] Neurophysiological studies can be helpful in the diagnostic workup of myoclonus (Table 1). EMG in CM reveals short bursts (usually <50 ms), and usually longer bursts in SM. EEG/EMG enables jerk-locked back-averaging to establish whether a cortical spike precedes the myoclonic jerk. Additional findings supporting a cortical generator are a positive coherence analysis, the presence of a C-reflex or SEP studies showing a giant potential. However, the sensitivity and specificity of these additional findings is unknown. Treatment of myoclonus in neurogenetic conditions is symptomatic and the choice of treatment is based on the anatomical classification (Table 1).[1] Advantages of clonazepam are effectiveness in both CM and SM, with often a good response to low doses.

Myoclonus has been described in many childhood-onset neurogenetic disorders (Supplemental Table). Here, we will discuss briefly what is known about myoclonus in DS, AT and CLS.

DS is an epileptic encephalopathy beginning in infancy, characterized by a tetrad of seizures, including myoclonic seizures. Two main types of myoclonus are usually described in DS: multifocal distal jerks and generalized jerks, the latter often having an obvious EEG correlate, originating from spread of CM activity. In cases 1 and 2, clinical and neurophysiological findings were compatible with CM. Their unexpected falls are illustrative of negative myoclonus. Our patients clearly illustrate that it is important to consider CM in addition to the epileptic seizures in DS. Although treatment options for both conditions are similar, adjustment of medication focused on the myoclonus should be considered.

In individuals with AT, myoclonus and tremor occur in at least 25% of patients.[3] Reports on the neurophysiological examination and treatment of myoclonus in AT are surprisingly scarce.[3] Although there are clues for a pathophysiological relationship between cerebellar pathology and CM,[3] the anatomical origin of myoclonus in AT is unknown. Therefore, we treated patient 3 with clonazepam, as it can be effective for both SM and CM.

With regard to CLS this is, to our knowledge, the first report of the presence of continuous myoclonic jerks, although other movement disorders and stimulus-induced drop episodes (SIDEs) have been reported in these patients.[4] The underlying mechanism for SIDEs is unknown. Our patient's SIDEs are most likely based on negative CM, as supported by the presence of the stimulus-sensitive positive myoclonus in other body parts, and the 'bouncing gait'. We therefore hypothesize that negative myoclonus also occurs in other patients with CLS. This idea is further supported by reports describing EMG/EEG recordings during SIDEs that revealed a brief loss of tone in the paraspinal or quadriceps muscles (Crow et al, Supplemental references) and the favorable effect of clonazepam in the treatment of SIDEs.[5]

In summary, we present four patients with childhood-onset neurogenetic disorders with disabling myoclonus that had gone unrecognized for many years, all of whom showing a good response to treatment. These cases highlight the importance of accurate clinical phenotyping, including a detailed movement disorder classification, even when a molecular diagnosis has already been established.

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References

1 Dijk JM, Tijssen MA. Management of patients with myoclonus: available therapies and the need for an evidence-based approach. Lancet Neurol. 2010;9(10):1028-36.
2 Obeso JA, Artieda J, Burleigh A. Clinical aspects of negative myoclonus. Adv Neurol. 1995;67:1-7.
3 Shaikh AG, Zee DS, Mandir AS, et al. Disorders of Upper Limb Movements in Ataxia-Telangiectasia. PLoS One. 2013;8(6):e67042.
4 Stephenson JB, Hoffman MC, Russell AJ, et al. The movement disorders of Coffin-Lowry syndrome. Brain Dev. 2005;27(2):108-13.
5 Arslan EA, Ceylaner S, Turanli G. Stimulus-induced myoclonus treated effectively with clonazepam in genetically confirmed Coffin-Lowry syndrome. Epilepsy Behav Case Rep. 2014;2:196-8.

Video legends

Video 1A.

Patient 1 and 2, twin brothers, aged 21 years, with Dravet syndrome (DS) due to a mutation of the *SCN1A* gene. Without clonazepam.
With arms and hands outstretched, myoclonic jerks are seen. Finger-to-nose tests show action myoclonus.

Video 1B.

Patient 1 and 2, with clonazepam.
Outstretched hands and arms and finger-to-nose tests demonstrate improvement of myoclonus.

Video 2.

Patient 3, aged 20 years, ataxia-telangiectasia.
When the patient stretches out his arms and hands in front of him myoclonic jerks are seen, as well as dystonia of the fingers. The finger-to-nose tests are hampered by both the ataxia and the prominent action myoclonus.

Video 3A.

Patient 4, aged 8 years, with Coffin-Lowry syndrome due to exon 22 deletion in the *RPS6KA3* gene. Without clonazepam.
The first segment shows a stimulus-induced drop episode. Six months later the frequent falling accidents had made the patient too insecure to walk without support. The last segment demonstrates that the myoclonic jerks are stimulus-sensitive.

Video 3B.

Patient 4, with clonazepam.
The patient regained the ability to walk without support.

Supplementary table. *Myoclonus in childhood- and adolescent-onset neurogenetic disorders*

Essential myoclonus
Myoclonus dystonia

Brainstem myoclonus
Hyperekplexia

Epilepsy syndromes
Benign myoclonic epilepsy of infancy
Juvenile absence epilepsy
Autosomal dominant cortical myoclonus and epilepsy
Juvenile myoclonic epilepsy
Dravet syndrome
Familial cortical myoclonic tremor with epilepsy Unverricht-Lundborg disease
Progressive myoclonus epilepsy caused by *PRICKLE1* mutations Progressive myoclonus epilepsy caused by *SCARB2* mutations Ramsay Hunt syndrome caused by *GOSR2* mutations Lennox-Gastaut syndrome
Doose syndrome

Mitochondrial disease
MERFF
MELAS
Alpers syndrome (*POLG*) PEO
Leigh syndrome
Leber disease

Lysosomal storage diseases
Lafora body disease
GM1 and GM2 gangliosidosis
Neuronal ceroid lipofuscinoses (CLN1, CLN2, CLN3, CLN5, CLN8) Gaucher type III
Sialidosis (type I and II)
Krabbe's disease
Nieman-Pick type C disease
Tay-Sachs disease

Spinocerebellar and basal ganglia degeneration
Ataxia telangiectasia
Friedreich's ataxia
Autosomal dominant cerebellar ataxias (SCA2, SCA14, SCA19)
Olivopontocerebellar atrophy
Dentatorubral-pallidoluysian atrophy (DRPLA)
Wilson's disease
PKAN
Huntington's disease
Kufor-Rakeb syndrome (PARK9)

Mental retardation syndromes
Coffin-Lowry syndrome
Angelman syndrome
Rett syndrome
ARX gene mutation

Selected inborn errors of metabolism
Biotinidase deficiency
GLUT-1 deficiency
Non-ketotic hyperglycinemia
Vitamin E deficiency

Note: This table contains the main childhood- and adolescent-onset neurogenetic disorders with myoclonus, however the list is not exhaustive.

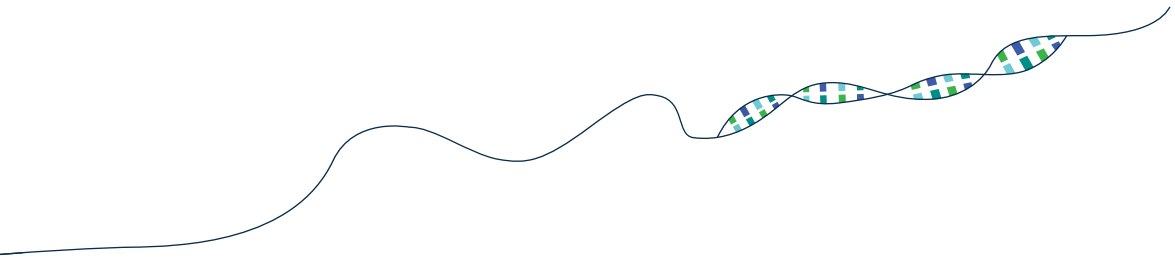
Supplemental references

- Borg M. Symptomatic myoclonus. Neurophysiol Clin. 2006;36(5-6):309-18.
- Canavese C, Canafoglia L, Costa C, et al. Paroxysmal non-epileptic motor events in childhood: a clinical and video-EEG-polymyographic study. Dev Med Child Neurol. 2012;54(4):334-8.
- Cassim F, Houdayer E. Neurophysiology of myoclonus. Neurophysiol Clin. 2006;36(5-6):281- 91.
- Crow YJ, Zuberi SM, McWilliam R, et al. "Cataplexy" and muscle ultrasound abnormalities in Coffin-Lowry syndrome. J Med Genet. 1998;35(2):94-8.
- Ganos C, Kassavetis P, Erro R, et al. The role of the cerebellum in the pathogenesis of cortical myoclonus. Mov Disord. 2014;29(4):437-43.
- Ghosh D, Indulkar S. Primary Myoclonus-Dystonia: A Diagnosis Often Missed in Children. J Child Neurol. 2013;28(11):1418-22.
- Guerrini R, Bonanni P, Parmeggiani L, et al. Pathophysiology of myoclonic epilepsies. Adv Neurol. 2005;95:23-46.
- Hahn JS, Hanauer A. Stimulus-induced drop episodes in Coffin-Lowry syndrome. Eur J Med Genet. 2012;55(5):335-7.
- Huntsman RJ, Lowry NJ, Sankaran K. Nonepileptic motor phenomena in the neonate. Paediatr Child Health. 2008;13(8):680-4.
- Ikeda A, Kakigi R, Funai N, et al. Cortical tremor: a variant of cortical reflex myoclonus. Neurology. 1990;40(10):1561-5.
- Meneret A, Ahmar-Beaugendre Y, Rieunier G, et al. The pleiotropic movement disorders phenotype of adult ataxia-telangiectasia. Neurology. 2014;83(12):1087-95.
- Panayiotopoulos CP, Tahan R, Obeid T. Juvenile myoclonic epilepsy: factors of error involved in the diagnosis and treatment. Epilepsia. 1991;32(5):672-6.
- Pranzatelli MR. Myoclonus in childhood. Semin Pediatr Neurol. 2003;10(1):41-51.
- Rosati A, Berti B, Melani F, et al. Recurrent drop attacks in early childhood as presenting symptom of benign hereditary chorea caused by *TITF1* gene mutations. Dev Med Child Neurol. 2015;57(8):777-9.
- Rubboli G, Tassinari CA. Negative myoclonus. An overview of its clinical features, pathophysiological mechanisms, and management. Neurophysiol Clin. 2006;36(5-6):337-43.
- Termsarasab P, Yang AC, Frucht SJ. Myoclonus in ataxia-telangiectasia. Tremor Other Hyperkinet Mov (N Y). 2015;5:298.
- Zutt R, Elting JW, Tijssen MAJ. Myoclonus. In: Wolters E BC, ed. Parkinson Disease and Other Movement Disorders: Motor Behavioural Disorders and Behavioural Motor Disorders. Amsterdam: VU University Press; 2014.

North Sea Progressive Myoclonus Epilepsy

Phenotyping

Chapter 9



Ramsay Hunt syndrome: clinical characterization of progressive myoclonus ataxia caused by *GOSR2* mutation

Chapter 9.1

M.E. van Egmond, C.C. Verschuuren-Bemelmans, E.A. Nibbeling, J.W. Elting, D.A. Sival, O.F. Brouwer, J.J. de Vries, H.P.H. Kremer, R.J. Sinke, M.A.J. Tijssen, T.J. de Koning

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Abstract

Background
Ramsay Hunt syndrome (progressive myoclonus ataxia) is a descriptive diagnosis characterized by myoclonus, ataxia and infrequent seizures. Often the etiology cannot be determined. Recently, a mutation in the *GOSR2* gene (c.430G>T, p.Gly144Trp) was reported in 6 patients with childhood-onset progressive ataxia and myoclonus.

Methods
We evaluated 5 patients with cortical myoclonus, ataxia and areflexia.

Results
All 5 patients had the same homozygous mutation in *GOSR2*. Here we present their clinical and neurophysiological data. Our patients (aged 7-26 years) all originated from the northern Netherlands and showed a remarkably homogeneous phenotype. Myoclonus and ataxia were relentlessly progressive over the years. Electromyography revealed signs of sensory neuronopathy or anterior horn cell involvement, or both, in all patients with absent reflexes.

Conclusions
Based on the presented phenotype, we would advise movement disorder specialists to consider mutation analysis of *GOSR2* in patients with Ramsay Hunt syndrome, especially when they also have areflexia.

Introduction

In 1921 James Ramsay Hunt defined the syndrome dyssynergia cerebellaris myoclonica as the triad of severe myoclonus, progressive ataxia, and mild epilepsy and cognitive change.[1] Subsequently this syndrome was referred to as Ramsay Hunt syndrome or progressive myoclonus ataxia (PMA). It shares overlapping clinical features with progressive myoclonus epilepsy (PME). PME refers to myoclonus with severe epilepsy and progressive neurologic decline, particularly dementia and ataxia. PMA is used in those cases where myoclonus and ataxia overshadow relatively mild epilepsy and mental retardation.[2] Particularly for movement disorder specialists, PMA is a recognizable phenotype within the broader context of the group of recessive ataxias.[3] Although a number of disorders can give rise to PMA, in many cases the underlying etiology cannot be determined.[3,4]

Recently, mutations in the *GOSR2* gene were identified as a cause of PME with childhood onset.[5] We now present clinical and neurophysiological data of 5 additional Dutch cases with *GOSR2* mutations. We show that the phenotype in our patients resembles PMA and should therefore be considered not only in the differential diagnosis of PME, but also of PMA.

Patients and methods

We evaluated all patients with genetically unresolved PMA seen in our pediatric and adolescent movement disorders outpatient clinic. We started in April 2012 and 46 patients with a variety of movement disorders have been evaluated. Of these patients, 7 patients had ataxia and myoclonus: 5 of them had a clinical picture compatible with PMA and 2 had a nonprogressive course with accompanying signs (severe mental retardation and spasticity or ichthyosis). All 5 patients with PMA also had areflexia and were tested for mutation in the *GOSR2* gene, by Sanger sequencing using routine procedures.[5] We reviewed medical records and video documentation. Digital video recording was performed according to a standardized protocol. In 2 patients we performed a new electromyography (EMG) recording because the latest EMG examinations were performed several years prior.

Results

All patients had a similar phenotype dominated by progressive cortical myoclonus and ataxia with areflexia as an additional feature. Mean age at onset was 2.8 years (range, 2-3 years) and mean current age was 16.8 years (range, 7-26 years). Homozygosity of the c.430G>T (p.Gly144Trp) mutation in *GOSR2* was confirmed in all patients. Clinical and laboratory findings of all cases are summarized in Table 1.

Factors making myoclonus worse were nearly identical in all patients: psychological stress; and visual, tactile and auditory stimuli. Most patients reported sudden falls, presumably caused by negative myoclonus of the legs. Ataxia and myoclonus were relentlessly progressive over the years, while cognitive function remained preserved.

Laboratory investigations showed mild elevation of serum creatine kinase (CK) in one patient. Brain magnetic resonance imaging (MRI) was normal. Simultaneous electroencephalography (EEG) and EMG recordings in 3 patients identified cortical spikes or spike-wave forms preceding myoclonic jerks, supportive of cortical reflex myoclonus. Somatosensory-evoked potentials (SEP) studies were performed in 4 patients, which led to giant SEPs in one.

Here we describe one illustrative case. Patient 1 is a 19-year-old young man who developed ataxia at the age of 2 years. At the age of 3 years, areflexia was noted. Three years later he developed multifocal, spontaneous and action-induced myoclonus, predominantly of the upper extremities and face. Both ataxia and myoclonus were progressive over the years. At age 9 years, he began having infrequent generalized tonic seizures at night. The myoclonic jerks and nocturnal attacks were treated by various combinations of antiepileptic drugs. Despite this treatment, almost continuous myoclonic jerks and approximately monthly seizures have persisted. His intellect is preserved.

On neurological examination (Video 1), aged 19 years, he had severe multifocal stimulus-sensitive myoclonic jerks. The action-myoclonus and prominent ataxia severely hampered his fine motor skills and normal daily functioning. His speech was dysarthric. Eye movements showed intermittent myoclonic jerks. His gait was ataxic. He had no sensory deficits. He had a thoracolumbar scoliosis.

