SUMMARY OF CHAPTERS

&

GENERAL DISCUSSION
Despite the increasing interest in childhood-onset movement disorders (MDs) including dystonia, the care for children and young adults with MDs remains a challenge (Chapter 1). This could be attributed to different factors. First, the assessment of pediatric MDs is often difficult due to the mixed phenotype, including both neurologic and non-neurologic features. [1] This may lead to under-recognition or misdiagnosis with consequences for diagnostic and therapeutic management.[2] Second, despite the fact that MDs are reported to be debilitating, the actual impact of pediatric MDs on health-related quality of life (HR-QoL) is still unknown.

Dystonia is, after tics, the second most prevalent MD in children and young adults, covering a wide range of (mixed) clinical pictures and etiologies.[3] Next to motor symptoms, non-motor symptoms (e.g. psychiatric disturbances, pain, sleep problems, and cognitive deficits) are increasingly recognized as important aspects of the dystonia phenotype.[4,5] In adult dystonia, non-motor symptoms correlate more strongly with HR-QoL than motor symptoms. Nevertheless, therapeutic interventions are still mainly measured and evaluated by their effect on motor symptoms.[6] In this perspective, it is important to elucidate the impact of both motor and non-motor symptoms in dystonic children and young adults.

In this thesis, the aims were to move forward in getting insight in how to optimize the care for young patients with MDs, in particular dystonia. The first part focused on the recognition and diagnosis of childhood-onset MDs. The second part aimed to explore the impact of motor and non-motor symptoms upon HR-QoL in young dystonia patients. The third part addressed the measurement of effectiveness of dystonia treatment.

The general discussion provides a summary of the chapters, after which the findings of the chapters will be integrated with existing knowledge. Finally, general considerations and future clinical and research perspectives will be discussed.

SUMMARY OF CHAPTERS

PART I – Recognition and diagnosis of childhood-onset movement disorders
Chapter 2 comprised the first retrospective and observational report of a multidisciplinary approach to the phenotypical and etiological diagnosis of children and young adults with childhood-onset MDs (n = 100), with a team consisting of a movement disorder specialist, a pediatric neurologist, a pediatrician specialized in metabolic disorders, and a clinical neuro-geneticist. In comparison to the diagnosis at referral, the team revised the MD
classification in more than half of the patients and was able to establish an etiology in 34% of the formerly undiagnosed patients (see examples as described in Chapter 2a and Chapter 2b). Despite the retrospective design and lack of a direct comparison to a ‘single expert approach’, these results highlight the potential benefits of a team approach to childhood-onset MDs.

Chapter 3 focused on the subpopulation of children with cerebral palsy (CP), the most common cause for pediatric MDs, such as dystonia and ataxia. Patients are categorized into primarily spastic, dyskinetic (dystonic), or ataxic CP. The pilot study aimed to evaluate whether clinicians are able to reliably distinguish these symptoms. Nine clinicians (pediatric neurologists, movement disorder experts, and physiatrists (rehabilitation physicians) labelled fifteen patients as primarily spastic, dystonic, or ataxic by looking at standardized video assessments. The results showed a ‘fair’ inter-observer and a ‘moderate’ intra-observer agreement, with frequent disagreements in the distinction between dyskinesia and spasticity. These data may highlight the difficulties that clinicians may experience by striving to obtain uniform and reproducible phenotypic assessments.

PART II – Impact upon health-related quality of life

Children with inborn errors of metabolism (IEM) represent an interesting sub-group of childhood-onset MDs. IEM are regularly diagnosed in children with MDs as part of a complex clinical picture. Chapter 4 assessed the type and impact of MDs in children with IEM on HR-QoL and adaptive functioning. Three MD specialists rated the presence and severity of MDs in twenty-four children with various IEMs. In addition, HR-QoL and adaptive functioning were assessed by standardized questionnaires. Dystonia, myoclonus and ataxia were most prevalent, and only a minority of patients (21%) received MD-targeted treatment. Impaired HR-QoL and adaptive functioning were reported on physical and psychosocial domains. MD severity negatively impacted HR-QoL and physical functioning, but not psychosocial functioning. Despite the small and heterogeneous sample, these results show the debilitating character of IEM and the importance of identifying MDs in patients in IEM, as they negatively impact HR-QoL.

