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Review

Morphometric Characteristics of Cerebral Structures in Gilles De La Tourette Syndrome

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Abstract: Tic disorders, in particular Tourette syndrome, are a neurodevelopmental disorder common in children. Clinical manifestations of these disorders vary significantly depending on individual characteristics, age, gender, and the presence or absence of comorbidities. The pathophysiology of these disorders is believed to include a combination of genetic, environmental, psychological, immunological, and neurobiological factors. From the point of view of fundamental neurophysiology, Tourette syndrome is associated with a neurochemical imbalance of monoamines and morphometric changes affecting, in particular, neural networks that provide motor acts: the basal ganglia, thalamus, and cingulate cortex. To date, numerous studies have demonstrated the involvement of many more brain areas, such as the prefrontal cortex and cerebellum. This article presents the latest studies affecting the morphometric features of cerebral structures in patients with Tourette syndrome. During the analysis of the literature, a connection was revealed between the clinical manifestations of the disease and the morphometric characteristics of the basal ganglia, thalamus, cerebellum, cingulate gyrus and prefrontal cortex of patients with Gilles de la Tourette syndrome.

Keywords: *Gilles de la Tourette syndrome, neuroanatomy, tics, basal ganglia, monoamines, prefrontal cortex.*

1. INTRODUCTION

Tourette syndrome or Gilles de la Tourette syndrome (TS) is the most severe form of tic hyperkinesis and is characterized by the presence of multiple motor tics, as well as one or more vocal tics. The disease is based on tic hyperkinesis - fast, violent, stereotypical movements that resemble voluntary ones and affect the muscles of the face, body and limbs, while changing in severity during the day, provoked by excitement, mental and physical stress and disappearing during sleep [1]. The first clinical manifestations of TS appear in childhood, on average, from 4 to 7 years old [3]. Diagnostic criteria for TS, according to ICD-10 (F.95.2), are represented by the following symptoms [2]:

1. Multiple motor and one or more vocal tics, although not always simultaneously;
2. Tics occur many times during the day, usually paroxysmally, almost daily or intermittently, for a year or more;
3. The number, frequency, complexity, severity and localization of tics vary;
4. The tic is not associated with diseases such as Huntington's disease, viral encephalitis, intoxication or drug-induced movement disorders.

Today, tic hyperkinesis remains one of the most pressing problems in neurology and psychiatry. In the child population, according to B. Kadesjö and C. Gillberg (2000), the prevalence of tics varies from 0.5% to 1.1% [4]. According to a 2018 epidemiological study among children aged 6 to 16 years in China, the prevalence of tic disorder was 2.5% [5].

The prevalence of TS in children in Brazil is 0.43%, reaching a maximum of 1% by the age of 9 [6]. N. Khalifa and A. von Knorring (2007) [7] identified TS in 0.6% of schoolchildren, which causes social and psychological problems in the integration of schoolchildren with tic hyperkinesis into the general educational process and productive interaction of patients with normotypic children. In Scandinavian countries, according to research data for 2008-2016, the prevalence of tics varied from 0.15% to 1.23%, and on average by the age of 12, TS was diagnosed in 0.43% of children, it is noteworthy that the incidence among boys is 4 times higher than among girls [8]. In the adult population, tics occurs 5-10 times less frequently than in children, according to various estimates, from 50 to 659 cases per 1,000,000 adults [6]. The results of M. Bloch et al. (2006) indicate that 25% of tics that once existed in children persist in the adult population [6]. Thus, it is in childhood that patients with tics and tics seek medical attention the most, and accordingly, such patients need personalized approaches to diagnosis, rehabilitation, drug and behavioral therapy.

To verify the correct diagnosis of TS, it is important to remember that symptoms can be caused, for example, by drug use or neurological diseases such as myoclonus, Huntington's chorea, restless legs syndrome, or neuropsychological disorders such as attention deficit hyperactivity disorder and obsessive-compulsive disorder. Therefore, it is always necessary to assess the presence or absence of certain symptoms characteristic of TS [10]:

1. The patient's ability to voluntarily exercise inhibitory control over the manifestation of a tic.

2. The presence of "precursor impulses". That is, unstructured sensations, perceptions or mental experiences that arise as a result of increased internal tension that precedes and finds subsequent relief in the expression of the tic.