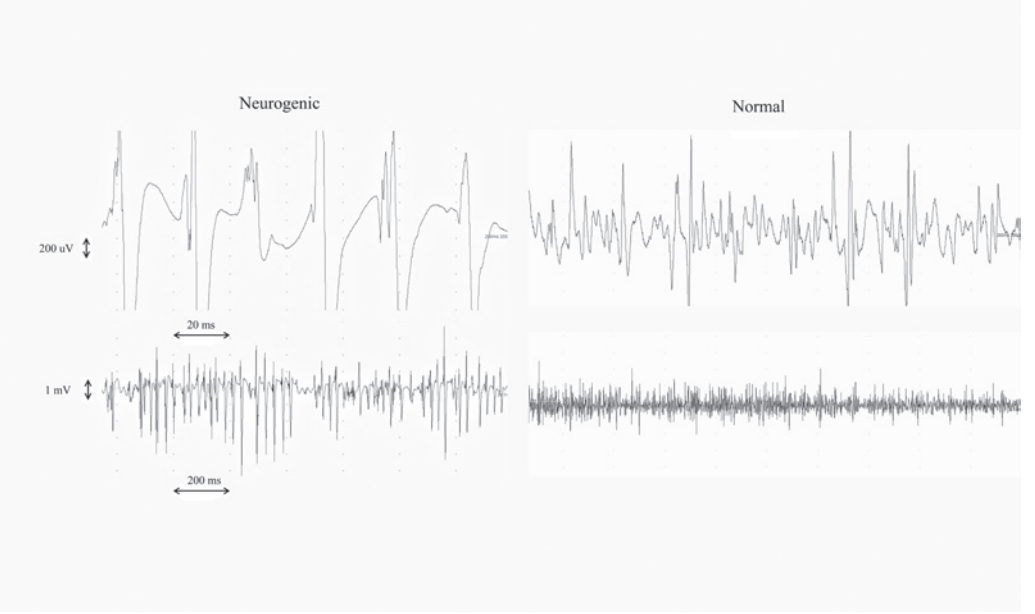

Figure 1. *Needle myography showing polyphasic motor unit action potentials with significantly increased duration and amplitude. Motor unit recruitment is considerably reduced (left panel) in the gluteus medius muscle. These abnormalities are indicative of chronic neurogenic abnormalities with motor unit remodeling. For comparison, normal needle myography findings in the same muscle of a healthy control are shown in the right panel.*

Sensory nerve conduction studies at the age of 15 years showed decreased sensory amplitudes in both upper and lower limbs, without a proximal to distal gradient, indicating sensory neuronopathy. Needle myography (Figure 1) showed polyphasic motor unit action potentials with remarkably increased duration and amplitude in all examined muscles, both proximally and distally in upper and lower limbs and in paraspinal muscles. Motor unit recruitment was significantly reduced, suggesting chronic partial denervation by anterior horn cell involvement. Mutation analysis showed a homozygous pathogenic mutation c.430G>T (p.Gly144Trp) in *GOSR2*.

Discussion

We present 5 patients (age 7-26 years) with the c.430G>T (p.Gly144Trp) *GOSR2* mutation. Their phenotypes include progressive cortical reflex myoclonus, ataxia, generalized seizures and preserved cognitive function, with areflexia as an additional feature. The phenotypes of our patients and the patients reported earlier[5] are remarkably uniform. In addition, we describe EMG findings that consistently demonstrate both sensory neuronopathy and chronic anterior horn cell involvement. This explains the clinical finding of areflexia and, at the same time, demonstrates the widespread effects of this particular *GOSR2* mutation throughout the central as well as the peripheral nervous system.

The phenotype of the *GOSR2* mutation evolves with age. Four of our patients presented with early onset ataxia at the age of 2 to 3 years. Within 4 years of disease onset, all cases were noted to have myoclonus and areflexia. The youngest patient described with the *GOSR2* mutation phenotype was 17 years of age.[5] Here, we provide descriptions of 2 children, 7 and 12 years old, respectively. Sequential video recordings show how the phenotype evolves over the years (Video 2).

Cognitive function remained stable in our patients, however Corbett et al.[5] reported some cognitive impairment in the third decade in 2 cases.[5] Scoliosis was not present in 2 of our subjects, while all earlier reported patients had scoliosis.[5] Brain MRI was normal, analogous to previously described MRI data.[5]

This is the first study reporting detailed EMG findings in patients with *GOSR2* mutations. Nerve conduction studies and needle myography showed consistent and significant abnormalities in all our patients with areflexia. The youngest patient had no areflexia when EMG was performed. EMG findings in the 4 patients with areflexia demonstrated sensory neuronopathy as well as chronic anterior horn cell involvement (Table 1, Figure 1). This suggests chronic, progressive neuronal cell loss in both the dorsal root ganglia and the anterior horn cells. Sequential EMG examinations in the 4 patients suggested that sensory neuronopathy arises before the age of about 10 years probably in step with the clinical sign of areflexia, while the chronic anterior horn cell involvement starts later, in the early teenage years. However, the significantly abnormal findings in our EMG examinations contradict the data presented by Corbett et al.[5] All their patients had had areflexia since early childhood but were reported to have normal EMGs. This discrepancy might be related to the timing of the EMG examinations or to the methodology applied.

Table 1. Summary of clinical and laboratory findings in five cases with homozygosity for the GOSR2 c.430G>T (p.Gly144Trp) mutation

Case	Sex	Age (y)	Presenting symptoms	Ataxia*	Myoclonus*	Seizures*	Areflexia	Motor function	Cognition[a]	Skeletal abnormalities	EEG	EMG	CK (U/l)	Muscle histology
1	M	19	gait disorder, clumsiness, 2 y	3 y	5 y	tonic seizures, 9 y	3 y	ambulant	normal	scoliosis	GED; PCR	SNP; AHI	normal	normal (age 5 y)
2	M	26	gait disorder, clumsiness, 2 y	3 y	6 y	GTCS, 11 y	6 y[b]	ambulant	Mild learning difficulties	no abnormalities	GED; PCR	SNP; AHI	normal	np
3	M	20	gait disorder, clumsiness, 2 y	2 y	6 y	GTCS, 6 y	9 y[b]	wheelchair, 8 y	Mild learning difficulties	scoliosis, syndactily	GED; PCR	AHI	normal	np
4	M	12	febrile seizures, 3 y	5 y	8 y	clonic seizures, 3 y	5 y	ambulant	normal	scoliosis	GED; PCR	SNP; AHI	400-500[#]	2x normal (age 7 and 10 y)
5	M	7	gait disorder, clumsiness, 3 y	3 y	6 y	-	3 y	ambulant	normal	no abnormalities	np	normal (age 3 y)	normal	np

** before this age reflexes were not tested*

[#] mildly elevated (normal < 200 U/l)

[¶] Both patients had mild non-progressive learning difficulties. Formal cognitive assessments: patient 2 had a score of 75-80 at the Wechsler Intelligence Scale for Children (WISC) at age 9 and a score of 89-99 at age 12. Patient 3 was tested at the age of 7, 10 and 12, test scores not available. Patient 1, 4 and 5 were not formally tested, however, their school performances were consistently at age-appropriate level.

Abbreviations: GTCS, generalized tonic clonic seizures; GED, generalized epileptic discharges (intermittently spikes, polyspikes or spike wave complexes); PCR, photoconvulsive response; SNP, findings indicating sensory neuronopathy; AHI, findings indicating anterior horn cell involvement; np, not performed.

In contrast to Corbett et al.'s study[5] in which all patients had an elevated CK, only 1 of our patients had a mildly elevated CK. Muscle histology was normal, both in the patients reported earlier[5] and in 2 of our subjects. The discrepancy between the abnormal needle myography findings and the normal muscle histology in our subjects might be explained by the fact that muscle biopsies were taken early in the disease course.

Treatment of our patients included several antiepileptic drugs, mainly targeted at reducing the myoclonic jerks, but its benefit was disappointingly limited. The frequency of the incidental seizures was slightly reduced.

The patients reported earlier[5] came from families of Dutch and North-West European ancestry and carried the same homozygous c.430G>T (p.Gly144Trp) *GOSR2* mutation, indicating a founder effect. In our cohort the same mutation was detected in all 5 patients with unexplained PMA. Possible explanations are that *GOSR2* mutation is common in genetically unresolved PMA cases or that the frequency of the *GOSR2* mutation is relatively high in the northern part of the Netherlands, as our 5 subjects all originated from this region. However, the current cohort of patients is small and therefore not representative.

In clinical practice, the workup and diagnosis of patients with cortical myoclonus or ataxia can prove challenging. It is therefore important to define clinical phenotypes carefully.[6-8] Particularly for movement disorder specialists, PMA is a useful clinical phenotype to describe a recognizable combination of symptoms, signs and evolution.[6, 8] Considering the disabling myoclonus and ataxia, the lack of cognitive deterioration and the relatively mild epilepsy in all cases identified thus far, we suggest this clinical phenotype due to *GOSR2* mutations can be classified both as PME and PMA.

We have presented strong evidence of the overlapping clinical phenotypes and characteristics in the 11 patients described to date with a homozygous c.430G>T (p.Gly144Trp) *GOSR2* mutation. We conclude that these patients present with a phenotype consistent with PMA, which is a useful clinical entity, particularly for movement disorder specialists. Testing of *GOSR2* should therefore be offered to patients with Ramsay Hunt syndrome, especially if areflexia is present. Future studies need to (1) elucidate whether mutations in the gene originate from a founder from North-Western Europe and (2) explore the phenotypic spectrum resulting from *GOSR2* mutations and possible genetic heterogeneity

Acknowledgements

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References

1 Hunt JR. Dyssenergia cerebellaris myoclonica - primary atrophy of the dentate system: a contribution to the pathology and symptomatology of the cerebellum. Brain. 1922;44(4):490-538.
2 Fahn S, Jankovic J, Hallett M. In: Jankovic J, Hallett M, eds. Principles and Practice of Movement Disorders (Second Edition). Edinburgh: W.B. Saunders; 2011:i-iii.
3 Marsden CD, Harding AE, Obeso JA, et al. Progressive myoclonic ataxia (the Ramsay Hunt syndrome). Arch Neurol. 1990;47(10):1121-5.
4 Visser JE, Bloem BR, van de Warrenburg BP. PRKCG mutation (SCA-14) causing a Ramsay Hunt phenotype. Mov Disord. 2007;22(7):1024-6.
5 Corbett MA, Schwake M, Bahlo M, et al. A mutation in the Golgi Qb-SNARE gene GOSR2 causes progressive myoclonus epilepsy with early ataxia. Am J Hum Genet. 2011;88(5):657-63.
6 van de Warrenburg BP, Sinke RJ, Kremer B. Recent advances in hereditary spinocerebellar ataxias. J Neuropathol Exp Neurol. 2005;64(3):171-80.
7 Wolters E, Berendse HW, de Koning-Tijssen MA. Parkinsonism & related disorders. Proceedings of the XVII WFN World Congress on Parkinson's disease and related disorders. Parkinsonism Relat Disord. 2007;13 Suppl 3:iii.
8 Marsden CD, Obeso JA. The Ramsay Hunt syndrome is a useful clinical entity. Mov Disord. 1989;4(1):6-12.

Video legends

Video 1.

Patient 1, aged 19 years. Examination of myoclonic jerks in the face and upper extremities. Action and tactile stimuli make the myoclonus worse. Nine hole PEG test is impossible because of the action myoclonus and prominent ataxia. His gait is irregular and broad based.

Video 2. Segment 1.

Patient 4, aged 5 years. Finger-to-nose tests show dysmetria and he is standing broad based.

Video 2. Segment 2.

Patient 4, aged 10 years. Myoclonic jerks are seen with arms and hands outstretched. Finger-to-nose tests show both ataxia and action myoclonus. Tandem gait is not possible without support.

Video 2. Segment 3.

Patient 4, aged 12 years. The finger-to-nose tests are hampered by both the ataxia and the prominent action myoclonus.

Cortical myoclonus in a young boy with *GOSR2* mutation mimics chorea

Chapter 9.2

M.E. van Egmond, A. Kuiper, J.W.J. Elting, O.F. Brouwer,
T.J. de Koning, M.A.J. Tijssen

Mov Disord Clin Pract 2015, 2(1), 61-63

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Introduction

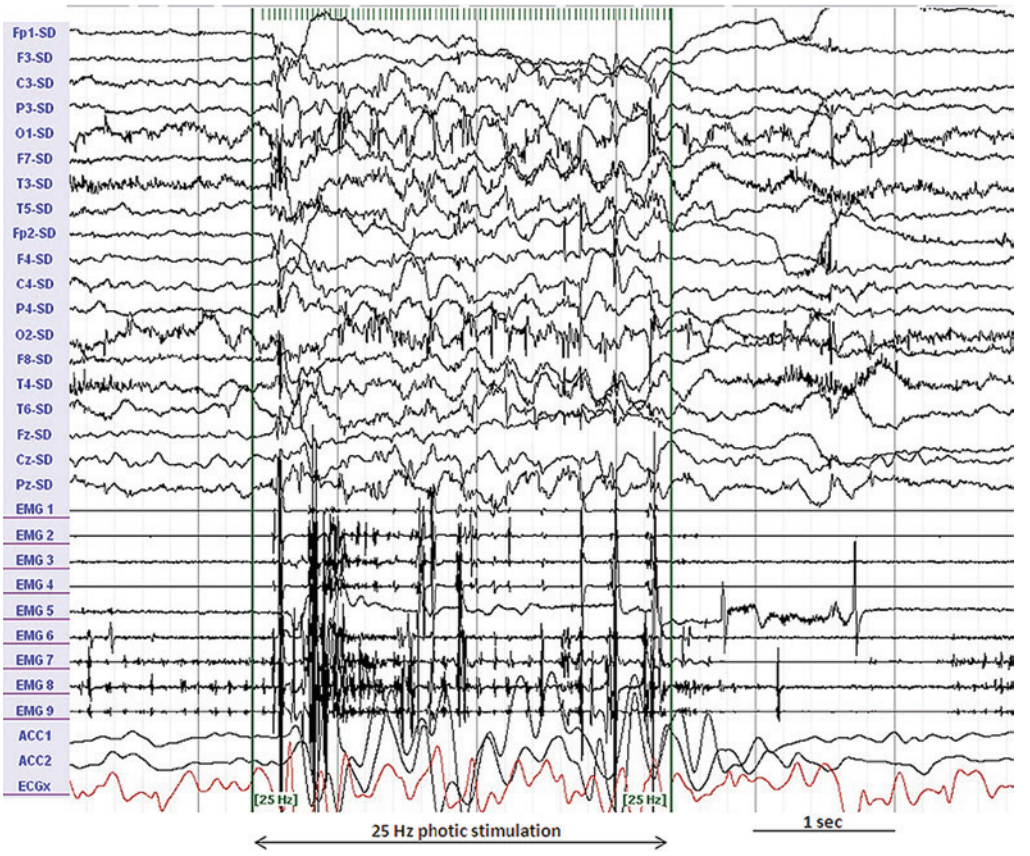
Myoclonus can resemble other abrupt movements such as chorea. The clinical distinction can be challenging, particularly at a young age. Myoclonus is defined as sudden, brief, shocklike involuntary movements caused by muscular contractions or inhibitions.[1] Chorea is a nonpatterned, involuntary, movement disorder, with continuous movements, variable in speed, unpredictable in timing and direction, and flowing or jerky in appearance.[1] Especially the jerky components of chorea may be difficult to distinguish from myoclonus.[2-5]
Here, we present the case of a young boy with hyperkinetic movements closely resembling chorea. EEG/electromyography (EMG) recordings showed cortical reflex myoclonus. This case demonstrates that myoclonus in young patients with *GOSR2* mutations can mimic chorea.

