DYSTONIA AND PSYCHIATRIC DISORDERS

A pathofysiological connection?

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ABSTRACT:

BACKGROUND: Combination of dystonia and psychiatric diseases is 91.4% in cervical dystonia. Common psychiatric disease differ per form of dystonia. We hypothesize a pathophysiological connection between psychiatric disorders and dystonia.
OBJECTIVE: This exploratory review focuses on the basal ganglia, as literature indicates that its dysfunction is related to either psychiatric disease and dystionia.
RESULTS: Although no specific mechanism was found, indications for a pathofysiological connection were identified. These indications include damage to parallel loops in the basal ganglia involved with the two diseases, an effect on serotonin via dopamine, a similar location in the brain and a primary link between psychiatric diseases and Parkinson's disease, which is also a motor disease. To identify a pathophysiological connection, additional research may be needed on this topic, for example combining other motor and non-motor diseases and try to relate their disease mechanism to dystonia.
CONCLUSION: The exact pathophysiological relationship between dystonia and psychiatric disorders remains unclear. Several theories have been proposed, but more research is needed to further elucidate the roles of different brain circuits.

WHAT IS KNOWN: There is a large correlation between dystonia and psychiatric disorders.

WHAT IS NEW: There might be a pathophysiological connection between psychiatric disorders and dystonia. This connection can possibly be found in the basal ganglia or the secretion of neurotransmitters. Additional research is needed.

KEYWORDS: Dystonia, psychiatry, basal ganglia, neurotransmitters

Introduction

Dystonia is a neurological movement disorder. Although basal ganglia dysfunction is commonly considered to be involved, precise pathophysiologic mechanisms are still unknown. Dystonia occurs in different forms, such as primary (i.e. no other feature than dystonia is involved) and secondary dystonia, for example due to a lesion of the basal ganglia or use of medication. An important characteristic of dystonia is that muscles are continuously strained, as will be further explained in the functional anatomy part.

There is a high co-incidence of dystonia and psychiatric diseases, being mainly depressions and anxiety disorders. In cervical dystonia for example, co-incidence of any psychiatric disease has been reported to be up to 91.4%, compared with 35% in the general population[1]. Furthermore, some dystonic patients are diagnosed with more than one psychiatric disorder. An epidemiological study[2] that included 28 dystonic patients showed that of dystonic patients with a major depressive disorder, 3 out of 7 also had to cope with a generalized anxiety disorder.

The fact that dystonia and psychiatric disease often go hand in hand, may suggest similarities in the underlying disease mechanisms, because of possible interactions between the disease mechanisms. If there are similarities in both disease mechanisms it is important to find these for different reasons. First, this would increase general knowledge of doctors, patients and society. For example, better understanding of dystonia-related psychiatric diseases will enhance acceptation of patients in society, instead of regarding psychiatric symptoms of dystonic patients as a result of their difficulty to cope with dystonia in daily life. Advanced patient education increases quality of life of patients, because they know what to expect. Second, the perspective on dystonia can be changed. Dystonia used to be seen as a purely physical disease. More and more, research shows involvement of non-motor brain elements. Dystonia can be recognized faster, and thus treatment can be started earlier, for a better outcome. Third, treatment of dystonia can possibly be broadened to treatment of psychiatric diseases. When the underlying mechanism of dystonia and psychiatric disease is linked, this could be an opportunity to implement treatment of psychiatric diseases in treatment of dystonia. In this explorative review, we analyze current knowledge about the pathophysiological link between dystonia and psychiatric diseases, to answer the following question: what is the role of basal ganglia and neurotransmitter (dys)function in the occurrence of psychiatric disorders as a co-morbidity in dystonic patients? To address this question, we searched for studies on comorbidity of psychiatric disorders and dystonia together with basal ganglia function and different neurotransmitters to summarize current knowledge on this topic.

Functional anatomy of the basal ganglia

In order to understand the mechanism of dystonia, we should be aware of the functional anatomy of the basal ganglia, along with the several existing circuits that connect it with the different parts of the brain. Knowledge on the basal ganglia can also give insight in the mechanism that plays a role in several related diseases with motor and non-motor symptoms, as will be discussed later in this review.