3. Variability. Tics can vary in duration, frequency, intensity, and location of the motor or vocal act, which clearly distinguishes them from purely neurological stereotypes observed in diseases such as Parkinson's disease or chorea.

2. MATERIALS AND METHODS

We analyzed more than 40 articles in English and Russian focused on neuroanatomical changes characteristic of Tourette's syndrome. The inclusion criteria for the search were as follows: 1) full original articles and reviews cited in databases such as PubMed, MedLine, Web of Science, and Scopus, 2) articles in English and Russian, 3) a search time frame of 30 years, 4) keywords: Gilles de la Tourette syndrome, neuroanatomy, tics, basal ganglia, monoamines, prefrontal cortex. The exclusion criteria included abstracts, monographs, manuals, and guidelines. The review was conducted in accordance with the PRISMA 2020 statement.

3. RESULTS

3.1 Pathophysiology of Tourette's syndrome

A significant role in the pathogenesis of TS is attributed to a violation of dopamine metabolism, namely, excessive release in the synapses of the striatum, which in turn leads to a neurotransmitter imbalance in the neural network neocortex - striatum - thalamus - neocortex. Genetic studies of the association of TS with mutations in the genes of dopamine receptors DRD2 (dopamine receptor D2) and DRD4 (dopamine receptor D4) have shown mixed results. For example, in a study by Yanji Qi. et al. (2017), positive associations with gene mutations were found in a group of 674 patients with TS, while in other studies in 343 patients with TS, the correlation of dopamine receptor mutations was not confirmed. These data to some extent explain the inefficiency of pharmacotherapy with neuroleptics in 40-60% of patients with TS; probably, with mutations in the genes of do-

pamine receptors, neuroleptics do not have the proper blocking effect on excessive dopamine activity. Mutations in the gene encoding the dopamine transporter DAT1 (dopamine transporter 1) were also studied. Upon completion of the study, a link with the DAT1 mutation was found in 574 patients with TS, while this link was not observed in 266 patients [11]. According to the latest hypotheses, with TS, a certain error in information counting occurs at the level of the striatal system, which leads to involuntary movement perceived in the cortico-striato-thalamo-cortical pathway as voluntary. In this regard, the possibility of selective action on the subcortical structures in order to remove the pathological program is assumed. The dopaminergic cortico-striatal-thalamo-cortical pathway is in constant interaction with the inhibitory function of gamma-aminobutyric acid (GABA) and serotonin. The role of serotonin in the development of tics and TS began to be discussed after mutations in the serotonin receptor genes 5-HTTLPR (serotonin transporter gene-linked polymorphic region), HTR2C (5-hydroxytryptamine receptor 2C) and polymorphisms of the serotonin transporter gene SLC6A4 (solute carrier family 6 member 4) were discovered [12-14]. In Russian studies [15] devoted to the metabolism of monoamines in the nervous system - dopamine, norepinephrine and serotonin in patients with childhood TS, a connection was shown between high serotonin levels and vocal tics, and dopamine - with motor tics, which allows for differentiated pharmacotherapy depending on the severity of vocal or motor symptoms of TS. Dysfunction of inhibitory influences in neural networks is considered as one of the priority hypotheses of the pathogenesis of tic hyperkinesis. GABA receptors, which cause inhibitory effects, account for up to 40% of all neurotransmitter receptors in the central nervous system (CNS), including intercalary inhibitory neurons of the cortex, striatum, cerebellum and spinal cord. A study was undertaken to find evidence for the concept of inhibitory dysfunction, which resulted in data on the relationship between mutations of GABA1/GABA4 receptors, acetylcholine receptor with the severity of clinical manifestations in TS. Thus, the study by Tian Y. et al. (2011) showed that several genes associated with GABA4/GABA1 receptors and the nicotinic receptor in patients with TS undergo abnormal, incorrect splicing (from the English splice - to join or glue the ends of something), which leads to aberrant (from the Latin aberrans, "to go astray", err) conformation (from the Latin conformation “shape, structure, arrangement”) of the receptor and, as a consequence, to disruption of normal functioning and the appearance of tics [16].