Case presentation

A Dutch boy presented at the age of 2 years with frequent falls and a clumsy gait. Brain MRI and EMG at the age of 2 - 5 years were normal. One year later he developed areflexia and a mild limb and gait ataxia. At the age of 6 multifocal hyperkinetic movements were observed. The family history was negative, his cognitive skills were normal and he had never had any seizures. The symptoms progressed gradually. At the age of 7 he was referred to our multidisciplinary pediatric movement disorder outpatient clinic. Neurological examination showed multifocal jerky movements, most pronounced in the face and distal part of the upper extremities and worsening with action and tactile stimuli (see Video 1). There was a mild limb ataxia and his gait was irregular. Tandem walking was hampered by both action myoclonus and ataxia. He had no sensory deficits and no skeletal abnormalities.

EEG/EMG recordings showed multifocal brief muscle contractions with a short burst duration (40-70 ms), supportive of cortical myoclonus. In addition to positive myoclonus, negative myoclonus occurred. Photic stimulation elicited myoclonic jerks and a photoparoxysmal EEG response, with a strict relation between the myoclonus and the EEG, consistent with cortical reflex myoclonus (Figure 1). Mutation analysis showed a homozygous pathogenic mutation c.430G>T (p.Gly144Trp) in the *GOSR2* gene.

Figure 1. *EEG/EMG recording*



Note: EEG/EMG recording showing cortical reflex myoclonus. Cortical activity was recorded by EEG, with 19 channels and a laplacian reference, using a 10 to 20 montage with average reference. Myoclonus was recorded by surface EMG: bilaterally from the biceps brachii muscles and triceps brachii muscles (EMG1-4); wrist flexor and extensor muscles (EMG5-8); and the abductor pollicis brevis muscle on the left side (EMG9). Accelerometer measures were recorded from the back side of both hands (ACC1 and ACC2). The registration revealed multifocal myoclonic jerks with a short burst duration (40–70 ms). Photic stimulation elicited myoclonic jerks and a photoparoxysmal EEG response, with a strict correlation between the myoclonus and the EEG, consistent with cortical reflex myoclonus (amplification, 150 lV/cm).

Discussion

This case demonstrates that hyperkinetic movements in a young patient with *GOSR2* mutation can mimic chorea, which is different from the thus far delineated phenotype of *GOSR2* mutations. At the Video Challenge of the Movement Disorder Society Congress 2014, the video of this case was shown and the majority of the expert panel classified the movement disorder as chorea.

Since the first report of the *GOSR2* mutation in 2011, 17 cases have been described worldwide,[6-8] including this case,[8] and until now, the clinical phenotype was classified either as progressive myoclonus epilepsy[6, 7] or as Ramsay Hunt syndrome.[8] This case emphasizes the importance of an accurate movement disorder characterization and the utility of neurophysiological studies, in order to achieve a correct phenotypic description to guide diagnostic testing.

In clinical practice, an important diagnostic clue for cortical reflex myoclonus is the stimulus sensitivity of the jerks, by tactile, visual or auditory stimuli. In contrast, chorea is not stimulus sensitive. Typical features of chorea are the constant flowing movements with random distribution and the incorporation into semivoluntary movements. A complicating factor is that abrupt jerks can be part of choreatic movements.[2, 9] This is supported by the fact that the clinical distinction between myoclonus dystonia and benign hereditary chorea can be challenging.[3-5]

In addition to a careful clinical examination, neurophysiological studies can be helpful in the diagnostic workup of rapid, jerky movements.[10] In cortical myoclonus, EMG shows bursts with short duration (< 50-70 ms) and sometimes also negative myoclonus can be observed. EEG/EMG coregistration enables jerk-locked back-averaging or coherence analysis to establish whether a cortical spike precedes the myoclonic jerk. In chorea, polymyography shows a random pattern of muscle activation and variable EMG burst length. Furthermore, there is no cortical correlate for the movements. In the case presented here, the EMG bursts were short and the EEG/EMG recordings demonstrated cortical myoclonus. This is in line with previous reports describing neurophysiological studies in patients with *GOSR2* mutations.[6-8]

The *GOSR2* phenotype evolves with age. Most patients present at the age of 2 to 3 years with early-onset ataxia, followed by areflexia, myoclonus and epilepsy (at the average age of 6.5 years).[6-8] In adolescence, many patients develop scoliosis.[6-8] It was named "North Sea" progressive myoclonus epilepsy.[7] As myoclonus and ataxia overshadow relatively mild epilepsy, the phenotype can also be described as Ramsay Hunt syndrome.[8]

In conclusion, our case illustrates that the phenomenology of cortical myoclonus in young children with *GOSR2* mutations can closely resemble chorea. Based on the presented phenotype, we recommend (pediatric) movement disorder specialists to consider electrophysiological tests and mutation analysis of *GOSR2* in young patients with clinical features resembling chorea, especially if areflexia is also present.

References

1 Fahn S, Jankovic J, Hallett M. In: Jankovic J, Hallett M, eds. Principles and Practice of Movement Disorders (Second Edition). Edinburgh: W.B. Saunders; 2011:i-iii.

2 Singer HS, Mink JW, Gilbert DL, Jankovic J.. Movement Disorders in Childhood. Philadelphia: Saunders: Elsevier 2010.

3 Schrag A, Quinn NP, Bhatia KP, et al. Benign hereditary chorea-entity or syndrome? Mov Disord. 2000;15(2):280-8.

4 Kleiner-Fisman G, Lang AE. Benign hereditary chorea revisited: a journey to understanding. Mov Disord. 2007;22(16):2297-305.

5 Asmus F, Horber V, Pohlenz J, et al. A novel TITF-1 mutation causes benign hereditary chorea with response to levodopa. Neurology. 2005;64(11):1952-4.

6 Corbett MA, Schwake M, Bahlo M, et al. A mutation in the Golgi Qb-SNARE gene GOSR2 causes progressive myoclonus epilepsy with early ataxia. Am J Hum Genet. 2011;88(5):657-63.

7 Boisse Lomax L, Bayly MA, Hjalgrim H, et al. 'North Sea' progressive myoclonus epilepsy: phenotype of subjects with *GOSR2* mutation. Brain. 2013;136(Pt 4):1146- 54.

8 van Egmond ME, Verschuuren-Bemelmans CC, Nibbeling EA, et al. Ramsay Hunt syndrome: clinical characterization of progressive myoclonus ataxia caused by *GOSR2* mutation. Mov Disord. 2014;29(1):139-43.

9 Gilbert DL. Acute and chronic chorea in childhood. Semin Pediatr Neurol. 2009;16(2):71-6.

10 Zutt R, Elting JW, Tijssen MA. In: Wolters E, Baumann, C, ed. Parkinson Disease and Other Movement Disorders VU Univ. Press; 2014:513–33

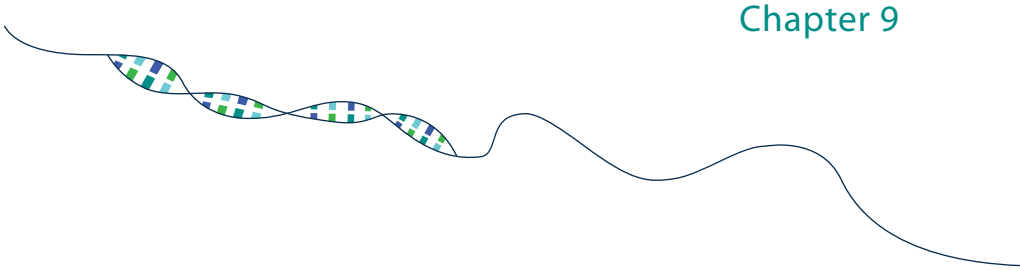
Video legends

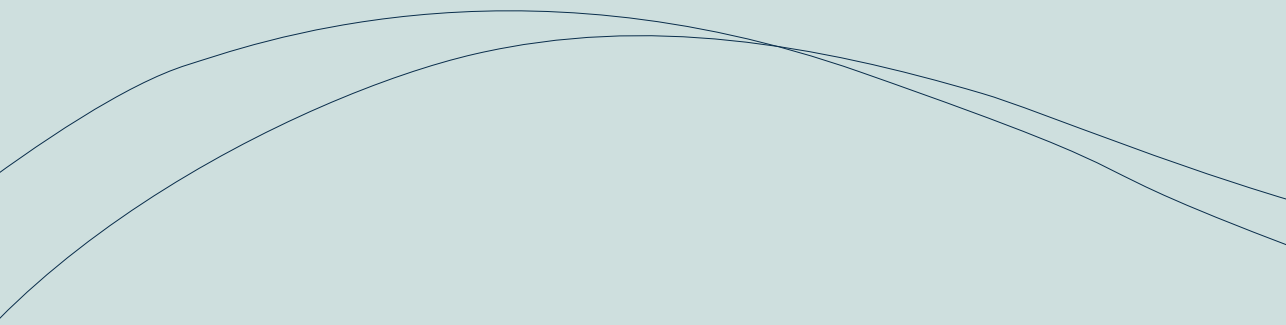
In the first fragment the patient is asked to sit still. Myoclonic jerks are observed in the face, limbs and trunk. The finger-nose-finger test and Nine Hole PEG Test show both ataxia and action myoclonus. When he stretches out his arms and hands in front of him, myoclonic jerks are observed, most pronounced in the fingers. His gait is irregular and intermittently broad based. Tandem walking is hampered by both action myoclonus and ataxia.

North Sea Progressive Myoclonus Epilepsy

Treatment

Chapter 9





The efficacy of the modified Atkins diet in North Sea Progressive Myoclonus Epilepsy: an observational prospective open-label study

Chapter 9.3

M.E. van Egmond*, A. Weijenberg*, M.E. van Rijn, J.W. Elting, J.M. Gelauff, R. Zutt, D.A. Sival, R.A. Lambrechts, M.A.J. Tijssen, O.F. Brouwer, T.J. de Koning

**Shared first authors*

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Abstract

Background

North Sea Progressive Myoclonus Epilepsy is a rare and severe disorder caused by mutations in the *GOSR2* gene. It is clinically characterized by progressive myoclonus, seizures, early-onset ataxia and areflexia. As in other progressive myoclonus epilepsies, the efficacy of antiepileptic drugs is disappointingly limited in North Sea Progressive Myoclonus Epilepsy. The ketogenic diet and the less restrictive modified Atkins diet have been proven to be effective in other drug-resistant epilepsy syndromes, including those with myoclonic seizures. Our aim was to evaluate the efficacy of the modified Atkins diet in patients with North Sea Progressive Myoclonus Epilepsy.

Results

Four North Sea Progressive Myoclonus Epilepsy patients (aged 7-20 years) participated in an observational, prospective, open-label study on the efficacy of the modified Atkins diet. Several clinical parameters were assessed at baseline and again after participants had been on the diet for 3 months. The primary outcome measure was health related quality of life, with seizure frequency and blinded rated myoclonus severity as secondary outcome measures. Ketosis was achieved within 2 weeks and all patients completed the 3 months on the modified Atkins diet. The diet was well tolerated by all 4 patients. Health-related quality of life improved considerably in one patient and showed sustained improvement during long-term follow-up, despite the progressive nature of the disorder. Health-related quality of life remained broadly unchanged in the other 3 patients and they did not continue the diet. Seizure frequency remained stable and blinded rating of their myoclonus showed improvement, albeit modest, in all patients.

Conclusions

This observational, prospective study shows that some North Sea Progressive Myoclonus Epilepsy patients may benefit from the modified Atkins diet with sustained health-related quality of life improvement. Not all our patients continued on the diet, but nonetheless we show that the modified Atkins diet might be considered as a possible treatment in this devastating disorder.

Background

North Sea Progressive Myoclonus Epilepsy (NSPME) is a rare but devastating disorder clinically characterized by progressive myoclonus, seizures, early-onset ataxia and areflexia. In the great majority of patients NSPME is caused by the same homozygous c.430G>T (p.Gly144Trp) mutation in the *GOSR2* gene, first reported in 2011.[1] In 2013 Boissé Lomax and colleagues coined the term NSPME, as all the patients described came from countries bounding the North Sea.[2]

The clinical picture of NSPME is dominated by spontaneous and action-induced myoclonic jerks and ataxia, which have a severe impact on daily functioning.[3] Most NSPME patients also have generalized tonic or tonic-clonic seizures, albeit that the seizures are relatively mild compared to the myoclonic jerks. Both myoclonic jerks and seizures can be treated with anti-epileptic drugs, but the benefits are disappointingly limited. Progressive myoclonic epilepsies, as a group, are not amenable to epilepsy surgery.[4] Vagus nerve stimulation can lead to seizure reduction, but does not help control the myoclonus. [5] This absence of an effective treatment for NSPME served as an impetus for exploring alternative treatment options.

The ketogenic diet (KD) has been proven to be effective in other drug-resistant epilepsy syndromes,[6, 7] including those with myoclonic seizures.[8, 9] The modified Atkins diet (MAD) is a less restrictive variant of the classical KD and has shown similar benefits in seizure disorders.[10] The KD is a high-fat, low-carbohydrate diet. In contrast to the classical KD, the MAD does not restrict protein- or calorie-intake. The MAD is therefore easier to maintain, facilitating long-term compliance, especially in adolescents and young adults.[11]

Our aim was to evaluate the efficacy of the MAD in patients with NSPME by measuring health-related quality of life (HRQL) as the primary outcome.

Methods

Participants

Four NSPME patients aged between 7 and 20 years, all with the known c.430G > T (p.Gly144Trp) mutation, participated in an observational, prospective, open-label study on the efficacy of the MAD in the University Medical Centre Groningen (UMCG) for 3 months (February to May 2013). They were 7, 12, 20 and 20 years old at the start of the trial. We offered 6 patients treatment with MAD, but 2 decided not to start with the diet. The study was performed according to the legal and ethical guidelines of the UMCG's medical ethics committee.

Modified Atkins diet

Pre-evaluation was made and dietary instructions given according to the recommendations of the international ketogenic diet study group during a 3-day hospital admission.[12] The MAD that was applied included a carbohydrate intake restriction, initially of 0.4 g per kilogram body weight, together with administration of the ketogenic formula: KetoCal 4:1 LQ®/ 12 ml per kilogram body weight. Fat and protein intake were unlimited. The diet was initiated stepwise at home over 7-10 days without fasting. When ketosis was adequately stabilized, carbohydrate intake was increased stepwise by 5 g per day as long as ketosis persisted. Patients were allowed to take

extra carbohydrates, on the condition of taking 4 g extra fat for every gram carbohydrate. Blood ketones and glucose were assessed by twice-daily home monitoring for at least the first month. After the first month stable ketosis had been reached in all patients and blood ketones and glucose measurements were gradually reduced from twice a day to eventually only once a week. On indication patients or their caregivers performed additional sampling of glucose and ketones.

Our dieticians helped the caregivers to offer a wide selection of alternative products to the patients. For instance written dietary exchange lists were provided, and patients were allowed to compensate the carbohydrate intake with fat emulsion, so they could choose their preferred dietary products.

During the first 6 weeks, the patients visited our multidisciplinary outpatient clinic every 2 weeks. In addition, at least once a week the dieticians had an telephone or e-mail consultation with the patients or their caregivers, or more frequently when necessary (sometimes daily contact).

Data collection

To evaluate the efficacy of the MAD we assessed several clinical parameters at baseline and after 3 months on the diet. HRQL was assessed by using the Dutch Generic Core Scale of the Paediatric Quality of Life Inventory (PedsQL) 4.0.[13] Each patient completed the age-specific version of the PedsQL and, in addition, the parents of the 2 paediatric patients completed the PedsQL parent proxy report. The PedsQL questionnaire asks patients and their parents to indicate to what extent the patient encountered problems in the last few months before baseline in physical, emotional, social and school-related domains.

