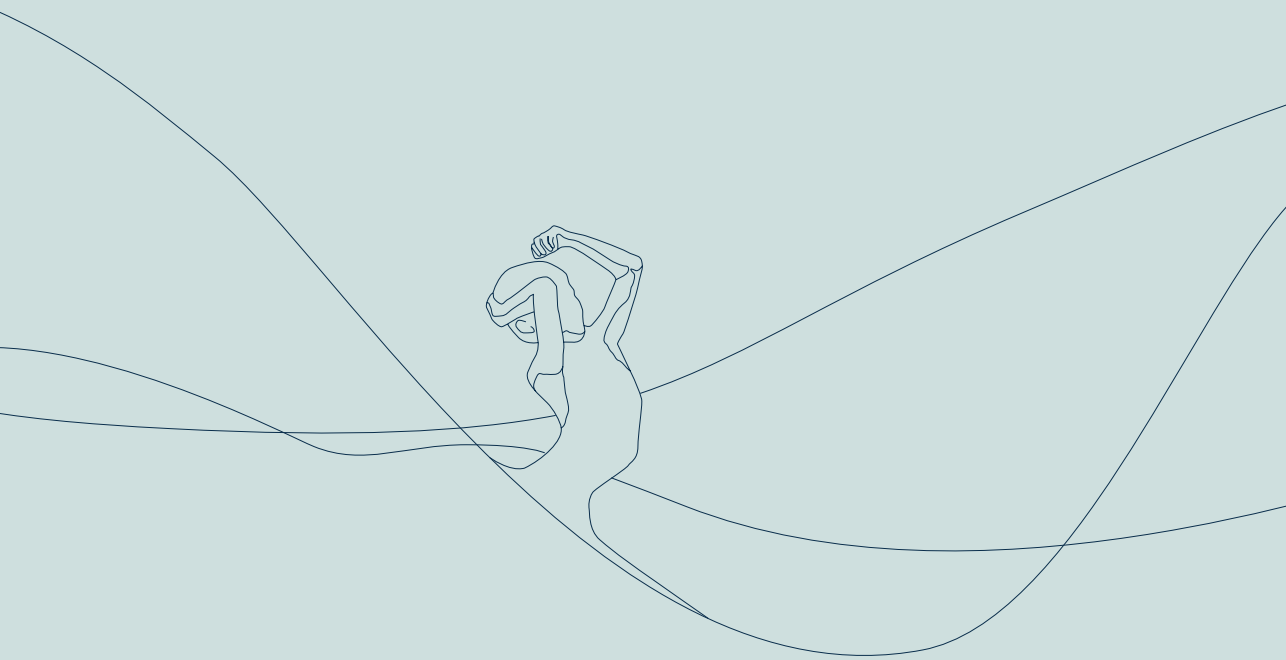

Crossing barriers: a multidisciplinary approach to children and adults with young-onset movement disorders

Chapter 2

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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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Dystonia

Part II