3.2 Features of cerebral structures in Tourette's syndrome

Despite the proven genetic, perinatal and immunological components of the pathogenesis of tic hyperkinesis, to date there is no clear understanding of the etiopathogenetic mechanisms of the onset and development of the disease. In recent years, the functional and structural changes characteristic of TS, affecting many cortical and subcortical structures, in particular the basal ganglia, have been studied in more detail. The coordinated activity of the cortico-striatal-thalamo-cortical pathways mainly coordinates complex motor acts, in addition, these same pathways are integrated into the regulation of emotional and cognitive functions [17, 18]. However, there is still no comprehensive neurobiological model capable of explaining the neuronal dynamics underlying the manifestation or suppression of tics. Based on this need, the goal we set for ourselves in this work is to scientifically analyze the main currently available evidence of structural and functional abnormalities in the brain structures involved in TS and compare them with normal neural functioning to more fully understand the pathognomonic neurobiological changes of TS.

The basal ganglia are monoaminergic nuclei primarily involved in the control and planning of voluntary movements. These include:

1. The striatum (which in turn consists of nuclei: the caudate, the putamen, which together form the lenticular nucleus, and the nucleus accumbens);

2. The globus pallidus, divided into an external (lateral) part and an internal (medial) part;

3. Subthalamic nucleus, thalamus and substantia nigra.

These structures as a whole act by integrating motor and/or cognitive inputs from the cortex and projecting to the striatum, which in turn transmits them to the thalamus, from where the information returns to the cortex where the motor act is planned and executed. In the neonatal period, before the cortical representations are fully developed, the basal ganglia are the highest centers of movement. There is much scientific evidence that demonstrates the involvement of the basal ganglia in the pathogenesis of TS. Most studies in patients with TS have found decreased functioning and decreased volume of these areas, all of which leads to dysfunction of the striatal GABAergic neural networks, which in turn leads to excessive dopamine release, which causes tic hyperkinesis [19]. Subsequent studies using functional magnetic resonance imaging have revealed morphological changes in patients with TS involving the caudate nucleus and striatum, the volumes of which were inversely correlated with the severity of tics manifested in early and adulthood [20]. Thus, Peterson BS et al. (2003) documented a decrease in the volume of the basal ganglia in a cohort of more than 150 patients, both adults and children, with TS [21]. In children, a decrease in the volume of the caudate nucleus was observed, while in adult patients, morphological changes were more widespread, affecting not only the caudate nucleus, but also almost all structures of the basal ganglia.

Interesting results concern specific vocal tics characteristic of TS such as, for example, constant coughing, grunting, swearing (coprolalia), repetition of terms and sounds (echolalia), despite the lack of specific data on the mechanisms and networks involved in their emission, a central role of the nucleus accumbens and the fibers that connect it to the limbic system is assumed, in animal models involving primates the central role of the nucleus accumbens was demonstrated [22]. Experimentally, by hyperstimulating the nucleus accumbens through microinjections of bicuculline, a GABA antagonist, the researchers induced complex repetitive vocalizations, which once again confirms the hypothesis of GABAergic deficit in TS.