From 4 weeks before baseline up until the end of the study, the patients and/or their parents recorded the seizure frequency in a daily diary. They also recorded any adverse effects of the diet and their perception of the myoclonus severity on a 10-point scale. In addition, an EEG and blinded rating of the myoclonus severity were performed at baseline and after 3 months. For the myoclonus rating we performed a videotaped examination using a standardized protocol. These videos were scored by 2 independent raters (JG and RZ), blinded for the condition of the patient (baseline or on the diet); they used the Unified Myoclonus Rating Scale (UMRS)[14] and the Clinical Global Impressions Scale.[15]

Furthermore, questionnaires were used to assess mood and behaviour. The self-rated version of the Inventory of Depressive Symptomatology (IDS) was used for the 2 adolescent patients.[16] Mood and behaviour in the 2 youngest patients were measured by a neuropsychologist consultation, with the Child Behaviour Check List completed by the parents, the Youth Self Report completed by the patients, and the Caregiver Teacher Report Form, completed by the school teacher. An occupational therapist used the Canadian Occupational Performance Measure (COPM) to identify and prioritize issues that restricted the patient's performance in everyday living; this provided the basis for setting intervention goals.[17] After 3 months, changes in the patient's self-perception of occupational performance were also evaluated with the COPM.

Table 1. Baseline characteristics of the patients

Patient	Sex	Age[a]	Motor function	Seizures	EEG	Medical treatment
1	M	12	Ambulant	Clonic seizures	GED, PCR	CLN, LEV, VPA
2	M	20	Ambulant + wheelchair	Tonic seizures	GED, PCR	CLN, ESM, LEV, VPA
3	M	20	Wheelchair	GTCS	GED, PCR	CLN, ESM, LEV, VPA
4	M	7	Ambulant	No	GED, PCR	None

[a] Age at start modified Atkins diet.

Abbreviations: CLN: clonazepam; EEG: electroencephalography; ESM: ethosuximide; GED: frequent generalized epileptic discharges; GTCS: generalized tonic-clonic seizures; LEV: levetiracetam; M: male; PCR: photoconvulsive response; VPA: valproic acid

Results

Patient characteristics are shown in Table 1. A detailed description of their clinical phenotypes has been reported elsewhere.[3] All patients completed a 3-month period on the MAD. The diet was well tolerated and none of the patients reported major side-effects. During this period there were no relevant changes in medication or in weight. The patients received 15, 19, 17 and 35 g of carbohydrates/day respectively, which was also based on bodyweight. Ketosis was reached within 2 weeks in all patients, but significant ketosis was only observed in the youngest patient (patient 4). He became ketotic after just five days on the diet and had average ketones of 4.3 mmol/L (range 2.5-6.6 mmol/L). The other child (patient 1) had average ketones of 2.3 mmol/L (range 1.3-3.7 mmol/L), while the 2 young adults had average ketones of 2.2 mmol/L (range 0.8-4.4 mmol/L) and 2.6 mmol/L (range 1.3-3.5 mmol/L), respectively. Stable ketosis was somewhat easier to achieve in the 2 youngest patients.

The results of the assessments at baseline and after 3 months on the diet are shown in Table 2. Patient 1 and his mother reported a 40% and 13% improvement in HRQL, respectively. The HRQL scores of patient 3 and 4 also showed improvement (5% and 14% respectively). Patient 2 and the parents of patient 4 reported a deterioration of the HRQL (19% and 39% respectively).

Blinded rating of myoclonus (UMRS), showed small but positive changes in all patient scores (both in rest and in action). The most evident improvements in UMRS score were seen in patients 1 and 2 (aged 12 and 20 years). Seizure frequency remained stable in the 3 patients who suffered from seizures.

Table 2. Results of the assessments at baseline and at 3 months on the modified Atkins diet in four patients with North Sea Progressive Myoclonus Epilepsy

Patient	HRQL[a]				UMRS[b]				Effect on seizure frequency[c]	EEG change[c]	Changes in mood and behaviour[c]
	Baseline	MAD at 3 months	Change	MAD at 3 years	Baseline	MAD at 3 months	Change	MAD at 3 years			
1	pt. 46 par. 50	pt. 27 par. 43	impr. 19 pts impr. 7 pts	pt 47 par. 37	71	64	impr. 7 pts	75	no change	no changes	n.d.
2	25	31	det. 6 pts	n.a.	72	58	impr. 14 pts	n.a.	no change	no changes	det. IDS 7 pts
3	58	55	impr. 3 pts	n.a.	87	85	impr. 2 pts	n.a.	no change	n.d.	det. IDS 8 pts
4	pt. 28 par. 19	pt. 24 par. 31	impr. 4 pts det. 12 pts	n.a.	57	56	impr. 1 pts	n.a.	n.a	no changes	no relevant change

[a] scores were calculated by the sum of all scores divided by the number of answered items (maximum score 92). A lower score represents a better HRQL

[b] UMRS: scores represent the sum scores of section 2, 3 and items A-G of section 4 of the UMRS, calculated by using the UMRS score sheet .[14] A lower score represents less myoclonus; for patient 2, 3 and 4 the scores are the average scores of the two raters; for patient 1 the consensus scores of the two raters are shown in the table (because in the individual scores there was one outlier, so a consensus meeting was organised where the raters rescored all videos together)

[c] change between baseline assessment and 3 months assessment during the MAD

Abbreviations:

Det., deterioration; EEG, electroencephalography; HRQL, health-related quality of life; IDS, inventory of depressive symptomatology; impr., improvement; MAD, modified Atkins diet; n.a., not applicable; n.d., no data; par., parents; pt., patient; pts, points; UMRS, Unified Myoclonus Rating Scale.

The EEGs of the 4 patients did not show a relevant decrease of epileptic discharges while on the MAD. Although patient 4 had presented no clinical seizures and only myoclonus and ataxia, his EEG did show epileptic activity and this did not change during the diet period. The results of the complementary assessments of mood, behaviour and occupational performance did not show relevant changes in the younger children, but the 2 adolescent patients reported negative effects. They felt more depressed due to the restricted diet, in particular they missed specific foods such as bread and potatoes in their daily diet. Their IDS- score declined by 7 and 8 points, respectively. Because the benefits did not match the efforts of maintaining the diet due to its restrictions, patients 2, 3 and 4 discontinued the MAD after a duration of 3, 3 and 5 months, respectively. The provided wide variation of alternative products and menus, and the intensive support from our dieticians could not prevent discontinuation. The parents of the youngest patient (patient 4, aged 7 years) said they would consider to restart the MAD in the future if their child's symptoms would become more severe.

To date, patient 1 is still on the MAD and his HRQL and blinded rating of myoclonus were reassessed after 3 years on the diet. Compared to the baseline measures, he reported the same HRQL, while his parents reported a sustained improvement of 25%, despite the progressive nature of the disorder. In parallel, the UMRS scores at 3 years remained broadly unchanged compared to baseline. He showed an improved and sustained physical fitness on the diet, and he recently switched from a school for physically handicapped children to regular secondary education.

Discussion and conclusion

Worldwide only 21 NSPME patients have been described.1-3 In this observational prospective study, we evaluated the efficacy of the MAD in 4 NSPME patients, with HRQL as our primary outcome measure. In our study one of the 4 patients showed an improved HRQL on the diet. This 12-year old boy reported a significant (40%) improvement in his HRQL after 3 months on the MAD. He decided to continue on the diet because he felt healthier and less tired, experienced less jerking in the evening and less nocturnal shaking, and could participate more at school and in social events. After 3 years on the MAD, his HRQL has stabilized compared to his baseline, despite the progressive nature of the disease. The other 3 patients reported varied changes in their HRQL and UMRS while on the diet, but all decided to stop after 3 to 5 months because the benefits were perceived to be too limited compared to their dietary restrictions.

Ketosis in the youngest patient (#4) was excellent while he was on the MAD; compared to the other patients he had milder myoclonus and no clinical seizures, but a comparable HRQL to patient 2, for instance. In this respect it was interesting to observe that his parents thought the burden of the diet was more relevant than the reduction in his myoclonus: they reported a deterioration in the HRQL. However, the patient himself reported a considerable improvement in his HRQL questionnaires, which illustrates that the parents and patient experienced the diet's burden differently , and this influenced their decision to continue the dietary treatment (Table 2).

The levels of plasma ketones of patient 1 were similar to those of patient 2 and 3. The benefit of the MAD observed in patient 1 and lack of benefit in patients 2 and 3 are therefore unlikely to be due to differences in the degree of ketosis achieved during the first 3 months.

Seizure frequency remained stable in all 4 patients while on the diet. Although epilepsy was not their main symptom, 3 of the 4 patients had generalized tonic, clonic or tonic-clonic seizures with a mean frequency of once a week. Neither the patients nor their parents reported a relevant decrease of seizure frequency while on MAD. EEG findings did not show a change in the epileptic discharges in any of the patients while on the MAD. The UMRS scores showed small, but positive, changes in all the patients on the diet, and the scores of patient 1 at 3 years remained broadly unchanged compared to his baseline, which is remarkable given the progressive nature of the disorder.

Reports on the effect of treatment with the KD in PME are scarce. The KD seems to be particularly effective in generalized forms of epilepsy, including epilepsies with myoclonus.[9, 18] The response rates in the randomized controlled trials of Neal et al. and Lambrechts et al.[6, 7] in children with refractory epilepsy were 38% and 50% respectively, with the percentage of patients who had >50% seizure reduction as the primary outcome measure. In our patients, not epilepsy but myoclonus was the major symptom, reported to interfere most with their activities of daily living. This makes it difficult to compare our results of the controlled KD trials. Despite our study showing improvement in only one out of 4 patients, for this single case MAD made a major and sustained difference to his HRQL and this was thus an excellent treatment result.

We chose HRQL as the main outcome measure and not seizure frequency or UMRS scores because we considered the sole use of impairment-focused measures to be too limited in scope to evaluate the overall effects of the diet effectively. It has been shown that disease severity rating scales might not always be suited to evaluating the overall effects of an intervention,[19] and in small groups of patients it is difficult to detect minor differences on disease severity scales.[20] For these reasons we chose HRQL as our primary endpoint.[19, 20] Koy et al.[21] supported this idea; they described how quality of life can improve significantly in children after deep brain stimulation for dystonia due to cerebral palsy, without any improvement shown on rating scales.[21] Moreover, HRQL likely includes all the different aspects of treatment sequelae in this very rare disorder, and importantly also takes into account the influence of the diet's restrictions on the patient's well-being. This is well illustrated by patient 2, in which an improvement of almost 20% was observed in blinded rating of his myoclonus, but the improvement was counteracted by a deterioration in his mood and a depressed state due to the diet.

There are several limitations to our study. First, we were only able to evaluate 4 patients and could not include a control group. However, given the rarity of NSPME and the number of patients reported worldwide with this disorder (n = 21), 4 patients is still a good size group to study. Second, the duration of follow-up of 3 of the 4 patients was relatively short because they decided to discontinue the diet.

In conclusion, this observational study shows that one out of 4 patients with NSPME had a favorable response to the MAD. This patient, who was 12 years old at the start of the study, has been on the diet for more than 3 years and has a stable HRQL, despite his progressive disorder. Therefore, the MAD might be considered in patients with NSPME, as it may improve or stabilize HRQL in this devastating disorder.

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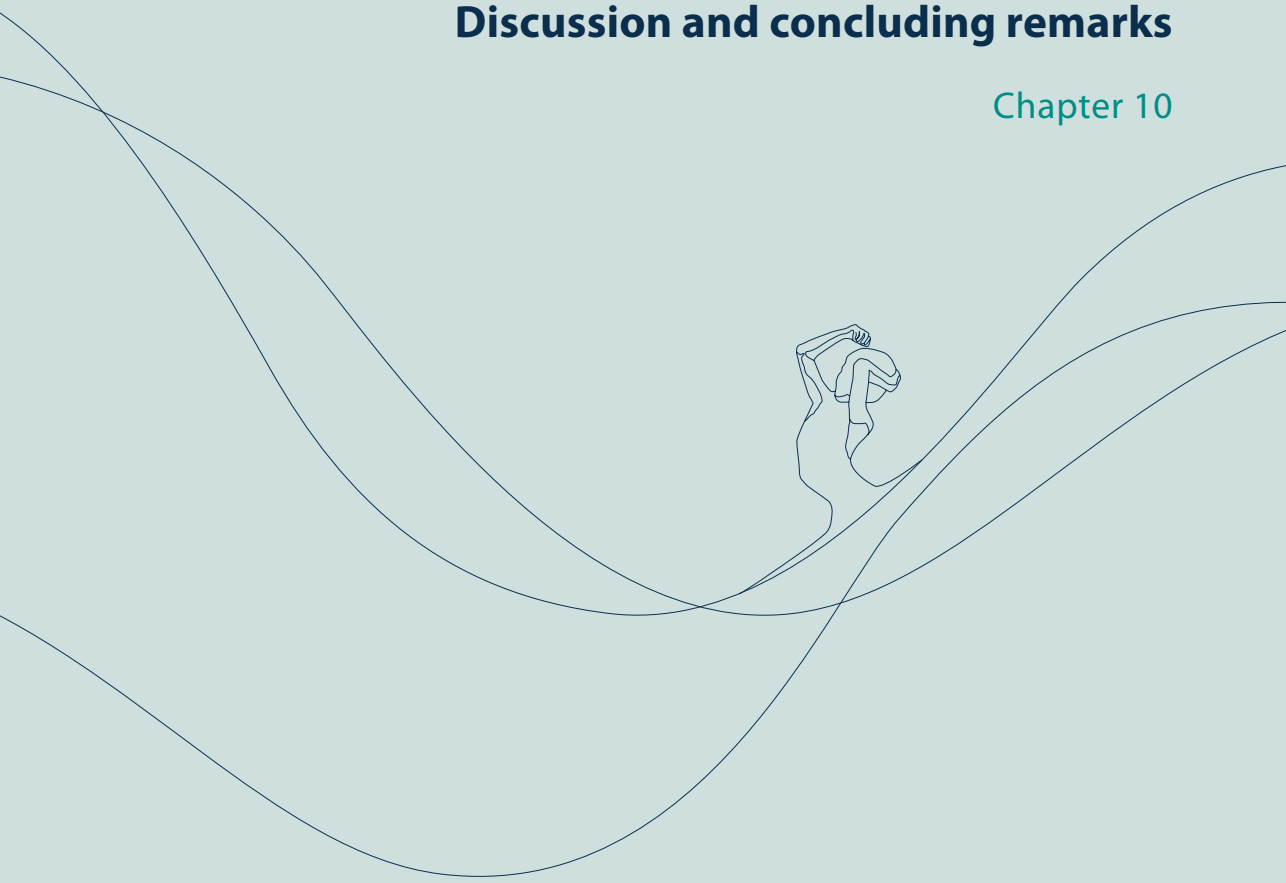
References

1 Corbett MA, Schwake M, Bahlo M, et al. A mutation in the Golgi Qb-SNARE gene GOSR2 causes progressive myoclonus epilepsy with early ataxia. Am J Hum Genet. 2011;88(5):657-63.
2 Boisse Lomax L, Bayly MA, Hjalgrim H, et al. 'North Sea' progressive myoclonus epilepsy: phenotype of subjects with GOSR2 mutation. Brain. 2013;136(Pt 4):1146- 54.
3 van Egmond ME, Verschuuren-Bemelmans CC, Nibbeling EA, et al. Ramsay Hunt syndrome: clinical characterization of progressive myoclonus ataxia caused by GOSR2 mutation. Mov Disord. 2014;29(1):139-43.
4 Malek N, Stewart W, Greene J. The progressive myoclonic epilepsies. Pract Neurol. 2015;15(3):164-71.
5 Fujimoto A, Yamazoe T, Yokota T, et al. Clinical utility of vagus nerve stimulation for progressive myoclonic epilepsy. Seizure. 2012;21(10):810-2.
6 Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008;7(6):500-6.
7 Lambrechts DA, de Kinderen RJ, Vles JS, et al. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand. 2017;135(2):231- 9.
8 Freeman JM, Vining EP, Pillas DJ, et al. The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. Pediatrics. 1998;102(6):1358- 63.
9 Wheless JW, Sankar R. Treatment strategies for myoclonic seizures and epilepsy syndromes with myoclonic seizures. Epilepsia. 2003;44 Suppl 11:27-37.
10 Porta N, Vallee L, Boutry E, et al. Comparison of seizure reduction and serum fatty acid levels after receiving the ketogenic and modified Atkins diet. Seizure. 2009;18(5):359-64.
11 Kossoff EH, Dorward JL, Turner Z, et al. Prospective study of the modified atkins diet in combination with a ketogenic liquid supplement during the initial month. J Child Neurol. 2011;26(2):147-51.
12 Kossoff EH, Zupec-Kania BA, Amark PE, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. Epilepsia. 2009;50(2):304-17.
13 Varni JW, Burwinkle TM, Seid M, et al. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr. 2003;3(6):329-41.
14 Frucht SJ, Leurgans SE, Hallett M, et al. The Unified Myoclonus Rating Scale. Adv Neurol. 2002;89:361-76.
15 Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4(7):28-37.
16 Rush A, Carmody T, Reimitz P-E. The Inventory of Depressive Symptomatology (IDS): clinician (IDS-C) and Self-Report (IDS-SR) ratings of depressive symptoms; 2000.
17 Law M, Baptiste S, McColl M, et al. The Canadian occupational performance measure: an outcome measure for occupational therapy. Can J Occup Ther. 1990;57(2):82-7.
18 McTague A, Cross JH. Treatment of epileptic encephalopathies. CNS Drugs. 2013;27(3):175-84.
19 Gimeno H, Tustin K, Selway R, et al. Beyond the Burke-Fahn-Marsden Dystonia Rating Scale: deep brain stimulation in childhood secondary dystonia. Eur J Paediatr Neurol. 2012;16(5):501-8.
20 Eggink H, Kuiper A, Peall KJ, et al. Rare inborn errors of metabolism with movement disorders: a case study to evaluate the impact upon quality of life and adaptive functioning. Orphanet J Rare Dis. 2014;9:177.
21 Koy A, Hellmich M, Pauls KA, et al. Effects of deep brain stimulation in dyskinetic cerebral palsy: a meta-analysis. Mov Disord. 2013;28(5):647-54.

