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Современный взгляд на роль тонзиллэктомии при тонзиллогенных неврологических заболеваниях и нейропсихических расстройствах

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АННОТАЦИЯ

В научной литературе представлено достаточно много сведений о связи хронического тонзиллита с неврологическими и нейропсихическими расстройствами. Их зависимость от стрептококковых инфекций считают очевидной, несмотря на отсутствие однозначного понимания патофизиологического механизма. Предполагают, что ведущее звено развития этой группы расстройств — перекрестная аутоиммунная реакция с антигенами, расположенными на базальных ганглиях головного мозга.

Наиболее изучены из них детские аутоиммунные нейропсихические расстройства — PANDAS. Основной метод лечения заболевания — антибактериальная терапия, но надежные рекомендации по ее применению отсутствуют.

После тонзиллэктомии не наблюдали значимой динамики в клинической картине заболевания, а положительные результаты, описанные в единичных обсервационных исследованиях, могли зависеть от использованных в послеоперационном периоде лекарственных препаратов.

В статье приведены сведения, показывающие возможность влияния хронического тонзиллита на риск развития других психических расстройств (обсессивно-компульсивное расстройство, биполярное расстройство, синдром дефицита внимания и гиперактивности, расстройство аутистического спектра, тревожное расстройство и др.), мигрени.

Для окончательных выводов о целесообразности тонзиллэктомии при PANDAS и других нозологиях необходимы крупные рандомизированные исследования. Одно из перспективных направлений — изучение микробиоты небных миндалин, способствующей развитию мигрени, что в случае подтверждения данных повысит значимость консервативного лечения небных миндалин в виде их тщательной санации.

Ключевые слова: хронический тонзиллит; бета-гемолитический стрептококк группы А; БГСА; тонзиллогенные неврологические заболевания; тонзиллогенные неврологические расстройства; детские аутоиммунные нейропсихические расстройства, связанные со стрептококковой инфекцией; PANDAS; тонзиллэктомия.

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A modern understanding of role of tonsillectomy in tonsillogenic neurological diseases and neuropsychiatric disorders

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ABSTRACT

The association between chronic tonsillitis and neurological and neuropsychiatric disorders is well described in the literature. The role of streptococcal infections is considered obvious, although there is no clear understanding of the pathophysiological mechanism. A cross autoimmune reaction with basal ganglia antigens is thought to play a key role in the development of this group of disorders.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) are the most studied conditions of these groups. Antibacterial therapy is the main treatment option, but there are no reliable recommendations for its use. No significant changes in the clinical manifestations were observed after tonsillectomy, and the positive results described in some observational studies could have been caused by postoperative treatments.

The paper suggests that chronic tonsillitis may have an effect on the risk of other mental disorders, such as obsessive-compulsive disorder, bipolar disorder, attention-deficit/hyperactivity disorder, autism spectrum disorder, anxiety disorders, and migraines.

Large randomized trials are needed to make definitive conclusions about the advisability of tonsillectomy in patients with PANDAS and other disorders. One of the most promising areas is to study the microbiota of the palatine tonsils and its contribution to migraine. If confirmed, these data will increase importance of nonsurgical treatment of palatine tonsils by their thorough irrigation.

Keywords: chronic tonsillitis; group A beta-hemolytic streptococcus; GABHS; tonsillogenic neurological diseases; tonsillogenic neuropsychiatric disorders; pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANDAS; tonsillectomy.

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ECO•VECTOR

BACKGROUND

Neurological diseases are the third most common cause of tonsillar-associated disorders. Tonsillogenic nerve damage can have several underlying mechanisms. Tonsilitis-induced lesions in human organs and tissues are thought to be toxic and allergic due to molecular mimicry caused by the structural antigenic similarity of Group A β-hemolytic Streptococcus (GABHS) and self-molecules of the human body. In addition, such disorders are thought to be neurodystrophic.

Both the parenchyma and the epithelium of the palatine tonsils contain numerous nerve endings represented by afferent and efferent fibers. During the inflammatory process, the afferent part is mainly affected, which leads to abnormal impulses to other organs. For example, increased sensitivity of vegetative hypothalamic formations is reported (according to Mostovoy et al. 1973) [1, 2].

As such neurological complications of tonsillar disorders, some authors consider conditions associated with encephalopathy or angiodystrophy due to dyscirculatory or toxic damage to the hypothalamus. Special attention is paid to pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), which have been actively studied by the world community in recent years.

The aim of the study was to evaluate the current role of tonsillectomy in the management of neurological and neuropsychiatric disorders associated with chronic tonsillitis, based on literature data.

PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH STREPTOCOCCAL INFECTION

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) represent a common type of metatonsillar disease that causes significant difficulties in diagnosis and especially in determining the management strategy by an otolaryngologist. PANDAS is estimated to occur in 1 in 200 patients. Boys are more likely to develop these disorders; the ratio of girls to boys is 2.6–4.7 : 1 [3]. PANDAS is a group of disorders characterized by isolated brain damage that manifests as obsessive-compulsive disorder (OCD) or tic disorder. It can be triggered by any streptococcal infection, including tonsillopharyngitis, erysipelas, myositis, etc. [3, 4]. Swedo et al. from the National Institute of Mental Health (Maryland, USA) described the first clinical case in 1995 and in 1998 published data on 50 children with OCD and/or tic disorder which were associated with GABHS and progressed from episode to episode [5]. Currently, PANDAS is considered one of the forms of pediatric acute-onset neuropsychiatric syndrome (PANS), a broader group that includes non-streptococcal disorders [6].

However, there is still no consensus among healthcare providers and researchers regarding epidemiology, pathophysiology, clinical manifestations, classification criteria, or even whether the disease really exists [3].

The association of PANDAS with streptococcal infection is supported by data on nervous system involvement in Sydenham's chorea (rheumatic chorea), which most commonly occurs in patients with acute rheumatic fever following a GABHS infection (the first condition to be differentiated with PANDAS). Symptoms are assumed to occur suddenly and 3 years earlier than if there was no streptococcal infection. PANDAS has a relapsing-remitting course with significant psychopathological symptoms. The most common signs and symptoms include emotional lability, separation anxiety, night terrors and bedtime rituals, cognitive deficits, oppositional behavior, and motor hyperactivity.

In 2017, the classic PANDAS criteria were modified [7] and currently include OCD and/or tic disorder; age (PANDAS symptoms are more common after 3 years of age and before puberty); acute onset and fluctuating course; clear association with GABHS infection (throat culture, rapid tests for streptococcal DNA, blood tests for antistreptococcal antibodies); neuropsychiatric syndromes (emotional lability, depression, irritability, aggression, etc.).

The theory of Swedo et al. on the relationship between GABHS-infection and mental disorders needs to be confirmed. The researchers based their claims on either culture results or elevated levels of antistreptococcal antibodies. The authors acknowledge that the time intervals between attacks of mental disorders and infectious diseases vary, and it is not always possible to obtain convincing evidence of the presence of streptococci.

Sydenham's chorea is considered the prototype of disorders where an infectious agent (e.g., GABHS) triggers an autoimmune disease accompanied by various neuropsychiatric symptoms. Chorea is clearly associated with acute rheumatic fever and previous GABHS infection and is currently recognized as a major Jones criterion for the clinical diagnosis of this disorder. The classic signs of Sydenham's chorea include hyperkinesis, incoordination of movements, muscle hypotonia, vascular dystonia, emotional lability (easy crying, mood instability). Sydenham's chorea is usually associated with other clinical criteria of acute rheumatic fever (carditis, polyarthritis, rarely annular erythema, rheumatic nodules) [8]. Chorea and PANDAS can be differentiated by the following criteria: subacute onset, fever and carditis for Sydenham's chorea and acute onset without systemic manifestations for PANDAS [9].

Previously, both diseases were thought to be related to the M protein of the GABHS cell wall, which is similar

in structure to protein molecules in the human body, and the abnormal changes depend on its different subtypes (predominantly M6 in Sydenham's chorea and M12 in PANDAS). Currently, researchers suggest cross-reactivity between the streptococcal dominant carbohydrate epitope N-acetyl-β-D-glucosamine (GlcNAc) and molecules in the human body, particularly gangliosides in the central nervous system [10].

Although the pathophysiological mechanism of streptococcal neuropsychiatric disorders is not fully understood, some facts are clear. It has been suggested that PANDAS is related to a cross autoimmune reaction with antigens located in the basal ganglia, predominantly in the striatum (caudate nucleus, putamen) [11], which is also supported by positron emission tomography data [12]. A placebo-controlled study in mice showed that passive intrathecal transfer of anti-GABHS antibodies from the serum of children with PANDAS disrupted Ca++/calmodulin-dependent protein kinase II (CaMKII) function, resulting in higher tyrosine hydroxylase activity and dopamine release. This disrupted signaling led to neuropsychiatric symptoms in mice [13]. Similar results have been reproduced in a recent human study, where antineuronal autoantibody titers and CaMKII pathway activity in neuronal cells increased in the acute phase of PANDAS and decreased with normalization of the condition [14].