3.3 Thalamus

A paired structure located bilaterally at the edges of the third ventricle that represents a "collection and sorting center" for ascending and descending sensory and motor information. Functional magnetic resonance imaging studies [23] have revealed specific hyperactivation of the thalamus during voluntary suppression of tic symptoms, suggesting that the thalamus must act in concert with other basal ganglia structures to inhibit tics. In addition, numerous studies have shown that the severity of TS symptoms is more closely correlated with greater activity in thalamic and subcortical regions compared to cortical representations, emphasizing the centrality of subcortical structures in the development of tic hyperkinesis [23]. Another study showed that thalamic damage of any etiology increases tics [24]. These and other findings have led to the hypothesis that dysregulation of thalamocortical activity may be a key cause of the symptomatic manifestation of tic syndromes. Regarding the morphometric characteristics of the thalamus in TS, there are ambiguous and contradictory results in the literature. For example, one study showed an increase in the size of the left thalamus in a sample of 18 adolescent males with TS, while the patients had never received pharmacological treatment [25]. Another study, which included 15 adult patients with TS, did not demonstrate any abnormalities in the size of the thalamus [26]. And finally, a third study revealed a decrease in the volume of the thalamus in children with TS who had not previously received pharmacotherapy. More recent work on a larger sample of patients with TS led by Miller A.M. (2010) demonstrated an increase in the size of the thalamus, especially on the left [27]. However, it should be said that the different clinical variants of tic hyperkinesis and pharmacotherapy in the anamnesis, as well as age, gender and sample size, in the analyzed works, together with significant differences in the image processing methods used, do not allow an adequate explanation and interpretation of the discrepancies between the results obtained, which indicates the need for more in-depth and methodologically thought-out studies in the future.

3.4 Prefrontal cortex

Most studies available in the literature to date have found the presence of various volumetric changes in the frontal-cortical regions in patients with TS. In particular, an increase in the size of the dorsal prefrontal and parieto-occipital regions was observed in both adults and children (more pronounced in boys), and, conversely, a decrease in the inferior occipital and premotor regions (more pronounced in girls and adults of both sexes) [28]. These differences, which correlate with the sex and age of patients, are believed to be explained by various factors, including the stages of brain development, the action of sex hormones, the severity of symptoms, plastic changes dependent on long-term activity (presumably adaptive or compensatory in nature), resulting from the persistence of tics even in adulthood [29]. Furthermore, since lower orbitofrontal and parieto-occipital volumes are often associated with more severe symptomatic manifestations of TS, the most common hypothesis is that patients who exhibit decreased activity in these regions also have a lower ability to control their emotions. In line with this, numerous preclinical and clinical studies suggest that the orbitofrontal cortex may play an important role, particularly in the inhibitory control of tics [30, 31]. Also supporting this theory is the observation that when patients with TS intentionally suppress tic releases, the prefrontal cortex is activated, which is usually accompanied by a simultaneous decrease in basal ganglia activity [32].

3.5 Cingulate gyrus

Situated above the corpus callosum, it can be divided into three main parts: anterior, medial and posterior. Each of these parts has a special cytoarchitecture and specific connections with other areas of the brain, which explains their respective specific functions.

The anterior part establishes numerous connections with the frontal cortex and prefrontal cortex, various limbic structures, suggesting that, among its many functions, the anterior part plays an important role in the emotional coloring of speech and movements, as well as the initiation and motivation of goal behavior [33, 42].

The middle part is connected with the dorsolateral prefrontal cortex, motor cortex, parietal cortex and spinal cord and is involved in decision-making mechanisms, formation of topokinetic memory and voluntary control of movements [42].

The posterior part interacts with the parietal and temporal lobes, the hippocampus and entorhinal cortex, and the anterior thalamic nucleus; hence, it is involved in the control and processing of memory and spatial orientation, associative learning, movement, and sensorimotor stimuli [33]. Studies in patients with TS using functional magnetic resonance imaging have shown a decrease in the anterior and middle parts, and, in contrast, an increase in the thickness of the posterior cingulate cortex [34]. It is suggested that these changes may reflect a deficient inhibition of local neural transmission by striatal GABAergic neurotransmitters, a hypothesis also supported by similar studies using magnetic resonance spectroscopy [35] and positron emission tomography [36].