In Chapter 5, a prospective and cross-sectional study evaluated the motor and non-motor determinants of HR-QoL in sixty children and young-adults with dystonic syndromes due to various etiologies, divided into non-lesional (primary) and lesional (secondary) etiologies. A multidisciplinary assessment quantified dystonia severity, motor functioning, pain, mood, and executive functioning. The measures were analyzed using a principal component
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analysis, resulting in three components (e.g. motor symptoms, mood and executive function, and pain). The association of these components with HR-QoL was assessed for the whole sample and the lesional and non-lesional subgroups. HR-QoL was related to motor symptoms as well as mood, executive function, and pain. For non-lesional dystonias, mood and executive function was the only significant contributor to HR-QoL. This was the first study to systematically explore HR-QoL in childhood-onset dystonia and the necessity to assess both motor and non-motor symptoms.

PART III – Effectiveness of treatment

With the increasing interest in the prevalence and impact of non-motor symptoms in dystonia, Chapter 6 systematically reviewed the effect of deep brain stimulation of the globus pallidus internus (GPi-DBS) upon these symptoms. Fifty-two studies were included, of which three were randomized clinical trials. Results were mainly based on case series and reports with non-motor symptoms as secondary outcomes and should therefore be interpreted with caution. GPi-DBS is likely to be beneficial in terms of pain relief, whereas it does not have a major impact upon mood, anxiety, and cognition. In contrast to motor outcome, the effect upon non-motor symptoms seems more stable across the entire spectrum of lesional and non-lesional dystonic syndromes but this has not been studied systematically.

Chapter 7 aimed to measure the effect of GPi-DBS differently from the current standard of changes in dystonia severity. In a prospective pilot in fifteen children and adults dystonia, dystonia severity was measured with the Burke-Fahn-Marsden dystonia rating scale. Additionally, individual priorities in daily life were identified and changes in the performance and satisfaction assessed before and one-year after DBS. The priorities varied greatly between patients. Results revealed a good motor response (>20% change in dystonia severity) coincided with an improvement on priorities. A significant improvement in priorities was also reported in four out of seven patients with an only limited motor response. Despite the small study sample, these results may illustrate the valuable insight that may be derived by using that a patient-oriented approach to measuring GPi-DBS effectiveness.

INTEGRATION OF FINDINGS

Tackling the complexity of care for childhood-onset movement disorders

Reliable recognition of childhood-onset MDs, including dystonia, is of crucial importance for targeted and individualized therapeutic strategies. Despite clear operational definitions,
clinical differentiation between MD types remains difficult.[1–3] In addition, childhood-onset MD patients frequently present with a mixed clinical picture, involving developmental, neurological, and non-neurological features.[1,10] In current practice, this results in an important percentage of young patients that are insufficiently diagnosed and treated.[1–3]

A multidisciplinary team approach (Chapter 2) may be a promising way to tackle the complexity of care for young patients with MDs for three important reasons. First, a multidisciplinary can approach the patient from various perspectives. In line with this, a multidisciplinary approach has been proven to be beneficial in other heterogeneous childhood disorders, such as epilepsy and neurovascular disorders.[11,12] A possible explanation could be that a combined approach allows a direct and ‘on the spot’ discussion regarding the phenotype. Agreement on the MD phenotype is of great importance as there is no gold standard for the clinical diagnosis. Discussion led to consensus on the phenotype in all patients in our study (Chapter 2). This is in contrast with the repeatedly reported only slight to moderate agreement achieved when clinicians individually phenotype MD patients (Chapter 3).[13–15] In a challenging and heterogeneous young-onset MDs population, it is essential to strive for a higher inter-observer agreement to improve diagnosis and management.

In addition to adequate phenotyping, recent advances in next generation sequencing (NGS) have resulted in an improved identification of the underlying etiology. NGS has provided clinicians with a rapidly expanding number of new causative genes for childhood-onset MDs. Still, a close collaboration between clinicians, clinical geneticists, and genome laboratory staff is essential for the selection of the right diagnostic strategy, a correct interpretation of genetic results, and dedicated counselling.[10,16,17] A team approach greatly facilitates this cooperation, leading to well-informed patients and caregivers and a higher diagnostic yield.

Finally, a multidisciplinary approach for complex MDs is time and cost-effective compared to standardly provided care where patients are seen by different specialists subsequently. The parallel strategy, with agreement upon phenotype and a diagnostic strategy being reached in only one clinic session may, therefore, reduce the significant burden for patients and their families, and reduce costs for our health care systems as well.

