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Motor and non-motor symptoms in cervical dystonia

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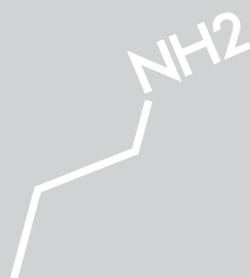
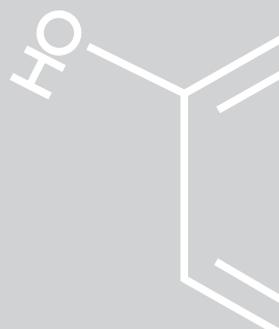
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CHAPTER 1

General Introduction

1



Historical background

Cervical dystonia (CD) is a hyperkinetic movement disorder characterized by sustained or intermittent contractions of the cervical musculature, leading to abnormal neck postures. It is the most common form of adult-onset focal dystonia, with a prevalence ranging between 28-183 cases per million people [1].

The first official description of dystonia dates back to 1911, when the Berlin neurologist Hermann Oppenheim (1858-1919) described a patient with dystonia musculorum deformans (now called early-onset generalized dystonia) [2]. However, one of the first descriptions of cervical dystonia dates from the sixteenth century, when Felix Platerus (1536-1614) described a case of '*spasmi species, in qua caput in sinistrum latus torquebatur*' (a kind of spasm in which the head was turned to the left side) [3]. Since this first description, there has been a continuous debate about the origin of cervical dystonia, either being psychogenic or organic. The geste antagonistique, used by patients to correct the position of the head by simply touching the face or neck, was one of the strongest arguments in favor of a psychogenic cause. Stories about patients who developed 'mental torticollis' as a consequence of pleasurable stroking movements by their mother, or after losing their job or money, strengthened the idea of a psychological cause. This debate lasted until 1975, when David Marsden (1939-1998) argued for an organic cause during the International Symposium on Dystonia and the organic origin became generally accepted. Ten years later, in 1985, twelve CD patients were successfully treated with botulinum toxin (BoNT) in order to relieve the dystonic posturing [4]. Currently, 31 years after the first introduction of BoNT, BoNT injections are still the golden standard in the cervical dystonia management.

Non-motor symptoms

Although CD is defined by its motor symptoms, non-motor symptoms (NMS) are increasingly recognized as integral part of the phenotype of CD [5,6]. These NMS mainly include psychiatric co-morbidity, pain, sensory abnormalities, sleep and fatigue, but also less frequently described symptoms like dizziness and problems with sexual behavior. Of the non-motor spectrum of CD, most research has been conducted on psychiatric co-morbidity. The prevalence of psychiatric disorders in CD can reach up to 91.4%, compared to 35% in the general population [7]. This could logically be the consequence of living with a chronic, visible and disabling disorder. However, when comparing the prevalence of psychiatric co-morbidity with other chronic and visible diseases, CD patients still have a significantly increased odds ratio to develop psychiatric co-morbidity [8]. Moreover, psychiatric co-morbidity often manifests before the onset of motor symptoms, which favors the idea of a shared neurobiology of motor- and NMS in CD [6].

Studies on the incidence of other NMS in CD are very limited and showed contrasting results. A feeling of discomfort months before CD develops and altered pain pressure thresholds suggests influence of the sensory system [9]. The 'geste antagonistique' is

currently considered an important supportive symptom in CD and indicates involvement of disturbed sensory afferent input (feedback) in dystonia. In this respect, disturbed prediction of the sensory consequences of movement (feed forward deficit) has also been suggested to play a role in the pathophysiology underlying dystonia [10,11]. Existing studies on the incidence of sleep disturbances or fatigue are also limited with contrasting results. Sleep quality seems to be impaired, but this is at least partially influenced by psychiatric co-morbidity [12]. Fatigue is highly prevalent, but the most important predictors of fatigue in CD are still unknown [13].

In this thesis, we will first focus on the frequency and severity of NMS in CD patients, including psychiatric co-morbidity, fatigue and sleep disturbances. To that end, we propose a short clinically applicable NMS screenings list. Particular attention will be given to the onset of NMS in relation to both the onset of motor symptoms and the severity of motor symptoms, to distinguish between a primary and secondary symptom.

Health-related quality of life

Importantly, a few studies showed that NMS and especially the psychiatric comorbidity are the most important predictors of decreased health-related quality of life (HR-QoL) [14–16]. This finding emphasizes the importance of not only to focus on motor symptoms in daily practice, but also to pay attention to NMS. After 31 years of only treating motor symptoms with BoNT, more personalized medicine, including both motor- and NMS, could significantly contribute to a better wellbeing of CD patients. For this, a better knowledge of the prevalence and influence of specific NMS in CD is important, as well as forth going insight in the pathophysiology.