Throughout the past, the classification of dystonia shifted from being a psychogenic disorder towards an organic movement disorder[3]. Nowadays, dystonia is defined as "a syndrome of involuntary sustained or

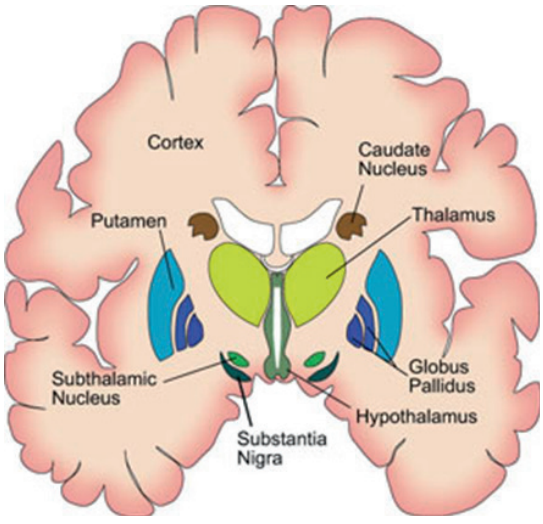

Figure 1 *Schematic representation of the major nuclei within the basal ganglia[16]. The different nuclei of the basal ganglia are spread through the brain, but mostly located in the inner part. The putamen, nucleus caudatus and substantia nigra form the outer border of the area where the basal ganglia are lain. The hypothalamus forms the center of this area. Basal ganglia are symmetrical.*

intermittent muscle contractions leading to twisting or repetitive movements or abnormal postures"[4]. The proposed core mechanisms of dystonia involve two principles: over-contraction of the muscles that normally are used for movements and over-flow contraction of muscles that could antagonize these primary movement muscles[5]. But what kind of mechanism is causing these abnormal muscle contractions? Research indicated that the basal ganglia play an important role in the onset of dystonia[6]. The basal ganglia are a group of nuclei that are located deep within the cerebral hemispheres, known for their role in movement control. The different nuclei of the basal ganglia are divided into functional subdivisions (Fig. 1). The caudate nucleus, nucleus accumbens and the putamen together form the corpus stratium. Two other structures of the basal ganglia are the external and internal globus pallidus and the subthalamic nucleus. Finally, the substantia nigra has a major influence on basal ganglia function, via its dopaminergic projections. Dopamine is the driving force of the basal ganglia and therefore needed for normal functioning of the basal ganglia[6]. Shortage or absence of dopamine is linked with movement abnormalities, including Parkinson's disease and some forms of dystonia[6]. The basal ganglia control movement initiation and suppression of unwanted motor activity by communicating with the cerebral cortex and the thalamus. The input for the basal ganglia comes from the cerebral cortex. The signals pass through different nuclei of the basal ganglia and communicate back to the cerebral cortex via the thalamus. This pathway is an example of the different functional loops that are present in the basal ganglia. In fact, there are many different loops present in the basal ganglia. These loops are grouped into three major functional categories that are functioning parallel to each other (Fig. 2). The first category is the motor loop. This loop communicates with the premotor cortex and is involved in the initiation and planning of movements. This motor circuit has a direct and indirect pathway in which it influences movement initiation and suppression. The direct pathway goes from the putamen to the internal globus pallidus and is responsible for the activation of movements. The indirect pathway is also going from the putamen towards the internal globus pallidus, but via the subthalamic nucleus and/or the globus pallidus externus. This pathway is responsible for the inhibition of movement. One could hypothesize that a defect or lesion in the motor circuit could result in an imbalance of the direct and indirect pathway. This imbalance could lead to over-contraction of primary muscles and over-flow contraction of secondary muscles, two principles by which dystonia is characterized. Control of movement is not the only function, because the basal ganglia are also involved in other processes, such as motivational, emotional, associative and cognitive processes[7]. The second and third loop, the associative and limbic loop, are responsible for these other processes. The associative loop is connected with the prefrontal cortex and may regulate the initiation and termination of cognitive processes such as planning, working, memory and attention. The limbic loop communicates with different parts of the limbic lobe of the cortex. This loop may be responsible for regulation of emotional and motivated behaviour and the reward system.

Figure 2 shows the motor and non-motor loops through the basal ganglia. In dystonic patients there are often psychogenic symptoms present besides the problems with movement. Because the loops of the basal ganglia are parallel to each other, we hypothesized that it may be possible that if one circuit is disturbed, the other two circuits also become affected, because of the connections between the three loops. This could explain that dystonia comes along with a lot of other psychological factors, for example depression or anxiety disorders.