**Motor symptoms in childhood-onset dystonic syndromes**

The majority of the adult-onset dystonia patients suffer from an idiopathic, isolated, and focal form of dystonia with clearly delineated etiological or clinical categories, enabling
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clinicians and researchers to study relatively homogeneous clusters of patients.[16] Childhood-onset dystonia covers a broad spectrum of various etiologies (Chapter 5), and a single etiology may still lead to a variety of different phenotypes (Chapter 3 and Chapter 4). This results in heterogeneous clinical pictures, which are difficult to diagnose.[1,18]

Of the clinical syndromes, cerebral palsy (CP) is the most common cause of dystonia in childhood. CP is defined as a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.[19] The most common underlying cause is perinatal asphyxia, resulting in damage of the brain structures with a high metabolic demand, such as the cerebral cortex, cerebellum and basal ganglia. Due to the involvement of the cerebro-cerebellar-basal ganglia motor network, it is not surprising that CP often presents with a mixed motor disorder phenotype, including spasticity, dystonia, and ataxia.[19] During follow-up and surveillance, the motor symptom features that dominate the clinical phenotype are often the first considered targets for pharmacological and surgical treatment.[20,21]

Our results revealed that the phenotypic inter-observer agreement on the main symptom is only moderate. Even experienced clinicians experience difficulties in discriminating between spasticity and dystonia (Chapter 3). This is in line with previous literature reporting on the challenges of recognizing MDs such as dystonia and ataxia in mixed phenotypes.[1,18,22] Altogether, these findings underline the problematic clinical demarcation between spasticity, dystonia, and to a lesser degree, ataxia.[7]

Our study used video recordings rather than ‘real time’ neurological examinations. It is not possible to conclude whether the use of videos might have contributed to the high level of disagreement. Interestingly, the use of videos is broadly accepted to measure symptom extent and therewith effect of treatments in interventional studies.[23] Despite the small sample, our results provide a warning against the reliability of videos to measure and evaluate symptom severity in mixed phenotypes, such as children with CP.

**Non-motor symptoms in childhood-onset dystonic syndromes**

Non-motor symptoms include pain, depressive and anxiety symptoms, sleep disorders and cognitive deficits and these symptoms have been increasingly reported in adult-onset, isolated forms dystonia.[5,24,25] Our cross-sectional study in sixty children and young adults with dystonic syndromes (Chapter 5) showed results in line with those in adult-on-
set dystonia. Patients and/or their caregivers reported a severe level of pain in 33% and depressive and/or anxiety complaints in 41% of patients. In adult dystonia patients, there is growing evidence that the non-motor symptoms are part of the dystonia phenotype, rather than due to the burden of living with a chronic disease.[24,26,27] Despite the fact that the our study cannot answer this difficult question, the reported high prevalence supports the need for a further systematic evaluation of non-motor features in children and young adults with dystonic syndromes.

Health-related quality of life determinants in childhood-onset dystonic syndromes

Health-related quality of life has emerged as a meaningful way to measure the impact of a disorder upon physical and psychosocial domains of functioning. Chapter 5 showed a significantly impaired HR-QoL children and young adults with dystonic syndromes associated with both motor and non-motor domains of functioning. In patients with lesional or ‘secondary’ forms of dystonia the motor functions as well as non-motor functions are significant contributors to an impaired HR-QoL. This is in line with the impaired HR-QoL found in children with IEM and movement disorders (Chapter 4). However, for patients with non-lesional dystonia or ‘primary’ dystonia syndromes, mood and executive functioning were the only variables correlating with HR-QoL. This is an important finding as most intervention studies in dystonia primarily focus on minimizing the motor features rather than non-motor features of dystonia. Our study was the first to systematically assess HR-QoL and its determinants in young patients with dystonic syndromes and, once again, stresses the importance of a systematic evaluation of these non-motor symptoms.[24,28] The findings emphasize the necessity for more personalized management, tailored to the individual motor and non-motor needs of the dystonia patient in order to improve HR-QoL.

Measuring the effectiveness of treatment in dystonia

As mentioned above, in most studies performed so far, effectiveness of interventions in dystonia patients are primarily measured by a reduction in motor symptoms (Chapter 6).[2,16,23,29,30] This is in spite of the increasing knowledge regarding the importance of non-motor features and the fact that it is not clear to what extent a reduction in dystonia reflects meaningful improvements in the daily life of patients.[23] Moreover, it is important to realize that video-recordings might be inadequate to rate mixed motor phenotypes with spasticity (Chapter 5).[31] Altogether, these data may highlight the necessity to use an alternative approach to measure the effect of interventions.
A relatively well studied intervention in dystonia is DBS of the globus pallidus internus (GPI-DBS). Our systematic review summarized non-motor outcome (e.g. pain, psychiatric issues and cognition) of GPI-DBS (Chapter 6). Although mainly based upon results gathered from case reports rather than randomized clinical trials, there were notable results to be discussed.

