GENERAL INTRODUCTION
CHAPTER 1

This thesis focuses on neurological movement disorders (MDs) in children and young adults, with special attention to hyperkinetic MDs, including dystonia. Childhood-onset MDs are a relatively new area of specialization within the field, differing considerably from those manifesting in adulthood. This thesis on childhood-onset MDs deals with the following topics: 1) how do we recognise them, 2) what is their impact on health-related quality of life (HR-QoL) and finally, 3) how can we measure the effect of treatment interventions.

Neurological MDs comprise a spectrum of clinical syndromes leading to a disruption in the execution of movements. They are subdivided into hyperkinetic (excess in movements), hypokinetic (decrease in movements) and ataxia (disturbance in the execution of coordinated actions). The exact pathophysiology of MDs is not fully clear, but the general consensus is that a dysfunctional signalling within the cortico/basal-ganglia/cerebellar network is involved. The subcortical nuclei and the cerebellum are densely connected with cortical areas of the brain, fulfilling a prominent role in motor control as well as in executive functioning and regulation of emotion and behaviour.[1,2] A disruption or dysfunction within the networks may therefore induce both motor and non-motor symptoms.

**CHILDHOOD-ONSET MOVEMENT DISORDERS**

There are three main elements in the approach to childhood-onset MDs that are characterized by three questions. The first is: ‘what symptom(s) do we see?’ This leads to two other, namely ‘what is the cause?’ and ‘what is the best treatment?’.

When referring to ‘what do we see?’, it is important to realize that childhood-onset MDs are considerably different from adulthood-onset manifestations. First, in childhood-onset MDs symptoms occur in a developing nervous system, which is important for the interpretation of the clinical picture. Immature motor behavior in healthy children is known to mimic features of MDs, such as ataxic or dystonic MD-like characteristics which are physiologically present until the age of twelve and sixteen years respectively.[3–7] Second, the prevalence of the MD subtypes differs between childhood and adulthood-onset MDs. [5] Hypokinetic MDs, such as parkinsonism, are rarely observed in children. Childhood hyperkinetic MDs are more common and can be classified as tics, dystonia, chorea, myoclonus, tremor and stereotypies, and form the majority. Third, childhood-onset MDs are often embedded in a complex clinical picture, not only involving mixed phenotypes with multiple MDs, but other neurological and non-neurological features as well (e.g. mental retardation, seizures, dysmorphias or deafness).[5]
With regards to the question ‘what is the cause?’, identification of the underlying etiology in childhood-onset MDs is of great importance. For instance, in treatable MDs, early adequate therapeutic intervention may minimize or even prevent the onset of symptoms.[8] In addition, identification of the cause will allow proper prognostic and genetic counselling of the patients and their families. The rapidly developing diagnostic techniques have led to a large, yet still expanding number of etiologies that can cause childhood-onset MDs in the acquired (e.g. ischemic, infectious, auto-immune, toxic, drug-related, or structural causes) and the genetic domain (e.g., metabolic, mitochondrial or neurodegeneration).[5,8,9]

The selection of the optimal treatment is the third aspect in the care for patients with childhood-onset MDs. Despite increasing pathophysiologic insights, treatment is mainly targeted at the presented symptomatology.[9] Randomized controlled interventional studies are lacking and existing literature, suggests that all MDs may require a different approach regarding pharmacological or surgical treatment.[9]

Altogether, these aspects may impose unique challenges to the doctors, parents and caretakers of patients with childhood-onset MDs. This highly heterogeneous population of patients warrants a broad expertise regarding (ab)normal development, MD characterization, interpretation of concurring neurological and non-neurological features and the wide spectrum of possible acquired and genetic etiologies.[10] In daily practice, this complexity may lead to diagnostic delays and uncertainty for the patients and their families. Analogous to other complex neurological syndromes (including epilepsy, neurovascular- and neuromuscular disorders), a multidisciplinary approach could be beneficial for the diagnostic procedure, treatment and surveillance of patients.[11-13] This enables clinicians from different backgrounds to combine their expertise in order to optimize the diagnosis and management of patients with complex disorders.