Pathophysiology

In the second part of this thesis, we will focus on the pathophysiology of CD. Until now, the pathophysiology of CD still remains largely unclear, although a few abnormalities in brain functions have been described. These abnormalities include sensory dysfunction, alterations of synaptic plasticity and loss of inhibition [17]. Sensory dysfunction relates to the mild sensory complaints of dystonia patients. It was shown that the ‘geste antagonistique’ modifies cortical EEG activity and globus pallidus local field potentials, even before actual touching the head [10]. Alterations of synaptic plasticity have been described in animal models and in patients with primary dystonia, and is characterized by a prevailing facilitation of synaptic potentiation. The third phenomenon, loss of inhibition, might be responsible for the excess of movement and the overflow phenomena in dystonia patients. Loss of inhibition is related to basal ganglia disorganization, with an imbalance between direct and indirect basal ganglia pathways [17]. Within the basal ganglia, the internal globus pallidus (GPi) appears to play a key role in the network underlying dystonia pathophysiology [17,18], which is also illustrated by the therapeutic effect of deep brain stimulation of the GPi for dystonia [18]. Disturbances in the direct and indirect basal ganglia pathways suggest involvement of basal ganglia neurotransmitter systems,

which is further strengthened by the absence of anatomical changes in the basal ganglia in CD patients. Dopamine, as one of these neurotransmitters, is known to play a key role in both hypokinetic and hyperkinetic movement disorders, and also acetylcholine is an important neurotransmitter involved in movement disorders like dystonia [19]. However, besides the role of dopamine and acetylcholine, serotonin is increasingly recognized for its possible role in movement disorders. In dopa-responsive dystonias, gene mutations directly affect the biosynthesis of monoamine neurotransmitters including serotonin. The role of serotonin in other forms of dystonia is less well known, but it may play a role in the pathophysiology as well. Moreover, within the substantia nigra, serotonergic neurons exert complex, mainly inhibitory effects on the dopaminergic system [20,21]. This interaction, associated with complex interactions of noradrenergic and cholinergic inputs [22], could contribute to the dystonia pathophysiology.

Involvement of the serotonergic system is well known in psychiatric disorders [8]. For many years, psychiatric disorders have been linked to serotonergic disturbances and psychoactive drugs often influence the serotonergic system [23]. As discussed above it is hypothesized that psychiatric symptoms are part of the dystonia phenotype with a shared neurobiology, so the psychiatric co-morbidity further supports a likely role of the serotonergic system in the pathophysiology of dystonia. Other NMS in CD like pain [24] and sleep disturbances [25] have also been related to serotonergic dysfunctions.

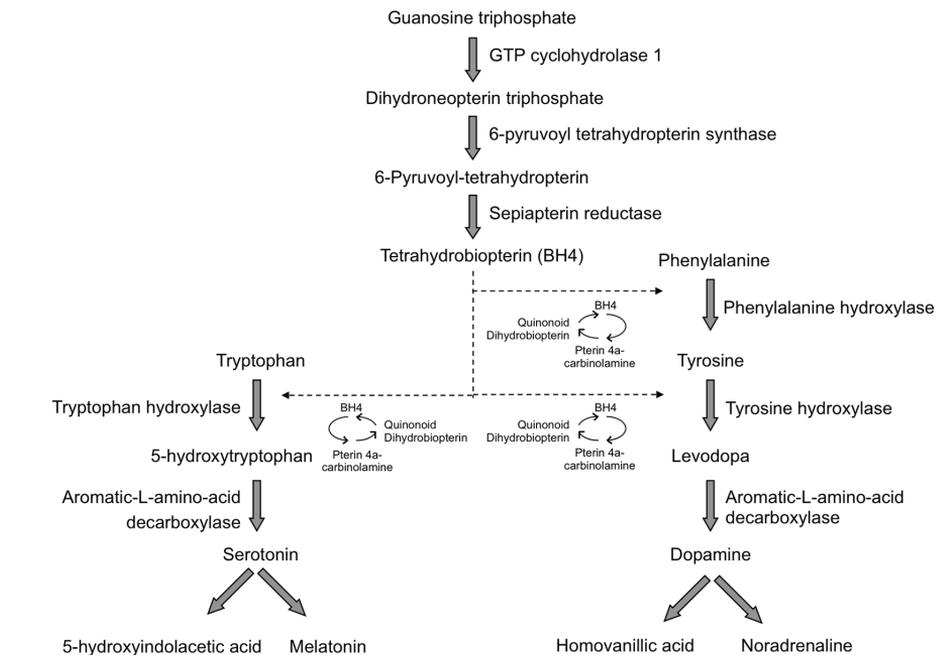
Serotonin

Serotonin, or 5-hydroxytryptamine, is synthesized from diet-derived tryptophan. In the brain, the rate limiting step is the conversion of L-tryptophan to 5-hydroxy-L-tryptophan (5-HTP) by tryptophan 5-hydroxylase 2 (Tph2). The second and final step is the conversion of 5-HTP to serotonin by aromatic L-amino acid decarboxylase (Figure 1). Once formed, serotonin is quickly transported into vesicles via the vesicular monoamine transporter 2 (VMAT2). Via exocytosis, serotonin is released into the synaptic cleft, where it can bind to at least eighteen different pre- and/or post-synaptic serotonin receptors. After release, the presynaptically located serotonin transporter (SERT) reuptakes serotonin back into the presynaptic neuron, where it is restored again, broken down by monoamine oxidase A (MAO-A) into 5-hydroxyindoleacetic acid (5-HIAA), or metabolized into melatonin in the pineal gland. The serotonin transporter is considered to be one of the most important regulators of the serotonergic system. It avoids desensitizing of the serotonergic receptors by regulating the amount of serotonin in the synaptic cleft [26].