An important conclusion is that pain is likely to be relieved by GPI-DBS in both non-lesional and lesional forms of dystonia. In addition, a dissociation in dystonia and pain relief after DBS was repeatedly reported and this may underscore the possible role of basal ganglia in the central pain network next to the motor and behavioral networks. [32] Regardless of the underlying mechanism, therapeutic evaluations of dystonia interventions should include pain evaluation, as this is the most frequently reported complaint. [5] By evaluating both pain and motor outcomes after DBS, one may obtain also obtain a more qualitative insight in the effects of DBS, from the patient’s point of view.

Mood, anxiety and, cognitive issues seem to stay relatively stable after the application of GPI-DBS in dystonia (Chapter 6). This mostly accounts for patients with no to mild psychiatric and cognitive issues. Only two case series included patients with a moderate to severe depression before the operation, showing a mild improvement. [33,34] It is, however, not clear whether reported changes in mood, anxiety, and cognition are secondary to symptom relief, a direct stimulation effect, or alterations in medications. The need for a more systematic evaluation of non-motor response of GPI-DBS is desirable, particularly when looking at the significance of these symptoms for disease burden and HR-QoL.

Our prospective pilot study aimed to measure the effect of GPI-DBS with a more patient-centered outcome (Chapter 7). Changes in individualized sets of functional priorities were compared to motor responses in fifteen dystonia patients. The pre-operatively set priorities substantially varied between patients reflecting the heterogeneity of the individual patients. The results show that a good motor response generally coincides with an improvement on functional priorities, but in half of the patients with an insignificant motor response, important changes on self-set priorities also were seen. Although based upon a small sample, these data may implicate that a motor response alone is insufficient to measure the true efficacy of interventions such as DBS in dystonia. When trying to improve the HR-QoL of a patient, it appears more effective to target the goals that are important for patients.
GENERAL CONSIDERATIONS

Selection of patients
The purpose of the thesis was to gain insight in the recognition, diagnosis, and impact of hyperkinetic MDs in children and young adults, with a special focus on dystonia. A careful patient selection is of great importance, with homogeneous patient samples being the most ideal situation from a research point of view. Our patient samples revealed that the population of young-onset MDs and dystonic syndromes is quite heterogeneous. This is also illustrated by the heterogeneity in underlying disorders and diagnoses, although, selection according to etiology (Chapter 3 and 4) or main symptom (Chapter 5 and 7) is unlikely to solve this problem. In addition, the frequently mixed clinical picture makes it almost impossible to study one isolated MD without interference of other MDs and/or (non-)neurological features. To enable studying more homogeneous groups, international multi-center trials are needed. Additionally, an alternative approach might be to accept the clinical reality of heterogeneity and focus on the individual needs of the patients.

Selection of measures
It is important to consider that most rating scales are insufficiently validated in children. The Burke-Fahn-Marsden dystonia rating scale (used in Chapter 5 and 7) is not validated for children and combined dystonia, and the Gross Motor Function Measure and the Melbourne Assessment of Upper Limb Function (used in Chapter 5) were originally developed for children with primarily spastic forms of CP. In spite of this, most of them were previously used in children and young adults with dystonic syndromes.[35,36] In addition, the application of movement disorder rating scales can be limited regarding potential floor or ceiling effects, implicating that potential clinical alterations in the least and most severely affected patients are not measured by the scale. In this perspective, our data can serve as a basis for future studies, in order to elucidate the presence of motor and non-motor symptoms in children and young adults with dystonia, to a further extent.

FUTURE DIRECTIONS

To a more consistent phenotype
The recognition of MDs in children and young adults is challenging, because of the frequent complex clinical pictures and the lack of a gold standard in the clinical diagnosis. This can largely explain why inter-observer agreement between clinicians is insufficient. To facilitate recognition, a more transparent way of phenotyping MDs could be helpful (e.g.
make clinicians speak the same language regarding involuntary movements), which can be further supported by qualitative and quantitative studies.

Qualitatively, exploring the approach of the individual clinician to MD patients may reveal which aspects of the neurological examination are predominantly used, and how this differs between clinicians. A subsequent discussion leading to consensus may result in a more consistent approach to MD patients. A team approach to complex young-onset MDs facilitates such direct discussion, the surplus of a team approach in comparison to a single expert should be compared to find out whether this leads to a significant higher diagnostic yield and better management of patient.