There is also evidence that antibodies act on dopamine type 2 receptors, lysoganglioside, and tubulin [13, 15]. In addition, a recent human study showed that striatal cholinergic interneurons may also be involved in the pathogenesis of rapidly evolving OCD and other disorders [16]. The high permeability of the blood-brain barrier in children is thought to facilitate the penetration of autoantibodies into brain tissue. The incidence of neuropsychiatric disorders in close relatives of children with PANDAS is higher than in the general population, suggesting a genetic predisposition [17].

The Cunningham Panel of antibodies is used to diagnose and monitor the severity of symptoms of autoimmune neuropsychiatric disorders. However, it has low specificity (10% for PANDAS and 6% for PANS) and variable negative predictive values (44%–74%) [18].

Antibacterial therapy is the primary treatment option for patients diagnosed with PANDAS. However, there are no reliable recommendations for its use, as only a few randomized, placebo-controlled trials have been conducted. Treatment regimens also include low-dose selective serotonin reuptake inhibitor antidepressants, anti-inflammatory drugs including corticosteroids, immunomodulators, and cognitive-behavioral therapy [19].

Only descriptive studies in the form of case reports discussing the benefits of surgical treatment of chronic tonsillitis (CT) in PANDAS can evaluate its efficacy.

Demesh et al. (2015) described a series of 10 case reports that strictly met the diagnostic criteria for PANDAS [20]. The authors compared parental reports of symptom severity at 3 time points, including at diagnosis, after antibiotic treatment (n = 10), and after tonsillectomy (n = 9). Symptoms were significantly less severe after tonsillectomy than after antibiotic therapy. Complete resolution was reported in 4 cases, favoring surgical treatment. However, the data were obtained retrospectively from parental reports using an unvalidated symptom severity scale.

Randomized trials suggest a lack of efficacy of tonsillectomy in PANDAS. The study by Murphy et al. (2013) [21] should be noted, which evaluated the correlation between surgery and decreased levels of circulating antistreptococcal antibodies and suggested a potential mechanism for the supposed effectiveness of tonsillectomy. In tonsillectomy and control groups, no significant differences were found in the severity of neuropsychiatric symptoms and levels of streptococcal antibodies. In addition, some subjects developed tics and OCD after tonsillectomy, confirming ineffectiveness of surgery in preventing further episodes of PANDAS. However, this statement is only probable because the study did not assess a time distribution of streptococcal antibody titers and there was no prospective follow-up of most of the children who underwent tonsillectomy.

In another prospective two-year study of a group of 120 children diagnosed with PANDAS, 56 who underwent tonsillectomy and/or adenoidectomy showed no significant differences in symptom progression, streptococcal and neuronal antibody levels, or severity of neuropsychiatric symptoms compared with a control group of 64 patients who did not receive surgical treatment [22]. Therefore, tonsillectomy remains a controversial treatment option for PANDAS, and the positive results reported in isolated observational studies may have been influenced by postoperative drug treatment [23].

There are some important points regarding PANDAS. Lack of consensus in the medical literature is mainly due to the lack of large randomized trials; the high incidence of both neuropsychiatric disorders (primarily tics, OCD, and emotional lability) and GABHS infection in children; the frequent inability to establish clear correlations between GABHS infection and the onset of symptoms; a constant proportion of asymptomatic GABHS carriers among children with neuropsychiatric symptoms; lack of data on the true efficacy of antibiotics in children with PANDAS, especially compared to placebo or other active agents [3].

OTHER NEUROLOGICAL DISORDERS

As for other neurological disorders in patients with tonsillar disorders, the literature presents unsystematic studies, often hypothetical. In 1991, Vinitsky and Vinitskaya

identified afferent connections between the palatine tonsils with subcortical formations and the posterior part of the hypothalamic subthalamus. According to the authors, these connections can trigger vascular and circulatory, toxic and infectious mechanisms of brain disorders. Possible manifestations include persistent decreases in peripheral arterial pressure (e.g., Raynaud's syndrome), migraine, Meniere's syndrome, encephalopathy, and a state of neurasthenia (general weakness, fatigue, meteosensitivity) [4]. In 1997, Dergachev et al. described a neuroendocrine type of disorder thought to be associated with damage to the ventromedial and ventrolateral nuclei of the hypothalamus. These include obesity or weight loss, loss of appetite, thirst, hyperhidrosis, irregular periods, and loss of sexual potency. In 1999, Ovchinnikov et al. added to this information by stating that chemotherapy caused progression of schizophrenia due to autointoxication [24]. However, these findings were not supported by other studies.