Discussion and concluding remarks

Chapter 10



Discussion and concluding remarks

Genetic advances are changing our clinical practice, also in the field of young-onset movement disorders (YMDs). In this thesis, we explored new diagnostic strategies to YMDs that clinicians can apply in light of the paradigm shift that has occurred in molecular genetics. This last chapter includes some general considerations, incorporating the main findings of the thesis, and suggestions for future research.

The benefits of a multidisciplinary approach to YMDs

The basis of our clinical approach to YMDs consists of good phenotyping, searching for etiology and applying optimal treatment. The wider availability of next-generation sequencing (NGS) requires clinicians to determine which YMD patients may benefit from these techniques, and generates new complexities of interpretation that require both genetic and clinical expertise.[1] A multidisciplinary team approach may help to face these challenges.

In 2012, a multidisciplinary tertiary outpatient clinic was started in the University Medical Center Groningen, with a team consisting of a movement disorder specialist, pediatric neurologist, pediatrician for inborn errors of metabolism (IEM) and a clinical geneticist. **Chapter 2** comprises a study investigating whether this new multidisciplinary approach was beneficial for the three main aspects of clinical practice: phenotyping (movement disorder classification), etiology (diagnostic yield), and targeted treatment strategies. Data were obtained from the medical records of the first 100 consecutive patients with YMDs (aged 0-35 years). The results showed that the patients had a mean age of 12.5 years and a mean disease duration of 9.2 years, which was 74% of their life spans. The team revised the movement disorder classification in the majority of patients (58%). Particularly dystonia and myoclonus were diagnosed frequently, supported by neurophysiological tests in 24/29 patients. Etiological diagnoses were made in 24/71 (34%) formerly undiagnosed patients, predominantly in the genetic domain (using single-gene testing in nine cases, targeted resequencing in three cases and whole exome sequencing in five cases). Treatment strategy was adjusted in 60 patients, and 40 (67%) of them reported a positive effect after 3-6 months.

The diagnostic yield in this study (34%) is high compared to previous literature.[2,3] For instance, in a recent study with 260 patients with non-tic YMDs in a tertiary referral center, a definitive genetic diagnosis was made by a neurologist specialized in YMDs in 44 of 260 (17%) patients.[3] It is hypothesized that the high diagnostic yield in our study is due to the team's broad and combined expertise. Yet, we need to interpret the results of this study with caution, because of the retrospective study design, the absence of a control group and relatively limited follow-up. In theory, a multidisciplinary strategy may facilitate immediate decision-making and minimize diagnostic delay compared to regular subspecialty care, which involves a serial process with multiple referrals. However, in our study the duration of diagnostic work-up was not investigated.

Future studies with a prospective design and standardized clinical assessments are important to investigate the cost-benefit ratio of a multidisciplinary strategy, and compare this to care-as-usual in a tertiary referral center.

Diagnostic algorithms incorporating NGS

More widely applied NGS testing in the field of movement disorders has demonstrated that a mutation in one gene can lead to many phenotypes, and that one phenotype can be caused by mutations in many genes.[4, 5] This clinical heterogeneity and this spectrum of associated clinical features of many disorders is much larger than previously expected.[5] For example, in GLUT1 deficiency syndrome, symptoms can range from severe psychomotor retardation, seizures, mixed movement disorders including dystonia to very mild exercise induced dystonia.[6] Consequently, it can be difficult for clinicians to predict all potential gene defects associated with a certain YMD syndrome, even after careful phenotyping.[5]

This also applies to the hyperkinetic movement disorders dystonia and myoclonus. Both can present with a great variability in clinical manifestations (phenotype) and a long lists of possible causes (both acquired and genetic).[4, 5, 7-9] Hence, diagnostic workup can be challenging for clinicians and burdensome for patients.

For this reason, and to ensure that patients optimally benefit from the availability of NGS techniques, a new diagnostic algorithm is proposed for young-onset dystonia and for myoclonus (**Chapter 3** and **Chapter 7**). Both algorithms are based on systematic reviews of the literature and incorporate the use of NGS techniques, with the aim to help clinicians to determine which patient may benefit by the use of these diagnostics.

The main principle of the algorithms is 'genetics first', with two important steps before applying NGS. First, if there are any clinical clues for an acquired disorder, such as a medication-induced movement disorder, infection or an immune mediated disorder. Second, if there are any clues for a treatable genetic disorder. In case of the latter, targeted biochemical investigations need to been done first or simultaneously to NGS, since these investigations may prove to be a faster diagnostic method than NGS. Early treatment of this group of disorders is important to stabilize or reverse the symptoms.

Historically, pattern recognition has been the cornerstone in the diagnostic evaluation of characteristic syndromes presenting with dystonia or myoclonus.[10-12] In the new diagnostic algorithms the approach is based on "red flags" rather than pattern recognition.

At present, pattern recognition is most successful in identifying classical phenotypes or textbook cases, but recognition of milder, intermediate and unusual phenotypes remains problematic. Another limitation of pattern recognition is that the prevalence of many of the disorders causing myoclonus or young-onset dystonia is so low that the majority of clinicians will encounter only a few patients with these rare disorders. Therefore, in many cases clinical experience will be limited and specific patterns will easily remain unrecognized.

These limitations of pattern recognition served as the incentive to use a "red flag" approach in the diagnostic algorithms. This approach facilitates recognition of only a limited number of disorders in which immediate diagnosis and treatment is necessary, providing guidance for both experienced and less experienced clinicians. Importantly, referral to a tertiary center is recommended for those cases that remain unsolved after NGS testing.

Future studies are needed to investigate the practical value of these new diagnostic algorithms in terms of diagnostic speed and financial costs, compared to the current diagnostic approach. Besides this, it is important to study the interrater agreement of the diagnostic algorithms, preferably both among experienced and less experienced clinicians.

NGS: a traditional diagnostic versus new 'agnostic' strategy

Before the NGS era, clinicians spent much time gathering data and formulating differential diagnoses to be able to choose a single gene test, or a small set of gene tests, to determine the most likely clinical diagnosis.[13] The broader availability of NGS now enables a "shotgun" approach to genetic disorders: with a single blood test clinicians can check all genes known to, for example, dystonia or myoclonus, even without knowing all details of the phenotype. So the traditional diagnostic strategy is evolving into an 'agnostic strategy', adapted to the new reality of the full arrival of NGS.[14]

The use of a gene panel for dystonia (**Chapter 4**) was studied in a post hoc study and comparing the traditional diagnostic strategy to the agnostic strategy, using a gene panel with 94 dystonia-associated genes. Sixty-one dystonia patients (72% young-onset) of the tertiary referral center were included. The outcome measures were diagnostic yield, cost and duration of diagnostic work-up. The results of diagnostic work-up with the gene panel (*the agnostic strategy*) were compared to the diagnostic strategy of clinical experts, who were asked to formulate their theoretical diagnostic strategies (without NGS) based on detailed case descriptions (*the traditional strategy*). Our findings showed that the experts tested on average three genes per patient. Overall, the agnostic strategy led to a higher diagnostic yield (14.8% versus 7.4%), a quicker diagnostic workup (28 days versus 102 days), and lower costs (€1822 versus €2660), representing a major improvement for patients and their families.

The use of gene panel analysis for dystonia in this study increased the diagnostic yield compared to of conventional diagnostic workup, with statistical analysis tending toward but not reaching significance. This may be due to the relatively small group of patients. Looking more closely at our results, we saw that particularly patients with an unusual or complex phenotype benefited from gene panel analysis, with disorders not considered in the initial differential diagnosis being identified. Importantly, three of these patients had a treatable form of an inborn error of metabolism, and diagnosis allowed prompt initiation of therapy.

With regard to the design of the study, it is important to mention that in an ideal situation we would have set up a prospective cohort study to compare the use of gene panel analysis to the traditional diagnostic approach. However, in such a study design, it would not be ethically justified to withhold the use of NGS testing to patients in the control group. Therefore, a study was designed with a theoretical control group and compared the diagnostic workup with and without gene panel analysis in the same patient: each patient served as his/her own control.

In this study targeted gene panel analysis was used, but a drawback of this technique is that new genes cannot be easily added to the panel, which limits the rapid introduction of newly published genes. In recent years, whole exome sequencing (WES) coverage has improved significantly at much lower costs, making it more accessible for routine diagnostic purposes. It is likely that in the near future, WES with targeted filtering likely will become the modality used by most well equipped diagnostic labs with sufficient genome staff and bioinformatics. With these advances, it will become easier to keep diagnostic tests up to date and a more widespread use of WES will aid in the discovery of new genes.

Next-generation phenotyping

The recent genetic and phenotypic advances in YMDs have only been possible because of detailed clinical phenotyping, which enables integration of phenotypic data with NGS results.[5, 13] For example, a prerequisite for adequate use of databases and online tools, is the consistent input of unequivocal phenotypic data. This entails 'next-generation phenotyping', so ongoing and detailed phenotyping and refinement of clinical diagnostic assignments.[13] This also means that we need reasonable consensus with regard to definitions and classification systems, to create useful data for clinical and research purposes. However, two recent studies showed that even experienced clinicians only moderately agreed on the clinical diagnosis of jerky movements, dystonia, spasticity and ataxia.[15, 16]

In line with these studies, a study was performed to assess the inter-rater agreement among experienced clinicians on the phenomenological and syndrome classification of dystonia (**Chapter 5**). Detailed clinical case descriptions were written of 56 dystonia patients (mean age 31 years, 73% young-onset) who attended the movement disorder outpatient clinic of our tertiary referral center. In an online research tool, for each vignette two experienced clinicians classified the phenomenological features of the patient according to the Axis I items of the dystonia classification (see Table 2 in Chapter 1), and also formulated the dystonia syndrome (see Table 3 in Chapter 1). The results showed that the clinicians reached moderate to substantial inter-rater agreement on the phenomenological dystonia classification and moderate agreement on the dystonia syndrome. Full agreement on all Axis I items and the dystonia syndrome was reached in only 7/56 cases (12,5%).

The results of this study are a reflection of variability in how experienced clinicians use clinical information, and how classification terms can be ambiguous. To our knowledge, this is the first study specifically investigating the interrater agreement of Axis I of the dystonia classification and syndrome definition. However, if we look at it from a broader perspective, our results are in line with a recent study addressing the interrater reliability for diagnosis of various subtypes of dystonia.[17]

A possible limitation of our study is that the patients were assessed only via written case descriptions instead of through video assessments or live examinations. However, it is hard to verify if the results would have been markedly different if video assessments would have been available. As far as we know, there are no comparative studies for dystonia comparing the interrater agreement of professionals seeing videos and professionals reading vignettes. Remarkably, some studies on other motor disorders show that videos might give rise to even more variability than written vignettes, presumably because with vignettes some choices regarding to clinical characterization have already been made by the author of the vignette.[15, 18] Another limitation of the study is that each vignette was assessed by only two clinicians, while in an ideal situation, the inter-rater agreement should be based on a larger number of raters.

Nevertheless, it is clinically relevant that for the majority of cases in our study, the classification and syndrome definition of dystonia differed considerably among clinicians. These differences carry the risk of different diagnostic and treatment strategies and may hamper the search for new disease-associated genes and phenotype-genotype correlations. Therefore, we advocate to open the discussion on how to improve the diagnostic accuracy of the dystonia classification

system and the definition of the dystonia syndrome. Possible options include adjustment of the classification criteria, organization of team assessments and consensus meetings, or offering a training program or e-learning to certify for the dystonia classification.

Evidently, classification systems for disease entities and the way we use them evolve over time. The process is and will be iterative: syndromes and genetic results will be analyzed back and forth to improve the accuracy and comprehensiveness of both. Future studies are needed to investigate which items of the classification are most useful for generating clinically meaningful groupings, and to study how the inter-rater agreement on these items might be improved.

Clinical expertise remains indispensable

In the study on the dystonia gene panel analysis (**Chapter 4**), the agnostic strategy with the NGS-based gene panel worked out better than the traditional diagnostic strategy. This raises the question: is clinical expertise still needed, or is this the end for the clinician?

As Hennekam and Biesecker stated, NGS and computers will not magically make diagnoses for us.[1, 13] With the arrival of NGS comes a number of challenges that we need to fully acknowledge, and that demand not only genetic but also clinical expertise, maybe even more than ever before.1 Here, some of these challenges will be discussed, and the important role clinicians have in recognizing these.

In the pre-NGS-test diagnostic phase, clinicians need to be fully aware of the limitations of NGS, such as a limited degree of coverage, the inability to detect triplet repeat disorders or copy number variations, and that the results do not include the mitochondrial DNA.[14, 19] Furthermore, clinicians need to acknowledge the complexities inherent to the interpretation and reporting of NGS data, to ensure reliable use in routine clinical practice.[14, 20] Another relevant issue is the possibility that the NGS results may show either variants of unknown significance (VUS), or a disease-causing mutation in a gene unrelated to the reason for which the NGS was requested, e.g. a mutation predisposing to breast cancer.[21-23] When planning NGS, the chance of such findings should be considered, and careful counselling of the patient and relatives by the treating clinician is essential.[13, 22]. Besides this, the clinical skills of movement disorder specialists, pediatric neurologists and pediatricians also remain crucial for correctly selecting those patients with YMDs who are likely to benefit most from NGS.[5]

Also in the post-NGS diagnostic phase, clinical expertise is vital for correct interpretation of NGS results, including interpretation of VUS.[1, 13, 14, 22] For example, in the literature, patients have been described with movement disorders that were attributed to a certain gene variant, but after accurate phenotyping the abnormal movements turned out to be acquired or functional.[14, 24, 25] Thus, clinical expertise continues to be key, both in pre-NGS diagnostic work-up as in post-NGS analysis, and close collaboration between geneticists and clinicians is pivotal.[1]

Even after a molecular diagnosis has been made, clinical expertise remains essential, for example to carefully evaluate the phenotype during the course of the disease. This is highlighted by our study on myoclonus in neurogenetic disorders (**Chapter 8**). This case series demonstrates that myoclonus in childhood-onset neurogenetic disorders frequently may go unnoticed. These cases underscore the importance of early identification and treatment of myoclonus in young-onset neurogenetic disorders, because symptomatic treatment resulted in marked improvement

of both myoclonus and overall functioning. To further improve the awareness and recognition of myoclonus in children, we provided a list of childhood-onset neurogenetic disorders with myoclonus as important associated feature (see supplement of **Chapter 8**).