In addition, quantifying characteristics of MDs can help to distinguish between symptoms. Available technological support systems can measure speed, direction and velocity of involuntary movements in combination with EMG registration. Integrating these quantifiable variables with clinical knowledge, may lead to the realization of a more consistent definition of MDs. This hypothesis has led to the initiation of the ‘Next Move in Movement Disorders’ project (NEMO). NEMO is a collaboration between the movement disorders expertise center of the University Medical Center Groningen and artificial intelligence, and comprises a computer-based learning approach in which MDs will be quantified. This quantification of MDs may lead to a more consistent phenotypical classification.

To a broader (non-)motor phenotype of dystonia
A multidisciplinary approach to young patients with dystonic syndromes is essential to obtain a more holistic picture of the impact of the disorder on daily live and functioning. In contrast to the current approach, which mainly targets motor symptoms, it is advisory to explore the impact of non-motor symptoms upon the perceived HR-QoL as well. In addition, a systematic evaluation of both motor and non-motor symptoms may lead to an increasing insight into the pathogenesis of dystonia. Hopefully, future studies also including neuro-imaging (e.g. functional MRI, PET scans), may address this point further.

A broader phenotype can also be interpreted as looking further into patients' symptoms as well as focusing on functioning. A patient is more than a cluster of symptoms, and one symptom may affect each individual patient in a totally different manner. Careful assessment of daily priorities of the individual, how these are affected and how care should be directed towards these priorities must be an integral part of the multidisciplinary approach to dystonic syndromes.
In childhood-onset dystonia, a multidisciplinary approach requires a broad-based team, including a neurologist, psychiatrist, physiatrist (rehabilitation physician) and allied health professionals (neuropsychologist, physiotherapist, occupational therapist and speech and language therapist). Such a multidisciplinary approach may seem costly; however, it could also be more cost-effective than current management. For instance, one could speculate that ‘serial’ referrals, i.e. from one caregiver to the next, could impair effectiveness. In this light, it could be of interest to compare the current care with a multidisciplinary approach, in terms of costs, patient satisfaction and outcome.

To a patient-centered management
Like every other human being, a dystonia patient is unique with his/her own priorities in daily life and functioning that are of crucial influence upon the perceived HR-QoL. Therefore, targeting and improving these individual priorities should be the main treatment goal.

A patient-centered management model with the identification of priorities in daily living has already led to the formation of new research projects. For instance, in our cohort, patients with generalized dystonia and their caregivers repeatedly reported challenges in finding a suitable wheelchair for children with a generalized dystonia. Because of their need for stability when sitting on the one and being able to move involuntary on the other side. Current wheelchairs only provide one or the other, highlighting the need for the development of a dystonia-proof wheelchair. A multi-center study has been initiated to try and tackle this problem. By continuing to systematically assess the everyday problems of patients, more patient-driven projects are likely to follow.

As a clinician, our primary aim is to improve our patients’ quality of life as much as possible and therefore management should be targeted at what patients report as important for their HR-QoL. In line with this, the effect of therapies should be primarily measured by evaluating changes in these priorities. When focusing on GPI-DBS, the effect in lesional dystonias is reported to be variable and frequently disappointing.[37] However, DBS effectiveness is still primarily measured by motor outcome parameters alone, even considering the fact that motor symptoms play a limited role in the perceived HR-QoL. Measuring the GPI-DBS effect in terms of reducing pain, one of the most and frequently reported complaints in dystonia patients, may elucidate a different treatment effect. Future investigators may hopefully consider a more holistic, patient-centred approach, so that outcome measures also reflect the perceived gain of the intervention in the benefit of the patient.
Patients with childhood-onset MDs form a highly heterogeneous population with respect to the diagnosis and care. This thesis showed that the recognition of MDs in young patients is challenging, but a dedicated team approach, involving neurologists, pediatricians and clinical geneticists, can lead to a higher level of agreement on the clinical phenotype and a subsequent higher diagnostic yield and improved therapies. Childhood-onset MDs have an important impact upon the perceived HR-QoL. In patients with dystonic syndromes, this impaired HR-QoL is influenced by both motor and non-motor symptoms, such as mood, anxiety, cognitive function and pain. The primary aim in the management of patients is to improve HR-QoL as perceived by patients. Therefore, the effect of interventional studies in dystonia patients should not only focus on the motor outcome. This thesis showed that for Gpi-DBS a more personalized outcome in dystonia patients may show meaningful improvements despite a seemingly disappointing motor response. A multidisciplinary approach to both diagnosis and management of patients with childhood-onset MDs is strongly recommended.
REFERENCES


Summary & Discussion