Neurotransmitters

There are several hypotheses about the underlying mechanism of dystonia, although the exact causes remain elusive. One of the most prevailing hypotheses is that dysfunction of the basal ganglia is due to abnormal neurotransmitter function in the basal ganglia, with special

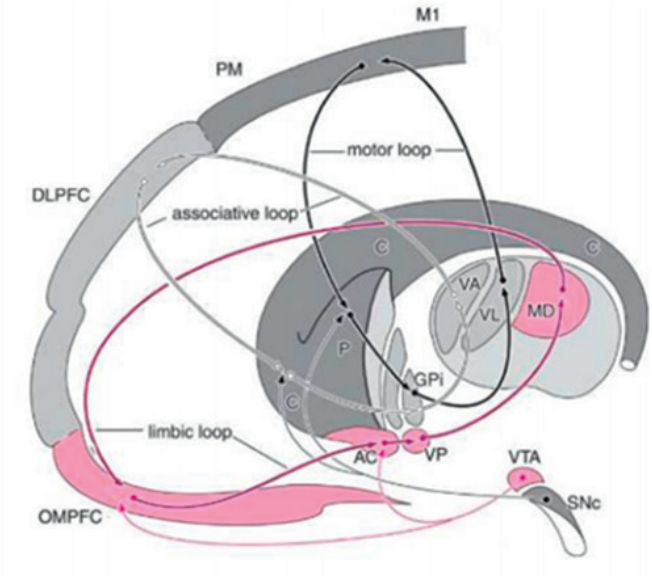

Figure 2 *Functional loops of the basal ganglia[17]. This figure shows different loops in which the basal ganglia are involved: the limbic loop, the associative loop and the motor loop. Abbreviations for the different parts that contribute to these loops are explained below.*

AC *Anterior commissure* ***C*** *Cortex* ***DLPFC*** *Dorsolateral prefrontal cortex* ***GPi*** *Globus pallidus interna* ***M1*** *Primary motor cortex* ***MD*** *Medial dorsal nucleus* ***OMPFC*** *Orbital and medial prefrontal cortex* ***P*** *Putamen* ***PM*** *Premotor area* ***SNc*** *Substantia nigra compacta* ***VA*** *Ventral anterior nucleus* ***VL*** *Ventral lateral nucleus* ***VP*** *Ventral pallidum* ***VTA*** *Ventral tegmental area*

attention to dopamine[11].
This section will be devoted to potential links between the mechanism underlying the motor facets of dystonia and the non-motor aspects of the disease. First of all, we will elucidate the several functions of dopamine on the motor aspects of dystonia. The second part of this first link will be dedicated to the interaction between dopamine and serotonin and the effect of this on the non-motor functions of the basal ganglia as serotonin is frequently involved in psychiatric diseases.[8] An effect of dopamine on serotonin could implicate an effect of dopamine on the motor system and an indirect effect of dopamine on the psychiatric situation of the patient. The section finishes with a hint to other neurotransmitter systems that could also play a role in dystonia.

Dopamine and the motor aspects of dystonia
There is substantial evidence that dopamine plays a crucial role in the development of the motor symptoms in dystonia. For example, DOPA-responsive dystonia (DRD), a disorder with a direct relationship to the lack of dopamine, responds very well to dopaminergic treatment. Several genes which are involved in the dopamine secreting and synthesis pathway have been linked with DRD, such as the gene encoding for guanine nucleotide binding protein, alpha activating activity polypeptide, olfactory type (GNAL)[9]. Of note, DRD might shed more light on the pathogenesis of other forms of dystonia than was previously thought [9]. The fact that several analogous genes for primary dystonia and DRD have been found could mean that there is a common causal pathway for primary dystonia and DRD[11]. The upcoming focus on dopamine as cause of motor symptoms in dystonia could be followed by a shift of attention to the effects of dopamine on the non-motor symptoms as well.

The effect of dopamine on serotonin
Another mechanism for dopamine to effect both motor and non-motor aspects of dystonia is through its effect on serotonin, which could be another link between motor and non-motor symptoms in dystonia patients. Serotonin is widely considered as an important neurotransmitter in the development of neuropsychiatric disorders. For example, the chronic use of levodopa, a drug used for treating Parkinson patients in order to replenish their dopamine level, reduces serotonin levels in the dorsal raphe nucleus[10]. Serotonin is widely known for its role in neuropsychiatric disorders[8]. Although levodopa is a precursor of dopamine, this does not mean that there is a direct negative relationship between the dopamine and serotonin levels because dopamine could also have an effect on other mechanisms that influence the level of serotonin. The abundance of dopamine might also influence other mechanisms such as neuroplasticity[11]. One must realize that dopamine is definitely not the one and only cause of either the motor or non-motor aspects of dystonia. The fact that there is a relationship between dopamine and serotonin, means that there may be an unidentified pathological mechanism in which dopamine and serotonin are involved. Moreover, the continuous findings of new pathways and mechanisms may imply that there are many other relationships to be uncovered and that there are, next to dopamine, several other neurotransmitters which play a role in dystonia and psychiatric disorders.