**THE CONCEPT OF DYSTONIA**

Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, abnormal posturing, or both.[14] Oppenheim introduced the term in 1911 to describe a clinical picture in four children.[15] Between then and now, it has become clear that dystonia is an umbrella term covering a broad range of syndromes secondary to acquired, hereditary, and idiopathic causes.[14]
The multifaceted nature of dystonia requires a clinical and etiological classification system. The first distinguishing clinical parameter is ‘age of onset’. In addition, patients are classified according to the anatomical distribution of symptoms (focal to generalized), temporal pattern (disease course and variability over the day), and the presence of associated features including other MDs and neurological or systemic manifestations. Etiology subdivides patients according to nervous system pathology (degeneration, structural lesions or no pathology) and mode of inheritance (inherited, acquired or idiopathic).

**Childhood-onset dystonia**

After tics, dystonia is recognized as the second most common childhood-onset MD. In contrast to adulthood-onset dystonia, childhood-onset dystonia has a tendency to spread to generalized dystonia. Moreover, as already explained, childhood-onset dystonia is often presented as a mixed and complex phenotype with additional (non-) neurological features. Etiologically, childhood-onset dystonia is more likely to have a detectable acquired or genetic cause compared to the mainly idiopathic forms of adult dystonia. The most common cause is hypoxic-ischemic encephalopathy (e.g. cerebral palsy; CP). In addition, there are numerous other etiologies including metabolic diseases. The wide spectrum of possible etiologies (genetic heterogeneity), and the fact that one etiology can lead to different clinical pictures (phenotypic pleiotropy), gives rise to a very heterogeneous patient population of childhood-onset dystonia.

**The phenotype of dystonia**

The term phenotype is derived from the Greek words ‘phainein’ (to show) and ‘typos’ (type) and refers to observable traits of a person, including appearance, development, and behavioral traits. The phenotype is the result of the genotype, environmental factors, and the interaction between the two, resulting in both motor and non-motor traits.

**Motor symptoms**

Accurate phenotyping (what do we see) of young patients with dystonia is essential for diagnosis and treatment aspects. A careful medical history and recognition and correct classification of the symptoms are crucial steps in search of the underlying etiology. Moreover, management of dystonia predominantly involves symptomatic treatment, targeted at the symptoms. Thus, irrespective of whether the etiological diagnosis is known, reliable phenotyping has consequences for the selection of an adequate treatment strategy.
However, the recognition of dystonia can be challenging. In adult dystonic patients, it has been indicated that MD experts only moderately agree on the classification of hyperkinetic MDs.\[19,20\] In children, such inter-observer study data on MD recognition are sparse. One pediatric pilot study reported a moderate agreement on the phenotypic recognition of early-onset ataxia.\[21\] Regarding the ongoing dispute that pediatric dystonia is often mistaken for spasticity in children with CP, one could anticipate that the agreement on pediatric dystonia recognition is limited too.\[22\] These findings give rise to the question whether clinicians can reliably distinguish MD symptoms and whether MD specialists speak the same language when they describe a MD phenotype in children.

**Non-motor symptoms**

Although dystonia is primarily defined by the distinct motor symptoms, there is an increasing interest for non-motor symptoms associated with dystonia. These comprise psychiatric disturbances, pain, sleep problems, and cognitive deficits.\[23,24\] Interestingly, it is now known in other basal ganglia disorders such as Parkinson’s or Huntington’s disease that non-motor symptoms are an integral part of the disease phenotype. In dystonia, the presence of non-motor symptoms is also not entirely explainable as a consequence of the motor symptoms.\[25\] In adult dystonia, this is underscored by only a weak relationship between non-motor and motor symptoms, as well as by the fact that non-motor features may already become manifest prior to motor features.\[23,24,26\] A possible explanation could be provided by the network connections between the basal ganglia, prefrontal cortex, hippocampus, limbic and paralimbic cortices.\[2\] These circuits underlie complex behavior, such as executive functioning and emotion regulation. In this perspective, it is important to elucidate all aspects of the dystonic phenotype, including the mixture of motor and non-motor features.

**Health-related quality of life in dystonia**

Over the past decades, self- or parent/proxy-reported HR-QoL has emerged as a meaningful way to measure the impact of a chronic condition upon physical and psychosocial domains of functioning.\[27\] To date, knowledge regarding HR-QoL in childhood-onset dystonia is scarce. Adulthood-onset forms of focal and generalized dystonia are known to negatively impact the HR-QoL.\[25,28\] Interestingly, the association between HR-QoL and dystonia severity is only modest. This could be explained by the fact that non-motor features, such as pain and psychiatric issues, are at least as important for the HR-QoL as motor features. Thus, recognition of non-motor symptoms is important for the perceived disease burden and quality of life of the dystonic patient.\[25\]
HR-QoL studies solely focusing on childhood-onset dystonic syndromes are lacking so far. In children with tic disorders, non-motor features have been shown to affect the HR-QoL. [29,30] In addition, it has been shown that children with cerebral palsy (CP), the most common cause of childhood dystonia, may suffer from a lower HR-QoL than children with other chronic childhood disorders.[31] Altogether, in childhood-onset dystonia, these data may implicate that systematic assessment of both motor and non-motor symptoms could contribute to the treatment and clinical surveillance of the patient.