3.6 Cerebellum

Traditionally associated with postural stability and programmed motor functions. Damage to this area (especially in the anterior lobe) can indeed lead to changes in temporal and spatial coordination of movements, hypotonia, postural instability, and motor learning disorders. However, in recent years, various studies have revealed its importance also in relation to higher cognitive abilities and behavior [42]. Several neural pathways have been discovered, such as the cortico-ponto-cerebellar pathway and the cerebellar-thalamo-cortical pathway, which connect the cerebellum with the frontal, temporal, and parietal cortex and with the paralimbic areas, suggesting its involvement in cognitive, emotional, linguistic, and even visual-spatial functions [37]. Thus, recent studies have demonstrated the involvement of the cerebellum also in the genesis of tics, especially in relation to TS [38]. Indeed, it has been observed that the increase in striatal dopamine

caused by dysfunction of the GABAergic networks in the basal ganglia, leading to focal abnormal excitation in the striatum, may also affect cerebellar activity, triggering a negative feedback mechanism - from the cerebellum to the basal ganglia - leading to disinhibition of descending motor pathways, which is the basis for the occurrence of tics [38, 42]. In addition, neuroimaging studies have shown changes in the cerebellar gray matter in patients with TS. Notably, in patients with TS combined with attention deficit hyperactivity disorder or autism spectrum disorder, hypotrophy of the cerebellar lobule, namely the subregion "Crus I" (an area associated with cognitive functions) was observed [39] ; while in patients with isolated TS, grey matter hypotrophy at the level of subregion "VIIIa" (mainly associated with sensorimotor processing) was demonstrated [40], indicating the need for a more in-depth study of the neuroanatomical characteristics and potential contribution of the cerebellum to the symptomatology and pathophysiology of TS and other tic disorders.

4. DISCUSSION

Tic disorders, particularly TS, present a complex and multifaceted clinical presentation. The manifestation of these disorders varies significantly depending on individual characteristics, age, gender, and the presence or absence of concomitant diseases. Clinical manifestations of tics and associated disorders with a wide range of psychoneurological symptoms are very diverse and depend on the age of the child and the degree of maturity of neuropsychiatric processes. Manifestations of tics are extremely diverse, and their nature periodically changes. Since their intensity also fluctuates over weeks and months, they often speak of a wave-like course of TS. After clinical deterioration in adolescence, spontaneous regression of tics occurs in most patients with TS in adulthood. However, 25% of them retain moderate or severe tics, and a significant number have disorders of social and psychological adaptation. It is assumed that the pathophysiology of these disorders includes a combination of genetic, environmental, psychological, immunological and neurobiological factors. It is believed that the main link in the pathogenesis of TS is a neurotransmitter imbalance, namely an excess of dopamine; changes probably also affect the serotonin, norepinephrine, glutamate, cholinergic, GABAergic and opioid systems. However, the specific mechanisms underlying this pathology remain unclear. In recent years, attempts have been made to find neuroanatomical and morphometric correlates of tic hyperkinesis. Thus, to date, as this scientific review of the literature shows, it can be said that neuroimaging studies have revealed structural and functional abnormalities in various areas of the brain, including the basal ganglia, thalamus, cingulate gyrus and cerebellum. These results indicate that the cortico-striatal-thalamo-cortical pathway, which is responsible for the control of habitual motor behavior, plays a decisive role in the development of tic hyperkinesis [41]. However, the heterogeneity of the patient population, the varying severity and intensity of symptoms, the presence of comorbidities, and the different pharmacotherapy strategies used by patients make it difficult to draw definitive conclusions about the pathophysiology of these disorders and the identified neuroanatomical correlates [42].

5. CONCLUSIONS

Thus, future studies should focus on well-defined patient samples and use strict inclusion and exclusion criteria. Longitudinal studies that follow the same patients from childhood to adulthood may provide valuable information on the development and symptomatic evolution and transformation of these disorders and their neuroanatomical changes over time. In addition, a better understanding of the characteristics of premonitory impulses and the mechanisms underlying tic inhibition may shed light on the neurobiological mechanisms of these phenomena. The knowledge gained may potentially

lead to the development of more effective diagnostic and treatment methods for TS and other tic disorders.

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