Treatment

Chapters 6 and **9** of this thesis highlight some of the possible therapeutic implications of a molecular diagnosis. Here, the main findings of these case studies will be briefly discussed.

For treatment with deep brain stimulation (DBS), a molecular diagnosis is important, as outcomes can vary considerably among the different subtypes of dystonia.[26] In two related patients with young-onset dystonia-deafness syndrome, we were able to identify the causative gene (β-actin), as described in **Chapter 6.1**. Both patients had a good clinical response to DBS, which is an important finding with possible therapeutic consequences for other patients with the same disorder. Similarly, our finding that status dystonicus could be reversed by relocation of pallidal electrodes in a patient with DYT6 generalized dystonia, can guide treatment choices in other patients with DYT6 dystonia (**Chapter 6.2**).

Chapter 9 of this thesis is dedicated to North Sea progressive myoclonus epilepsy (NSMPE). This is an extremely rare disorder characterized by young-onset myoclonus and ataxia, seizures and areflexia. In 2011 Corbett and colleagues discovered the causative gene (*GOSR2*).[27] Currently, worldwide less than 30 patients with NSPME have been described, and almost all described patients carry the same homozygous c.430G>T (p.Gly144Trp) *GOSR2* mutation, indicating a founder effect.[27-31] The mutation might originate from Friesland, the northern part of the Netherlands, as the frequency of the *GOSR2* mutation seems to be relatively high in this region.[31]

The molecular diagnosis of NSPME allowed us to explore and describe the phenotypic spectrum of NSPME, as described in **Chapter 9.1** and **9.2**. The clinical picture of NSPME is dominated by spontaneous and action-induced cortical myoclonus and ataxia, with severe impact on daily functioning. Most NSPME patients also have seizures, but these are relatively mild compared to the myoclonic jerks. Myoclonic jerks and seizures can be treated with anti- epileptic drugs, however the benefits are limited. Other features of NSPME are areflexia, scoliosis, relative preservation of cognitive function, and abnormal electrophysiological findings suggestive of sensory neuropathy and anterior horn cell involvement.

We explored a new treatment strategy for NSPME, as is illustrated by **Chapter 9.3**. In this observational, prospective study, we evaluated the efficacy of the modified Atkins diet in four NSPME patients, with health-related quality of life (HRQL) as primary outcome measure. One of the patients showed an sustained improvement of HRQL on the diet. The HRQL of the other three patients remained broadly unchanged and they did not continue the diet. Despite the small number of patients in this study and the relatively short duration of follow-up, this observational study indicates that the modified Atkins diet might be considered in patients with NSPME, as it may improve or stabilize HRQL in this devastating disorder.

Future directions

Future directions with regard to a multidisciplinary approach to YMDs

Remarkably, 61% of the 100 patients with YMDs (**Chapter 2**) in our outpatient clinic, had not been given any treatment for their movement disorder before they visited our multidisciplinary clinic. As follow-up, it would be useful to design a prospective study to explore the long term benefits of a multidisciplinary approach to YMDs, with standardized clinical assessments to systematically evaluate treatment effects on motor symptoms, disability and quality of life. Furthermore, it would be interesting to investigate the effect of a multidisciplinary team approach on recognition and treatment of non-motor symptoms, since recent studies have been pointing out the importance of non-motor symptoms in YMDs.[32-34]

In the coming years, genetic advances will probably further transform the diagnostic process in YMDs. Third-generation technologies (real-time DNA sequencing) are expected to lead to another revolution in speed and capacity.[22] Also in this context, it is likely that patients with complex YMDs will benefit from an integrated multispecialty approach, because close collaboration among the different clinicians may facilitate a profound understanding of the neurological and systemic phenotype and promote targeted treatment.

Future directions with regard to dystonia

In terms of continuing our own research, it would be relevant to develop a diagnostic algorithm for adult-onset dystonia incorporating NGS diagnostics. Another logical next step would be to investigate the cost-effectiveness of whole exome sequencing in dystonia, taking into account diagnostic yield and cost, but also the occurrence of VUS and incidental findings.[35, 36]

Our study on the inter-rater agreement of the dystonia classification and syndrome definition showed considerable differences in classification and syndrome definition among clinicians. These differences carry the risk of different diagnostic and treatment strategies, and may hamper the search for phenotype-genotype correlation and treatment choices. Consequently, our findings call for a discussion on the current classification system. How can we describe and report dystonia in a more consistent and unambiguous way? Should we use the classification system in different ways for various needs? As Albanese and colleagues pointed out in their paper on the dystonia classification: it is challenging to design a classification system that is satisfactory for all needs.[37] These needs include: (1) to aid in diagnosis and diagnostic testing, (2) to facilitate correct interpretation of the results of diagnostic (NGS) tests, (3) to evaluate treatment effects and (4) to organize current knowledge for research purposes.[37]

We hypothesize that for the first need, to guide diagnostic testing, a strategy incorporating a diagnostic algorithm (**Chapter 3**) might be a more pragmatic approach than an approach based on the classification system and the syndromic approach.[37] However, the inter-rater agreement of our diagnostic algorithm has never been investigated. To do this, a study with a similar design as our diagnostic agreement study on the dystonia classification (**Chapter 5**) could be conducted, either based on written vignettes or video assessments. It would be interesting to see whether different clinicians would select the same diagnostic tests for a certain patient, if they would use the stepwise approach of the diagnostic algorithm. In this way, the inter-rater agreement

on the diagnostic steps of the algorithm could be assessed and be compared to the inter-rater agreement on the dystonia classification and syndrome diagnosis.

For the other three needs (interpretation of diagnostic tests, evaluation of treatment effects and research), the current classification system presumably will remain as important as ever, but future studies are needed to investigate how the inter-rater agreement might be improved. Theoretically, diagnostic agreement might increase by formulating more stringent criteria for some items, and to simplify the criteria for other items (**Chapter 5**). Another interesting topic to investigate would be whether diagnostic agreement might improve either by clinical assessments by a team of clinicians in challenging individual cases, or by offering training programs, video-based e-learnings and serious gaming.

In the area of DBS for dystonia, worldwide many fascinating studies are going on, or will be launched in the near future, including studies on the effect of DBS on non-motor symptoms in (young-onset) dystonia.[32-34] Particularly in combined forms of dystonia, DBS may lead to a meaningful change across multiple domains of functioning, even in the absence of a significant change in dystonia rating scales.[32] This corresponds with our own clinical experience. Therefore, we are currently investigating the effect of DBS upon individualized goals, i.e. goals stated by dystonia patients themselves.[38, 39] In the future, it would be interesting to conduct a randomized controlled trial to systematically evaluate the effect of DBS on motor, non-motor symptoms and individualized goals, particularly for patients with combined forms of dystonia.

Another intriguing topic with regard to DBS in dystonia is the role of genetic factors in the outcome of DBS. The available evidence indicates that genetic factors play an important role in outcomes.[26] Interestingly, genetic factors may be even under-appreciated in presumably acquired dystonias, such as cerebral palsy and tardive dystonias.[26, 40-43] A multicenter study offering whole exome sequencing to all patients with dystonia undergoing DBS and systematically evaluating outcomes, may provide valuable information for patient selection and outcome prediction.

Future directions with regard to myoclonus

As a follow-up to our study on a new diagnostic approach to patients myoclonus, it would be useful to investigate the efficacy of a NGS-diagnostics-first strategy for myoclonus. The design of such a study could be similar to our study on gene panel analysis in dystonia (**Chapter 4**), with diagnostic yield, cost and duration of work-up as outcome measures.

Our case series on myoclonus in neurogenetic disorders highlights the need for actively searching for myoclonus, also when a molecular diagnosis has already been established, since symptomatic treatment significantly improved daily functioning of these patients. These findings are in line with another study, showing that movement disorders in patients with IEM were frequently overlooked and significantly influenced health-related quality of life.[44] Therefore, larger studies should be performed systematically investigating the incidence of movement disorders in neurogenetic disorders, with the aim to raise awareness among clinicians and to promote targeted treatment.

For NSPME patients and their families, the discovery of the *GOSR2* gene has been an important step, as it marked the endpoint of a long search to an etiological diagnosis.[27] At present, the main necessity regarding NSPME is further insight in the pathophysiological mechanisms underlying

this devastating disorder, as this may hopefully lead to targeted treatment. At the same time, continuous critical evaluation of current symptomatic therapies is required.[29, 45] Recently, in our center the first steps have been undertaken towards an animal model for NSPME, which is a potential gateway to the development of new mechanism-based therapies.

Overall, NGS has led to the discovery of many new genes and phenotypes in the field of YMDs, as has been described in this thesis. As with NSPME, the next crucial step for these genetic YMDs is to define the underlying disease-mechanisms.[14] Data sharing, prediction models and international collaborations may elucidate gene-environmental interactions and pathophysiologic mechanisms of disease, potentially leading to the development of novel therapies and personalized medicine.[22] Furthermore, in recent years gene-editing techniques, such as CRISPR (clustered regularly interspaced short palindromic repeats), have been developed.[46-49] Gene editing already has had a profound effect on biomedical research, and may in the future -in strictly regulated form- also have an impact on medical practice.[50- 52]

Conclusion

This thesis provides new diagnostic strategies to YMDs in light of the paradigm shift that has occurred in molecular genetics. The benefits of a multidisciplinary team approach to complex YMDs were described, and for dystonia and myoclonus new diagnostic algorithms were proposed, incorporating the use of new genetic techniques. With regard to dystonia, gene panel analysis proved to facilitate molecular diagnosis in complex cases of dystonia, with a quicker diagnostic workup and lower costs, representing a major improvement for patients and their families. The dystonia classification and syndrome definition were shown to be ambiguous, and therefore we advocate starting a discussion on how to improve the diagnostic accuracy of the dystonia classification system. With regard to myoclonus, the importance of early identification and treatment of myoclonus in neurogenetic disorders was demonstrated. Furthermore, the phenotypic spectrum and the effect of the modified Atkins diet was explored in NSPME, a rare disorder with young-onset myoclonus which is caused by a mutation in the *GOSR2* gene. The mutation might originate from Friesland, as the prevalence of the *GOSR2* mutation seems to be relatively high in this region. In the following years, the next crucial step for genetic YMDs will be to elucidate the underlying disease-mechanisms, as these will hopefully lead to the development of more targeted therapies.

References

1 Foley AR, Donkervoort S, Bonnemann CG. Next-generation sequencing still needs our generation's clinicians. Neurol Genet. 2015;1(2):e13.
2 Neveling K, Feenstra I, Gilissen C, et al. A post-hoc comparison of the utility of sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. Hum Mutat. 2013;34(12):1721-6.
3 Bäumer T, Sajin V, Münchau A. Childhood-Onset Movement Disorders: A Clinical Series of 606 Cases. Movement Disorders Clinical Practice. 2017;4(3):437-40.
4 Olgiati S, Quadri M, Bonifati V. Genetics of movement disorders in the next- generation sequencing era. Mov Disord. 2016;31(4):458-70.
5 de Koning TJ, Tijssen MA. Movement disorders in 2014. Genetic advances spark a revolution in dystonia phenotyping. Nat Rev Neurol. 2015;11(2):78-9.
6 Pearson TS, Akman C, Hinton VJ, et al. Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS). Curr Neurol Neurosci Rep. 2013;13(4):342.
7 Dijk JM, Tijssen MA. Management of patients with myoclonus: available therapies and the need for an evidence-based approach. Lancet Neurol. 2010;9(10):1028-36.
8 Garcia-Cazorla A, Wolf NI, Serrano M, et al. Inborn errors of metabolism and motor disturbances in children. J Inherit Metab Dis. 2009;32(5):618-29.
9 Mink JW. Special Concerns in Defining, Studying, and Treating Dystonia in Children. Movement disorders : official journal of the Movement Disorder Society. 2013;28(7):921-5.
10 Fung VS, Jinnah HA, Bhatia K, et al. Assessment of patients with isolated or combined dystonia: an update on dystonia syndromes. Mov Disord. 2013;28(7):889-98. 264
11 Caviness JN, Truong DD. Myoclonus. Handb Clin Neurol. 2011;100:399-420.
12 Schneider SA, Bhatia KP. Secondary dystonia--clinical clues and syndromic associations. Eur J Neurol. 2010;17 Suppl 1:52-7.
13 Hennekam RC, Biesecker LG. Next-generation sequencing demands next-generation phenotyping. Hum Mutat. 2012;33(5):884-6.
14 Sethi KD, Lang AE. Will New Genetic Techniques Like Exome Sequencing Obviate the Need for Clinical Expertise? No. Movement Disorders Clinical Practice. 2017;4(1):39-41.
15 van der Salm SM, de Haan RJ, Cath DC, et al. The eye of the beholder: inter-rater agreement among experts on psychogenic jerky movement disorders. J Neurol Neurosurg Psychiatry. 2013;84(7):742-7.
16 Eggink H, Kremer D, Brouwer OF, et al. Spasticity, dyskinesia and ataxia in cerebral palsy: Are we sure we can differentiate them? Eur J Paediatr Neurol. 2017;21(5):703- 6.
17 Beghi E, Regio V, Papantonio A, et al. Reliability of clinical diagnosis of dystonia. Neuroepidemiology. 2014;43(3-4):213-9.
18 Stroink H, van Donselaar CA, Geerts AT, et al. Interrater agreement of the diagnosis and classification of a first seizure in childhood. The Dutch Study of Epilepsy in Childhood. J Neurol Neurosurg Psychiatry. 2004;75(2):241-5.
19 Keogh MJ, Daud D, Chinnery PF. Exome sequencing: how to understand it. Pract Neurol. 2013;13(6):399-407.
20 Brownstein CA, Beggs AH, Homer N, et al. An international effort towards developing standards for best practices in analysis, interpretation and reporting of clinical genome sequencing results in the CLARITY Challenge. Genome Biol. 2014;15(3):R53.
21 Kohane IS, Masys DR, Altman RB. The incidentalome: a threat to genomic medicine. JAMA. 2006;296(2):212-5.
22 Bonifati V. Will New Genetic Techniques Like Exome Sequencing and Others Obviate the Need for Clinical Expertise? Yes. Movement Disorders Clinical Practice. 2017;4(1):36-8.
23 Directors ABo. ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. Genet Med. 2015;17(1):68-9.

24 Dawson SB, Morgan JC, Sethi KD. Other causes of ataxia in patients with SCA mutations. Clin Neurol Neurosurg. 2007;109(1):85-7.

25 Lines MA, Jobling R, Brady L, et al. Peroxisomal D-bifunctional protein deficiency: three adults diagnosed by whole-exome sequencing. Neurology. 2014;82(11):963-8.

26 Jinnah HA, Alterman R, Klein C, et al. Deep brain stimulation for dystonia: a novel perspective on the value of genetic testing. J Neural Transm. 2017;124(4):417-30.

27 Corbett MA, Schwake M, Bahlo M, et al. A mutation in the Golgi Qb-SNARE gene GOSR2 causes progressive myoclonus epilepsy with early ataxia. Am J Hum Genet. 2011;88(5):657-63.

28 Boisse Lomax L, Bayly MA, Hjalgrim H, et al. 'North Sea' progressive myoclonus epilepsy: phenotype of subjects with GOSR2 mutation. Brain. 2013;136(Pt 4):1146- 54.

29 Anderson DG, Németh AH, Fawcett KA, et al. Deep Brain Stimulation in Three Related Cases of North Sea Progressive Myoclonic Epilepsy from South Africa. Movement Disorders Clinical Practice. 2017;4(2):249-53.

30 Praschberger R, Balint B, Mencacci NE, et al. Expanding the Phenotype and Genetic Defects Associated with the GOSR2 Gene. Movement Disorders Clinical Practice. 2015;2(3):271-3.

31 van Egmond ME, Verschuuren-Bemelmans CC, Nibbeling EA, et al. Ramsay Hunt syndrome: clinical characterization of progressive myoclonus ataxia caused by *GOSR2* mutation. Mov Disord. 2014;29(1):139-43.

32 Gimeno H, Tustin K, Selway R, et al. Beyond the Burke-Fahn-Marsden Dystonia Rating Scale: deep brain stimulation in childhood secondary dystonia. Eur J Paediatr Neurol. 2012;16(5):501-8.