Other important neurotransmitters in the basal ganglia
Dopamine is obviously not the only neurotransmitter active in the basal ganglia. The three most important neurotransmitters of the basal ganglia are γ-Aminobutyric acid (GABA), glutamatic acid and dopamine[12]. GABA is the most important inhibitory neurotransmitter and glutamate is an excitatory neurotransmitter. Research has shown that disturbances in the glutamate level can lead to many different neuropsychiatric disorders such as schizophrenia and mood disorders[13]. Antagonizing the N-methyl-aspartate receptor (one of glutamate's main receptors) reduces the activity of inhibitory neurons, which then again results in the disinhibition of glutamate[15]. We could not identify any reports on the possible effects of GABA or glutamate on the motor functions in the human brain or in the basal ganglia. Possibly, future research could be done on these different neurotransmitters and their possible effect on either dopamine or directly on the motor loop in the basal ganglia.

Combined psychiatric and motor diseases

Possible mechanisms underlying the combination of psychiatric disease and dystonia have not been studied yet. A more studied example of psychiatric symptoms combined with motor disease is Parkinson's disease.

Depression related to Parkinson's disease
The depressive symptoms in Parkinson's disease are probably primary linked to the disease mechanism of Parkinson[14]. However, no linear correlation of depressive symptoms with duration or severity of Parkinson's disease was found. Assumably, depression in Parkinson's disease is caused by the degeneration of monoaminergic neurotransmitter systems. Another possibility is fronto-cortical dysfunction[15]. Nowadays, there is still a lack of knowledge of the pathofysiological mechanism of depression in Parkinson's disease. Although this is the case, it can be suggested that just like in Parkinson's disease, dystonia's non-motor symptoms are not a result of the dystonia but part of the disease's mechanism.

Discussion and conclusion

Dystonia is a complex disease and still very few is known about the causal mechanism behind the disease. In this review we chose to discuss the basal ganglia circuitry and its function, because these brain networks are seen as the key players in motor control and classically their dysfunction is linked to dystonia. We have discussed the three major loops that are present in the basal ganglia and how their parallel organization may lead to interaction; a potential cause of concomitant motor and non-motor symptoms in dystonia. We also hypothesized that dopamine and serotonin have a role in the occurrence of dystonia. Finally, other diseases with both motor and non-motor functions were discussed and compared to dystonia. We conclude that the mechanism of disease of dystonia probably not only leads to the obvious motor symptoms, but also has a result on non-motor functioning of the patient.

A limitation of this review is that we only discuss the basal ganglia, which does not show the complete picture of the disease. In fact, the view on dystonia is shifting towards a broader network disorder. The basal ganglia are not the only structures that are involved in movement initiation and control. For example, the cerebellum also plays a role in motor control and research showed that the cerebellum is connected to the basal ganglia. Furthermore, in our review we focused on the psychiatric co-morbidity in dystonia. We hypothesized that the basal ganglia are more involved in this co-morbidity than the cerebellum, as more scientific evidence can be found on the relationship between the basal ganglia and psychiatric disorders.

Another limitation is the large amount of different possible causes for the motor and non-motorsymptoms of dystonia. In our review, we focused on the several neurotransmitters which could possibly play a role in dystonia, because they are often associated with both motor and non-motor disorders. However, it could be possible that other factors or other neurotransmitters, besides the ones mentioned in our review, are involved in the onset of the motor and non-motor symptoms.

It should not be forgotten that the non-motor symptoms of dystonia possibly do not even share a similar disease mechanism as the motor symptoms. A possibility is that both symptoms have a common cause,

but not a common pathway. In this review, the emphasis is put on a common pathway for the motor and non-motor symptoms of dystonia. However, there are several other possibilities for the cause of the non-motor symptoms of dystonia. A reason for this hypothesis is that not all dystonia patients are affected by the non-motor aspects, which might indicate that either there are many different causes of dystonia, or the non-motor symptoms of dystonia are a psychological result of the motor aspects.

In conclusion, exact mechanisms about the onset of psychiatric disorders along with dystonia remain elusive. However, several potential links about these mechanisms were summarized in this review. Additional research on these links, for example on the basal ganglia interactions, need to be carried out in order to clarify the exact disease mechanisms. Clearly, more research is needed to further identify the links between dopamine and both the psychiatric and movement disorders in dystonia. Perhaps data on Parkinson's disease patients could also contribute here, since Parkinson's disease is caused by a shortage of absence of dopamine. Finally, it will be useful to further look at other combined motor and non-motor disease and try to relate their disease mechanism with dystonia.

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