In the brain, serotonergic neurons arise from the raphe nuclei in the brainstem. From these nuclei, 300.000 serotonergic projections reaches to various subcortical (basal ganglia) and cortical regions, as well as downward to spinal neurons. It serves many functions, like maintaining a circadian rhythm, the regulation of appetite and cognitive and autonomic functions. Furthermore, it's functioning is strongly age-related, with an increasing risk of problems with sleep, sexual behavior and mood in elderly people [26].

Figure 1

The metabolic pathway of serotonin and dopamine.



Investigating the serotonergic system by using positron emission tomography

An important technique explored in this thesis is PET, a nuclear medicine functional imaging technique. To conduct a PET scan, a radioactive isotope is incorporated into a biologically active molecule, thereby making a radiotracer, and administered intravenously. After injection, the radioisotope undergoes positron emission decay, whereby a positron is emitted. After travelling for a short distance (usually less than 1mm), the positron loses kinetic energy, decelerates, and then interact with an electron. The following annihilation between the positron and electron produces two 511 keV gamma rays moving in opposite directions. When the scintillator detectors in the PET camera detects these 2 photons at the same time (typically within 4 to 6 ns), a so-called coincidence detection took place. The detection line between these detectors is then called the line of response. A three dimensional PET image is eventually formed by combining the information from millions of these lines of responses using a process called image reconstruction. The reconstructed PET image then represents the distribution of the radiotracer over the body and/or within organs over time.

Several tracers for both presynaptic and postsynaptic receptors of the serotonergic system are available [27]. In our study, we used the [^{11}C]DASB tracer, which binds specifically to

one of the most important regulators of the serotonergic system, namely the serotonin transporter [28–30].

Moreover, a specific kinetic model can be used to describe the observed time activity curve of the tracer and information about specific tracer binding and/or relative cerebral blood flow (rCBF) could be derived from these kinetic models [31]. The method of rCBF measurement has been employed in studying the pathophysiology of dystonia [32], showing changes in cerebral networks involved in dystonia. In this thesis, we investigated differences in rCBF between CD patients and controls, and investigated whether such changes were related to motor and NMS.

Cervical dystonia treatment

Currently, there are no good (pharmaco)therapeutic options for CD or associated non-motor symptoms. Symptomatic treatment with oral medications like trihexyphenidyl and clonazepam could provide benefit, but the required high doses to reduce symptom severity are often accompanied by major disadvantages and are not effective in all patients. The most effective treatment currently is injections in dystonic muscles with BoNT to alleviate the dystonic posturing and pain. Unfortunately, this has only a partial and temporarily effect [33]. Moreover, BoNT treatment can be insufficient, contra-indicated, or technically difficult, especially in patients with antecollis. For these patients, surgical treatment with deep brain stimulation (DBS), thalamotomy or pallidotomy can be considered, but these treatment options are not effective in all patients and can also have rare but (major) disadvantages, such as bleeding or infection [34].

A better understanding of the role of serotonin could help to improve treatment, not only symptomatically but also to target the underlying pathophysiology. Aberrations of the serotonergic system, related to both motor- and NMS, could lead to more rational therapeutic strategies in CD by modulating the serotonergic system.

Aims and outline

The aim of this thesis was threefold. First, we systematically investigated the prevalence and severity of psychiatric co-morbidity (Chapter 2) and sleep disturbances and fatigue (Chapter 3) in a cross-sectional study in CD patients and controls. Attention was given to the onset of these symptoms in relation to the onset of motor symptoms and its influence on HR-QoL. Furthermore, we assessed the prevalence of a range of NMS using an extended NMS-questionnaire combined with the self-perceived impact of motor and non-motor symptoms in CD patients. We highlighted a limited number of NMS with a high impact on patient's life. This shortlist of NMS can easily be screened for in daily practice (Chapter 4).

Second, existing literature was reviewed to assess the current knowledge of involvement of serotonin on both motor- and NMS in patients with several forms of dystonia (Chapter 5).

The final aim was to perform [¹¹C]DASB PET in CD patients and controls to assess the role of central serotonergic functioning as well as changed relative cerebral blood in the pathophysiology of CD, including motor- and NMS. First, we describe the binding to the serotonin transporter in the brain and its relation with clinical characteristics in CD patients and healthy controls in vivo, as measured with [¹¹C]DASB and PET (Chapter 6). Second, derived from the same data, we calculated the relative tracer delivery to specific brain regions as compared to the reference region, to generate a measure of the relative cerebral blood flow (rCBF). We hypothesized that an abnormal rCBF pattern, as an index for abnormal regional cerebral activity, would add insight in the pathophysiology of CD concerning network changes involved in both motor and NMS (Chapter 7).

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