33 Peall KJ, Kuiper A, de Koning TJ, et al. Non-motor symptoms in genetically defined dystonia: Homogenous groups require systematic assessment. Parkinsonism Relat Disord. 2015;21(9):1031-40.

34 Koy A, Timmermann L. Deep brain stimulation in cerebral palsy: Challenges and opportunities. Eur J Paediatr Neurol. 2017;21(1):118-21.

35 Frank M, Prenzler A, Eils R, et al. Genome sequencing: a systematic review of health economic evidence. Health Econ Rev. 2013;3(1):29.

36 Warman Chardon J, Beaulieu C, Hartley T, et al. Axons to Exons: the Molecular Diagnosis of Rare Neurological Diseases by Next-Generation Sequencing. Curr Neurol Neurosci Rep. 2015;15(9):64.

37 Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863-73.

38 Kubu CS, Ford PJ. Beyond Mere Symptom Relief in Deep Brain Stimulation: An Ethical Obligation for Multi-faceted Assessment of Outcome. AJOB Neurosci. 2012;3(1):44-9.

39 Kubu CS, Cooper SE, Machado A, et al. Insights gleaned by measuring patients' stated goals for DBS: More than tremor. Neurology. 2017;88(2):124-30.

40 McMichael G, Bainbridge MN, Haan E, et al. Whole-exome sequencing points to considerable genetic heterogeneity of cerebral palsy. Mol Psychiatry. 2015;20(2):176- 82.

41 MacLennan AH, Thompson SC, Gecz J. Cerebral palsy: causes, pathways, and the role of genetic variants. Am J Obstet Gynecol. 2015;213(6):779-88.

42 Aquino CC, Lang AE. Tardive dyskinesia syndromes: current concepts. Parkinsonism Relat Disord. 2014;20 Suppl 1:S113-7.

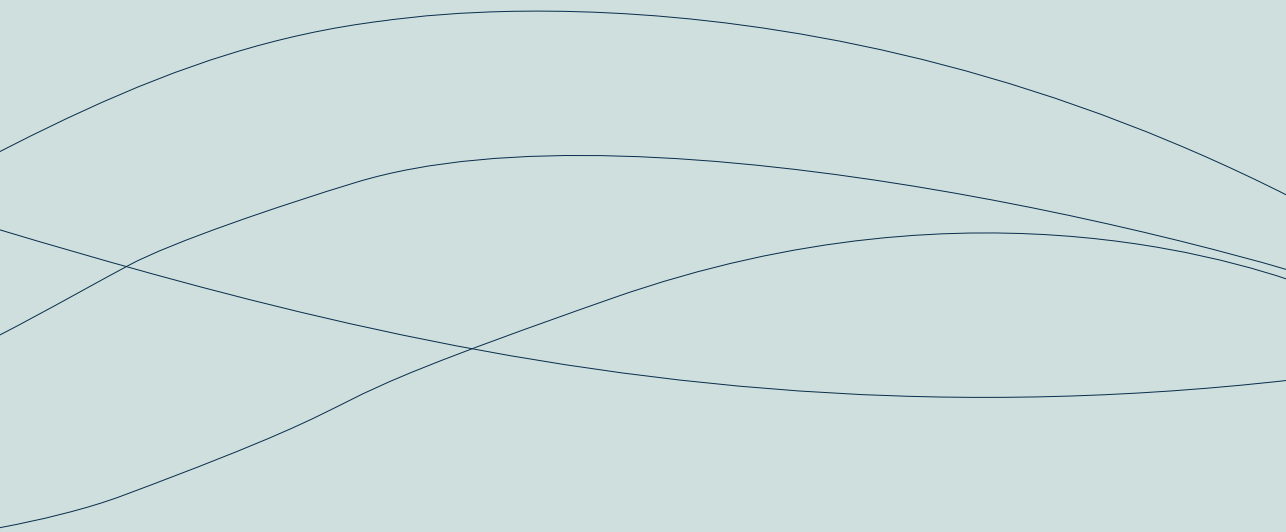
43 Moreno-De-Luca A, Ledbetter D, Martin CL, et al. Genetic insights into the causes and classification of cerebral palsies. Lancet neurol. 2012;11(3):283-92.

44 Eggink H, Kuiper A, Peall KJ, et al. Rare inborn errors of metabolism with movement disorders: a case study to evaluate the impact upon quality of life and adaptive functioning. Orphanet J Rare Dis. 2014;9:177.

45 van Egmond ME, Weijenberg A, van Rijn ME, et al. The efficacy of the modified Atkins diet in North Sea Progressive Myoclonus Epilepsy: an observational prospective open-label study. Orphanet J Rare Dis. 2017;12(1):45.

46 Jinek M, Chylinski K, Fonfara I, et al. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science. 2012;337(6096):816-21.
47 Gasiunas G, Barrangou R, Horvath P, et al. Cas9-crRNA ribonucleoprotein complex mediates specific DNA cleavage for adaptive immunity in bacteria. Proc Natl Acad Sci U S A. 2012;109(39):E2579-86.
48 Cong L, Ran FA, Cox D, et al. Multiplex Genome Engineering Using CRISPR/Cas Systems. Science (New York, N.Y.). 2013;339(6121):819-23.
49 Mali P, Yang L, Esvelt KM, et al. RNA-guided human genome engineering via Cas9. Science. 2013;339(6121):823-6.
50 Komaroff AL. Gene Editing Using CRISPR: Why the Excitement? JAMA. 2017;318(8):699-700.
51 Komor AC, Kim YB, Packer MS, et al. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. Nature. 2016;533:420.
52 Kim YB, Komor AC, Levy JM, et al. Increasing the genome-targeting scope and precision of base editing with engineered Cas9-cytidine deaminase fusions. Nat Biotechnol. 2017;35(4):371-6.

Appendix



Summary in Dutch / Nederlandse samenvatting

Bewegingsstoornissen met debuut op jonge leeftijd
Innovaties in de genetica vragen om een nieuwe klinische benadering

Dit proefschrift gaat over *young-onset movement disorders* (YMDs), bewegingsstoornissen die beginnen op de kinderleeftijd (0-18 jaar). Hierbij staan twee bewegingsstoornissen centraal: dystonie en myoclonus. Er zullen verschillende aspecten aan de orde komen, met als rode draad de recente innovaties in de genetica die vragen om een nieuwe aanpak van YMDs in de dagelijkse klinische praktijk.

Klinische benadering van YMDs

Er zijn verschillende soorten bewegingsstoornissen. *Hyperkinetische bewegingsstoornissen*, ofwel overtollige bewegingen, zijn op de kinderleeftijd verreweg het meest voorkomend. Hieronder vallen dystonie, myoclonus, chorea, ballisme, tremor, stereotypieën en tics. Een ander type bewegingsstoornis is *ataxie*, waarbij er een verstoring is van het evenwicht en bij het aansturen van bewegingen. Tot slot kan een bewegingsstoornis *hypokinetisch* zijn, ofwel bewegingsarmoede. Een hypokinetische bewegingsstoornis op de kinderleeftijd is zeer zeldzaam.

Tics zijn de meest voorkomende bewegingsstoornis op de kinderleeftijd. Een tic stoornis is meestal relatief makkelijk te herkennen en diagnosticeren. Bij zeldzamere YMDs, zoals dystonie en myoclonus, of bij een mengbeeld van verschillende bewegingsstoornissen, is herkenning en classificatie daarentegen vaak veel moeilijker.

Dystonie is het onwillekeurig aanspannen van de spieren, waardoor draaiende bewegingen of abnormale houdingen ontstaan, of beide. Dystonie wordt vaak uitgelokt of neemt toe bij activiteit. *Myoclonieën* zijn schokken van de spieren (positieve myoclonus), of juist het kortdurend wegvallen van spiertonus (negatieve myoclonus).

Bij elke patiënt met een YMD zijn de drie belangrijkste vragen:

1. wat zijn precies de symptomen en verschijnselen? (fenomenologie)
2. wat is de oorzaak? (etiologie)
3. wat is de beste behandeling?

Voor het beantwoorden van de eerste vraag gaat het niet alleen om het classificeren van de bewegingsstoornis, maar ook om het in kaart brengen van andere neurologische en niet-neurologische verschijnselen. Het geheel van deze kenmerken vormt het *fenotype*. Elk fenotype wordt bepaald door de erfelijke informatie die is vastgelegd in ons DNA (*genotype*) in samenspel met invloeden van buitenaf (omgevingsfactoren).

Na het in kaart brengen van de symptomen en verschijnselen, het *fenotyperen*, is de volgende stap om de onderliggende oorzaak op te sporen. Dit is meestal niet eenvoudig, want er zijn zeer veel mogelijke oorzaken van YMDs beschreven. De oorzaak kan erfelijk zijn, maar ook verworven, zoals bijvoorbeeld zuurstofgebrek bij de geboorte of een doorgemaakte infectie. Het vinden van de oorzaak is belangrijk, niet alleen omdat hiermee een einde komt aan een vaak jarenlange

zoektocht, maar ook omdat er voor sommige aandoeningen een ziekte-specifieke behandeling beschikbaar is.

Innovaties in de genetica

In de afgelopen jaren zijn de diagnostische mogelijkheden waarmee de code van het DNA kan worden ontrafeld enorm verbeterd. Met zogenaamde 'next-generation sequencing' (NGS) technieken is het nu mogelijk om binnen enkele weken iemands gehele DNA in één keer te onderzoeken op alle bekende ziekte-veroorzakende mutaties. Bij patiënten met een erfelijke YMD kan hiermee vaak veel sneller een diagnose worden gesteld dan met de klassieke gen- voor-gen methode. Verder zijn NGS-technieken de laatste jaren steeds goedkoper geworden, waardoor de beschikbaarheid ervan is toegenomen. Deze revolutie in de moleculaire genetica heeft geleid tot de ontdekking van veel nieuwe YMD-geassocieerde genen, nieuwe fenotypes en fenotype-genotype correlaties.

De bredere beschikbaarheid van NGS-onderzoek vraagt om een nieuwe benadering van YMDs in de klinische praktijk. Soms kunnen NGS-technieken bij YMD patiënten leiden tot de diagnose, soms zijn eerst andere onderzoeken nodig. Clinici moeten dus bij elke patiënt zorgvuldig afwegen welke diagnostische techniek op welk moment moet worden ingezet. Daarnaast brengt de beschikbaarheid van NGS-diagnostiek een aantal nieuwe uitdagingen en problemen met zich mee waarvoor zowel genetische als klinische expertise noodzakelijk is. Al met al geen geringe opgave.

Het **doel van dit proefschrift** is het onderzoeken van nieuwe diagnostische strategieën die clinici kunnen toepassen bij YMDs, in het licht van de revolutie die heeft plaatsgevonden in de moleculaire genetica

Multidisciplinaire benadering van YMDs

Eén voorbeeld van een dergelijke nieuwe diagnostische strategie is een multidisciplinaire benadering van YMDs. In **Hoofdstuk 2** worden de resultaten beschreven van een studie naar de toegevoegde waarde van een multidisciplinair team voor YMDs in een universitair centrum.

Sinds 2012 is er in het Universitair Medisch Centrum Groningen een multidisciplinair spreekuur voor complexe YMDs, met als doel het geven van advies t.a.v. diagnose en behandeling. Het team bestaat uit een bewegingsstoornissen neuroloog, kinderneuroloog, kinderarts metabole ziekten en een klinisch geneticus.

Voor deze observationele studie werden de klinische gegevens van de eerste 100 patiënten geanalyseerd die dit multidisciplinaire spreekuur bezochten. De uitkomsten van de studie laten zien dat de multidisciplinaire benadering van YMDs een gunstige invloed heeft op het fenotyperen en op de herkenning van zeldzame aandoeningen. Het percentage van de patiënten bij wie een etiologische diagnose kon worden gesteld was hoog, met relatief weinig vertraging in het diagnostisch traject.

Nieuw diagnostisch stroomdiagram voor dystonie en voor myoclonus

De bovengenoemde innovaties in de genetica hebben geleid tot veel nieuwe inzichten op het gebied van YMDs. Dit geldt ook voor dystonie en myoclonus, waarbij duidelijk is geworden dat de

fenotypische variatie groot is en dat er zeer veel mogelijke onderliggende oorzaken zijn. Bij elke individuele patiënt moet de clinicus beslissen welk aanvullend onderzoek nuttig is en welk aanvullend onderzoek beter achterwege kan worden gelaten. Om hen hierbij te helpen hebben we een nieuw diagnostisch stroomdiagram ontwikkeld voor dystonie (**Hoofdstuk 3**) en voor myoclonus (**Hoofdstuk 7**). Deze stroomdiagrammen hebben als doel het diagnostisch proces te faciliteren en om de NGS-technieken optimaal te benutten.

Een belangrijk en nieuw uitgangspunt van deze twee stroomdiagrammen is dat NGS-diagnostiek in principe wordt toegepast bij alle patiënten, op twee uitzonderingen na. De eerste uitzondering is wanneer er aanwijzingen zijn voor een verworven aandoening, bijvoorbeeld een medicatie-geïnduceerde bewegingsstoornis. De tweede uitzondering is wanneer er aanwijzingen zijn voor een behandelbare erfelijke stofwisselingziekte. De biochemische diagnostiek om dergelijke ziekten aan te tonen is namelijk op dit moment nog sneller dan NGS-testen. Daarom moet er in deze situatie naast NGS-diagnostiek ook biochemisch bloedonderzoek gedaan worden, zodat de behandeling zo snel mogelijk kan worden gestart.

Bij het aanvragen van NGS-diagnostiek is het van belang rekening te houden met de beperkingen van NGS, zo worden structurele veranderingen en mutaties in mtDNA niet gerapporteerd bij routine NGS-diagnostiek en moeten apart worden aangevraagd. Ook is het belangrijk dat de patiënt en zijn familie zorgvuldig worden voorgelicht over de mogelijke uitkomsten van NGS, zoals de kans op variaties waarvan de betekenis niet bekend is ('variants of unknown significance') en de kans op toevalsbevindingen.

In de toekomst zal de beschikbaarheid van NGS steeds verder toenemen en NGS zal daardoor steeds meer deel gaan uitmaken van de gewone dagelijkse praktijk. De nieuwe diagnostische stroomdiagrammen voor dystonie en myoclonus zullen clinici helpen een zo hoog mogelijke diagnostische opbrengst van NGS te realiseren in een zo kort mogelijk tijdsbestek. Ook zal door het gebruik van deze stroomdiagrammen onnodig aanvullend onderzoek zoveel mogelijk worden vermeden.

Genen panel analyse voor het opsporen van de oorzaak van dystonie

In **Hoofdstuk 4** wordt de toepassing van bovengenoemd diagnostisch stroomdiagram voor dystonie onderzocht bij 61 patiënten met dystonie in een tertiair centrum. Het gaat om een post-hoc studie waarin de klassieke gen-voor-gen methode wordt vergeleken met het gebruik van NGS-diagnostiek. In dit geval ging het om het gebruik van een panel met 94 dystonie-geassocieerde genen. Uit de resultaten blijkt dat de strategie met NGS niet alleen leidde tot een hogere diagnostische opbrengst (14.8% versus 7.4%), maar ook tot een goedkoper (€1822 versus €2660) en korter (28 dagen versus 102 dagen) diagnostisch traject, een belangrijke verbetering voor patiënten en hun families.

Next-generation phenotyping

De recente toename van kennis op het gebied van genetische oorzaken en fenotypische variatie van YMDs is niet alleen te danken aan de beschikbaarheid van NGS, maar ook aan het zorgvuldig in kaart brengen van het fenotype ('fenotyperen'). Hierdoor konden klinische gegevens worden gekoppeld aan uitkomsten van NGS-onderzoek. Voor het optimaal benutten van (online)

databases is het daarom essentieel om klinische gegevens op een consistente en eenduidige manier te beschrijven en in te voeren. Dit vergt 'next-generation phenotyping': gedetailleerde fenotypering met diagnostische criteria die voor iedereen helder zijn.