**EFFECTIVENESS OF TREATMENT IN DYSTONIA**

Over the past several decades, pharmacological, surgical, and paramedical treatment options have been developed for dystonia. These treatment options mainly focus on diminishing motor symptoms and their efficacy is mainly assessed with dystonia rating scales (e.g. Burke-Fahn Dystonia Rating Scale (BFMDRS)).[32-34] One of the limitations of these scales is that they do not assess non-motor symptoms. This may implicate that not all therapeutic effects of an intervention would be measured when the BFMDRS would be the solitary outcome. Until now, it is still unclear how motor symptom reduction can be translated in terms of HR-QoL or other aspects of daily functioning important to patients and their caregivers. Furthermore, in a heterogeneous population such as childhood-onset dystonia, one might question whether a single rating scale can adequately capture meaningful changes for the full range of syndromes.[35,36]

A suitable example in the abovementioned discussion is deep brain stimulation of the globus pallidus internus (GPI-DBS). GPI-DBS comprises the neurosurgical insertion of one unilateral or two bilateral electrodes into the GPI nucleus of the basal ganglia. A subcutaneously located neuro-stimulator generates regular pulses from the electrodes. Although the exact mechanism of GPI-DBS is unknown, it has emerged as a safe treatment option. In patients with isolated dystonia, it exerts an overall good response (40-90% symptom relief), but in patients with acquired or lesional forms of dystonia, the response is more variable. Remarkably, in spite of the significance of non-motor symptoms in dystonia, the effect of GPI-DBS on these symptoms is not well established.

There are repeatedly reported discrepancies between the ‘objective’ effect measured with the BFMDRS and the ‘subjective’ improvement experienced by patients after GPI-DBS, especially in lesional or secondary dystonia.[37] For example, a minimal BFMDRS change in a patient being able to independently steer an electric wheelchair after DBS. Despite
limited rating scale improvement, it is important to realize that a functional effect may still be important for the quality of daily living. Furthermore, the final outcome should be interpreted from both motor and non-motor changes.

To elucidate the real clinical effect of interventions, it may be important to re-define outcome parameters to establish effectiveness -- for example, by setting individual treatment goals, which is already routinely done in rehabilitation medicine. This does not only provide a unique insight into the priorities of the patient, but also helps the clinician to select the most appropriate treatment strategy.[38]

**OBJECTIVES**

This thesis aims to contribute to the clinical care of patients with childhood-onset MDs through the assessment of the recognition of the phenotypes, the impact of motor and non-motor features upon HR-QoL, and the evaluation of meaningful outcome parameters.

In the first part, Chapter 2 reports how a multidisciplinary approach may facilitate diagnosis and treatment of complex MDs in children and young adults. Chapter 2a and 2b serve as examples to underscore the benefits of this multidisciplinary approach. Chapter 3 studies how clinicians describe and agree with each other and themselves on phenotyping children with CP, the most common cause of childhood-onset dystonia.

The second part of the thesis focuses on the impact of childhood-onset dystonic syndromes upon HR-QoL. In Chapter 4 the impact of MDs in children with inborn errors of metabolism (IEM) on HR-QoL and adaptive functioning is discussed. Chapter 5 provides a systematic evaluation of motor and non-motor symptoms and their impact on HR-QoL in patients with childhood onset dystonia.

The third part focuses on the efficacy of GPi-DBS as treatment strategy in patients with dystonia. Chapter 6 comprises a systematic review of the existing literature regarding non-motor outcome of GPi-DBS. Finally, Chapter 7 addresses the GPi-DBS treatment effect by elucidating how different outcome parameters (dystonia rating scale scores and patient-set priorities) can influence the interpretation of effectiveness.
REFERENCES


PART I

RECOGNITION AND DIAGNOSIS OF CHILDHOOD-ONSET MOVEMENT DISORDERS