Isung et al. (2019) [25] found an association between CT and the risk of mental disorders. Patients with tonsillectomy (*n* = 210,686) and their siblings discordant for tonsillectomy (*n* = 317,214) were compared. History of tonsillectomy was considered an indirect sign of CT. A history of tonsillectomy is associated with an increased risk of mental disorders (OCD, major depressive disorder, attention deficit hyperactivity disorder and Tourette's syndrome, autism, bipolar and other mood disorders, agoraphobia), substance use and suicidal behavior. The authors explain the possible pathophysiological mechanism by the increased production of proinflammatory cytokines by innate immune cells in patients with CT. When these cytokines reach the brain, they can cause a wide range of symptoms, from attention deficit and irritability to anhedonia and sleep disturbances.

However, a study of the same factors based on Mendelian randomization failed to prove the assumption of causality between CT, tonsillectomy, and susceptibility to mental disorders [26].

In addition, some studies in recent years consider tonsillectomy not as an indicator of the presence of CT, but as a surgical treatment that causes severe pain syndrome that can lead to mental disorders. Post-operative sore throat can be so severe that it can alter synaptic connections and dopamine release in the brain, becoming a risk factor for depression. For example, Chang et al. (2024) evaluated the medical records of nearly 30,000 patients with CT and found that tonsillectomy was associated with a 30% increased risk of depression over the next 5 years compared with patients without tonsillectomy [27].

Russian studies emphasize the correlation between CT and attention deficit disorder. Tikhomirova (2021) found a correlation between groups of children with CT and minimal brain dysfunction syndrome (attention deficit hyperactivity disorder) [28]. But the question is, what comes first in this tandem: chemotherapy or a neurological disorder? It is possible that this correlation is coincidental due to the widespread prevalence of both conditions. For example, Belousov and Khrabrikov (2018) found that tonsil disorders had no effect on levels of situational and personal anxiety and depression. In contrast, euphoria is the most common disease attitude in patients with CT. However, regular non-surgical treatment of CT (irrigating the tonsils) is associated with lower scores of depression and psychopathy [29].

An interesting study by Gonzalez et al. (2016) suggests that facultative anaerobic bacteria in the oral cavity may contribute to the increase in nitric oxide that causes migraine [30]. Oral microbiome samples obtained in migraine sufferers were found to have significantly higher levels of nitrate, nitrite, and nitric oxide reductase genes than healthy individuals. Through the activity of these enzymes, nitrates in foods can be reduced to nitrites and then induce formation of nitric oxide, a vasodilator that can cause headaches. If the effect of bacteria on the development of headaches is confirmed, sanitation of the oral cavity and pharynx, possibly including tonsillectomy, appears to be a promising method for the treatment and prevention of migraine.

CONCLUSION

Although there is sufficient evidence to support the association of CT with PANDAS disorders due to cross-reactivity to autoimmune antigens located on the basal ganglia, the efficacy of tonsillectomy in these disorders is controversial due to the low quality of the studies, which are mainly case reports. Isolated cases support tonsillectomy, but some studies with larger populations of children with PANDAS have not shown significant improvement in disease outcome after tonsillectomy. Current guidelines do not offer options to control the primary source of infection in the tonsils. New large randomized controlled trials are likely to expand our understanding of the profiles of patients who respond favorably to surgery, allowing future selection of patients with PANDAS for tonsillectomy.

Current data on the relationship between CT and other neuropsychiatric disorders are still hypothetical and unsystematic and have no practical use, so further clinical studies are needed.

ADDITIONAL INFORMATION

Author contribution. All the authors made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before publication.

Personal contribution of the authors: *T.S. Zaitseva, A.A. Nesterova* — literature review, translation of English-language sources, analysis of the data obtained, writing the text, making corrections; *K.I. Nesterova* — concept and design of the study, planning, coordinating, editing the work, including mentoring, making final

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Вклад каждого автора: *Т.С. Зайцева, А.А. Нестерова* — обзор литературы, перевод англоязычных источников, анализ полученных данных, написание текста, внесение правки; *К.И. Нестерова* — концепция и дизайн исследования, планирование, координирование, редактирование работы, включая наставничество, внесение окончательной правки; *Р.Г. Миракян* — сбор и обработка материалов, обзор литературы; *И.А. Щербина* — сбор и обработка материалов по направлению «неврология».

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