In dit kader hebben we een onderzoek gedaan naar de eenduidigheid van de diagnostische criteria voor dystonie (**Hoofdstuk 5**). Het doel van deze oriënterende studie was om na te gaan in hoeverre ervaren clinici het met elkaar eens waren ('inter-rater agreement') over de classificatie en syndroom diagnose van dystonie.

Voor deze studie hebben deze acht ervaren clinici gedetailleerde casusbeschrijvingen (vignetten) beoordeeld van 56 dystonie patiënten. Aan de beoordelaars werd gevraagd om de vignetten te classificeren volgens de verschillende onderdelen van de huidige dystonie classificatie, en om een dystonie syndroom diagnose te formuleren. Elke casus werd door twee clinici beoordeeld. Vervolgens werden deze twee beoordelingen met elkaar vergeleken. De resultaten lieten zien dat de overeenstemming matig tot redelijk was voor de dystonie classificatie, en matig voor de syndroom diagnose. Slechts in 12,5 % van de casus waren de beide beoordelaars het op alle punten met elkaar eens.

In een ideale situatie zou deze studie zijn uitgevoerd met meer dan twee beoordelaars per vignet. Desalniettemin laten de resultaten zien dat er veel variatie bestaat in de manier waarop ervaren beoordelaars omgaan met klinische informatie. Ogenschijnlijk heldere classificatie criteria bleken lang niet altijd eenduidig te zijn. Deze verschillen in interpretatie kunnen leiden tot onnodige variatie in diagnostiek en behandeling. Bovendien kan dit gebrek aan eenduidigheid een struikelblok vormen bij de zoektocht naar nieuwe dystonie-geassocieerde genen en fenotype-genotype correlaties. Het is daarom van belang na te gaan hoe de eenduidigheid van de classificatie criteria kan worden verbeterd. In **Hoofdstuk 5** worden hiervoor een aantal suggesties gedaan.

Klinische expertise blijft onmisbaar

Zoals hierboven beschreven bleek uit **Hoofdstuk 4** dat de diagnostische strategie waarbij gebruik werd gemaakt van NGS duidelijk meerwaarde had ten opzichte van de traditionele diagnostische strategie. Deze uitkomst zou de vraag kunnen oproepen of klinische expertise nog wel nodig is, of dat we het stellen van een diagnose beter aan computers kunnen overlaten.

Inmiddels is duidelijk dat, ook in dit NGS-tijdperk, klinische expertise onmisbaar blijft. Dit geldt voor de fase voorafgaand aan het aanvragen van genetische testen, maar ook in de fase daarna, waarbij de interpretatie van NGS-uitkomsten centraal staat. Zo zijn er in de medische literatuur verscheidene voorbeelden terug te vinden van patiënten bij wie de bewegingsstoornis in eerste instantie werd toegeschreven aan een genetische afwijking. Na zorgvuldig fenotyperen bleek later toch dat de oorzaak een verworven aandoening was.

Ook wanneer er geen twijfel meer bestaat over de definitieve genetische diagnose blijft klinische deskundigheid nodig, onder andere om veranderingen in het fenotype te signaleren. Dit aspect wordt belicht in **Hoofdstuk 8**, een studie over myoclonus bij neurogenetische aandoeningen. In dit hoofdstuk worden een aantal ziektegeschiedenissen beschreven waaruit

blijkt dat myoclonus bij jonge patiënten met neurogenetische aandoeningen makkelijk over het hoofd kan worden gezien. Herkenning en symptomatische behandeling van myoclonus leidde bij de beschreven patiënten tot duidelijke verbetering in het algeheel functioneren. Hieruit blijkt het belang van tijdige herkenning van myoclonus bij deze patiëntengroep.

Behandeling

In **Hoofdstuk 6** en **Hoofdstuk 9** wordt aandacht besteed aan de behandeling van genetische YMDs. **Hoofdstuk 6** is gewijd aan behandeling met diepe hersenstimulatie (DBS).

In **Hoofdstuk 6.1** worden twee verwante patiënten beschreven met dystonie en doofheid, de oorzaak bleek een mutatie in het beta-actine gen te zijn. Beide patiënten hadden duidelijk baat bij behandeling met diepe hersenstimulatie. Dit is een belangrijk gegeven, niet alleen voor de twee patiënten zelf, maar ook voor andere patiënten met dezelfde aandoening.

In **Hoofdstuk 6.2** wordt een jonge patiënt beschreven met gegeneraliseerde dystonie o.b.v. een mutatie in het *THAP1*-gen. DBS-behandeling had in eerste instantie goed effect, maar later trad er verslechtering op en ontwikkelde hij een levensbedreigende status dystonicus. Na een operatie waarbij de DBS-elektrodes werden verplaatst, knapte hij op. Ook voor deze casusbeschrijving geldt dat de bevindingen van belang kunnen zijn voor andere patiënten met hetzelfde ziektebeeld.

Hoofdstuk 9 gaat over de Noordzeeziekte. Deze ernstige aandoening begint op jonge leeftijd en wordt gekenmerkt door myoclonus, ataxie, epilepsie en afwezige reflexen. De oorzaak is een mutatie in het *GOSR2*-gen. De ziekte is zeldzaam, op dit moment zijn er wereldwijd niet meer dan 30 patiënten beschreven. Zij, of hun (voor)ouders zijn allemaal afkomstig zijn uit landen rondom de Noordzee, vandaar de naam 'Noordzeeziekte'. Opvallend is dat vrijwel alle patiënten precies dezelfde mutatie hebben en dat de aandoening in Friesland relatief veel voorkomt, mogelijk is de mutatie ooit in deze regio ontstaan.

Hoofdstuk 9.1 bevat een gedetailleerde beschrijving van het klinische en neurofysiologische fenotype bij vijf patiënten met de Noordzeeziekte. Bij één van deze vijf patiënten leken de myoclonieën sterk op chorea, waardoor clinici op het verkeerde been kunnen worden gezet. De ziektegeschiedenis van deze patiënt wordt daarom nader uitgediept in **Hoofdstuk 9.2**. In **Hoofdstuk 9.3** wordt een observationele, prospectieve studie gepresenteerd naar het effect van een variant van het Atkins dieet bij vier patiënten met de Noordzeeziekte. Dit is een vetrijk dieet met weinig koolhydraten. De primaire uitkomstmaat in deze studie was de gezondheid-gerelateerde kwaliteit van leven. Bij één van de vier patiënten had het dieet een gunstig effect op de kwaliteit van leven, de andere patiënten merkten geen verschil. Deze studie heeft een relatief korte duur en een klein aantal patiënten, desondanks laten de resultaten zien dat behandeling met dit dieet het overwegen waard kan zijn bij patiënten met de Noordzeeziekte.

Het proefschrift eindigt met een algemene discussie waarbij de belangrijkste bevindingen in een breder kader worden geplaatst en waarin aanbevelingen worden gedaan voor toekomstig onderzoek. De verwachting is dat de kennis over erfelijke YMDs in de komende jaren zal toenemen. Het ontrafelen van de onderliggende ziekte-mechanismen zal hierbij van groot belang zijn, om zo de ontwikkeling van nieuwe behandelingen een stap dichterbij te brengen.

Conclusie

Samenvattend worden in dit proefschrift nieuwe diagnostische strategieën gepresenteerd voor YMDs, in het licht van de revolutie die heeft plaatsgevonden in de moleculaire genetica. Zo wordt het gunstige effect van een multidisciplinaire team benadering voor YMDs beschreven, en worden twee nieuwe diagnostische stroomdiagrammen voor dystonie en myoclonus gepresenteerd. Ook tonen we de meerwaarde aan van het gebruik van genen panel analyse voor de diagnose van dystonie. Tot slot wordt er in dit proefschrift aandacht besteed aan het fenotype en de behandeling van de Noordzeeziekte, een zeldzame aandoening waarbij myoclonus op de voorgrond staat en waarvan de oorzaak een genetische mutatie is die wellicht ooit in Friesland is ontstaan.

De inhoud van dit proefschrift is van belang voor de dagelijkse klinische praktijk, en draagt daarnaast bij aan de discussie over de manier waarop we onze klinische expertise kunnen inzetten voor het optimaal benutten van de nieuwste genetische technieken.

List of main abbreviations

AT	ataxia-teleangiectasia
BFMDRS	Burke-Fahn-Marsden Dystonia Rating Scale Movement
CM	cortical myoclonus
CP	cerebral palsy
CLS	Coffin-Lowry syndrome
CSF	cerebrospinal fluid
DBS	deep brain stimulation
DC	dystonia of childhood
DDS	dystonia-deafness syndrome
DS	Dravet syndrome
EEG/EMG	electroencephalography/electromyography
GPA	gene panel analysis
GPi	globus pallidus internus
HRQL	health-related quality of life
IEM	inborn errors of metabolism
KD	ketogenic diet
MAD	modified Atkins diet
MD	movement disorder
mtDNA	mitochondrial DNA
NGS	next-generation sequencing
NSPME	North-Sea Progressive Myoclonus Epilepsy
PMA	progressive myoclonus ataxia
PME	progressive myoclonus epilepsy
SD	status dystonicus
SEP	somatosensory evoked potentials
SIDEs	stimulus-induced drop episodes
SM	subcortical myoclonus
TRS	targeted resequencing
UMRS	Unified Myoclonus Rating Scale
VUS	variants of unknown significance
WGS	whole genome sequencing
WES	whole exome sequencing
YMDs	young-onset movement disorders

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List of publications

- **van Egmond ME**, Lugtenberg CHA, Peall et al. Dystonia classification and syndrome definition: moderate agreement among experienced clinicians. Provisionally accepted in Mov Dis.

- Piña-Fuentes D, Beudel M, Little S, van Zijl J, Elting JW, Oterdoom DLM, **van Egmond ME**, Brown P, van Dijk JMC, de Koning-Tijssen, MAJ. Towards adaptive deep brain stimulation for dystonia. Neurosurg Focus 2018. In press.

- **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 Dis 2018;5:3.

- Oterdoom DLM, **van Egmond ME**, Ascencao LC et al. Reversal of status dystonicus after relocation of pallidal electrodes in DYT6 generalized dystonia. Tremor Other Hyperkin Mov 2018;8:530.

- H. Eggink, D. Kremer, O.F. Brouwer, M.F. Contarino, **M.E. van Egmond**, et al. Spasticity, dyskinesia and ataxia in cerebral palsy: Are we sure we can differentiate them? Eur J Paediatr Neurol 2017;21:703-6.

- **van Egmond ME**, Weijenberg A, van Rijn ME, et al. The efficacy of the modified Atkins diet in North Sea Progressive Myoclonus Epilepsy: an observational prospective open-label study. Orphanet J Rare Dis. 2017;12(1):45.

- **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(4):569-75.

- Eggink H, **van Egmond ME**, Verschuuren-Bemelmans CC, et al. Dystonia-deafness syndrome caused by a β-actin gene mutation and response to deep brain stimulation. Mov Disord 2017; 32(1):162-5.

- Kuiper A, **van Egmond ME**, Harms MP, et al. Clinical Pearls - how my patients taught me: The fainting lark symptom. J Clin Mov Disord. 2016;3:16. eCollection 2016.

- van Rappard DF, Boelens JJ, **van Egmond ME**, et al. Efficacy of hematopoietic cell transplantation in metachromatic leukodystrophy: the Dutch experience. Blood. 2016; 127(24):3098-101.

- Zutt R, **van Egmond ME**, Elting JW, et al. A novel diagnostic approach to patients with myoclonus. Nat Rev Neurol. 2015;11(12):687-97.

- **van Egmond ME**, Elting JW, Kuiper A, et al. Myoclonus in childhood-onset neurogenetic disorders: The importance of early identification and treatment. Eur J Paediatr Neurol 2015; 19(6):726-9.

- **van Egmond ME** Kuiper A, Elting JW, et al. Cortical myoclonus in a young boy with *GOSR2* mutation mimics chorea. Mov Dis Clin Pract. 2015;2(1):61-63.

- **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(7):774-81.

- **van Egmond ME**, Verschuuren-Bemelmans CC, Nibbeling EA, et al. Ramsay Hunt syndrome: clinical characterization of progressive myoclonus ataxia caused by *GOSR2* mutation. Mov Disord. 2014;29(1):139-43.

- **van Egmond ME**, Pouwels PJ, Boelens JJ, et al. Improvement of white matter changes on neuroimaging modalities after stem cell transplant in metachromatic leukodystrophy. JAMA Neurol. 2013;70(6):779-82.

- van Lierop AH, Hamdy NA, **van Egmond ME**, et al. Van Buchem disease: clinical, biochemical, and densitometric features of patients and disease carriers. J Bone Miner Res. 2013;28(4):848-54.

- **van Egmond ME**, Dikkers FG, Boot AM, et al. A rare cause of facial nerve palsy in children: hyperostosis corticalis generalisata (Van Buchem disease). Three new pediatric cases and a literature review. Eur J Paed Neurol. 2012;16(6):740-3.

- **van Egmond ME**, Vermeulen RJ, Peeters-Scholte CM, et al. Familial Hemophagocytic Lymphohistiocytosis in a pediatric patient diagnosed by brain magnetic resonance imaging. Neuropediatrics. 2011;42(5):191-3.

- **van Egmond ME**, Luijckx GJ, Kramer H, et al. Diaphragm paralysis caused by neuroborreliosis. Clin Neurol Neurosurg. 2011;113(2):153-5.

- **van Egmond ME**, Bakker NA. A toddler with vomiting and abnormal eye movements. Ned Tijdschr Geneeskd. 2010;154:1697.

About the author

Martje van Egmond (April 21st, 1980) was born and raised in Groningen, the Netherlands. After completing secondary school at the Praedinius Gymnasium in Groningen, she started her medical education at the University of Groningen. During medical school, she participated in a research project on Tourette syndrome at the Yale Child Study Center, in New Haven, USA (Prof. Dr. J.F. Leckman). She obtained her bachelor degree in 2003 and her medical degree in 2005, both cum laude. Subsequently, she started her training as a medical resident at the Department of Neurology (Prof. Dr. J.H.A. de Keyser, Prof. Dr. H.P.H. Kremer) of the University Medical Center Groningen (UMCG).

During her residency, she focused on pediatric neurology. She worked during 12 months at the Department of Child Neurology of the UMCG (Prof. Dr. O.F. Brouwer) and during 3 months at the Department of Child Neurology of the VU University Medical Center (VUMC) in Amsterdam, the Netherlands (Prof. Dr. M.S. van der Knaap). Besides this clinical work, she participated from 2009 and completed this in 2014. in the Distance Learning Program of the British Paediatric Neurology Association. In 2012, she was involved in a research project on metachromatic leukodystrophy at the VUMC (Dr. N.I. Wolf, Prof. Dr. M.S. van der Knaap)

After completing her residency in neurology in 2012, Martje did a fellowship in movement disorders at the UMCG (Prof. Dr. M.A.J. de Koning-Tijssen, Prof. Dr. van Laar). During this this fellowship she focused on hyperkinetic movement disorders, mainly dystonia and myoclonus, and she participated in the multidisciplinary outpatient clinic for young-onset movement disorders. Since 2013, she is combining her clinical work with research on these topics.

Since 2014 she is working as a clinical neurologist at the Ommelander Ziekenhuis Groningen and in the UMCG as neurologist for dystonia patients who are treated by deep brain stimulation. In 2015, Martje was awarded the annual prize of the Dutch Movement Disorder Society for the best scientific paper in 2014-2015 'Dystonia in children and adolescents: a systematic review and a new diagnostic algorithm' (published in the *Journal of Neurology, Neurosurgery and Psychiatry*). Since 2017 she is member of the medical advisory board of the Dutch dystonia patient association.

In recent years, she has given lectures at several (inter)national congresses and patient meetings, including a lecture at the international Movement Disorder Society congress in Vancouver in 2017. Currently, she is involved in organizing a national congress 'Masterclass Movement Disorders' (Schoorl, June 2018) and an international congress 'Movement Disorders in Children and Adolescents' which will be held in Groningen in November 2018.

Martje is not (yet) married to Marinus Oterdoom and they have two sons, Teun and Mannes.