

# *Clinical Presentation, Diagnosis And Differential Diagnosis Of PANDAS Syndrome In Children: Review*

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**Abstract** – In recent years, an assumption has been made about the connection of various choreiform hyperkineses, tics, myoclonus, and neurosis-like obsessive states in children with  $\beta$ -hemolytic streptococcus group A (BHSA). Currently, early diagnosis of a number of autoimmune diseases, including those caused by  $\beta$ -hemolytic streptococcus group A and the development of differential diagnostic criteria for PANDAS syndrome, as well as the choice of treatment tactics and the prevention of complications in this pathology, is very relevant. PANDAS syndrome, in contrast to minor chorea, is characterized by local, easily stopped tics, with debut disease from 5 years to 12 years. The developed differential diagnostic criteria and the algorithm for the diagnosis of PANDAS syndrome will allow timely diagnosis and application of the necessary treatment tactics.

**Keywords** – PANDAS syndrome, disease, children,  $\beta$ -hemolytic streptococcus group A.

## **I. PURPOSE OF THE RESEARCH**

To study the clinical and differential diagnostic criteria for PANDAS syndrome and chorea minor in children and introduce it into clinical practice.

## **II. RESEARCH OBJECTIVES**

1. To study the clinical and neurological manifestations of PANDAS syndrome and small chorea.
2. To identify laboratory-biochemical, cardiological and neuropsychological parallels of chorea minor and PANDAS syndrome.
3. To develop differential diagnostic criteria and an algorithm for the diagnosis of PANDAS syndrome.

## **III. OBJECT OF RESEARCH**

The research will be carried out in the GKDH № 4 in the department "Somatoneurology". 60 patients from 5 to 15 years old will be examined.

I gr. – 25 children with PANDAS syndrome.

II gr. - 25 children with small chorea.

III gr. - 10 children with chronic tonsillitis (control group)

#### IV. RESEARCH METHODS

1. Examination of the somatic and neurological status.
2. Research of psychological status (according to the method of Luria, Luscher and according to the OCD-Yale Brown questionnaire).
3. Laboratory biochemical research.
4. Instrumental research methods (ECG, EchoCG, EEG, MRI of the brain).

#### V. SCIENTIFIC NOVELTY OF THE RESEARCH

1. The clinic, diagnosis and course of the PANDAS syndrome will be described in detail.
2. Differential diagnostic criteria for PANDAS syndrome with chorea minor will be carried out.
3. A differential diagnosis algorithm for PANDAS syndrome and chorea minor will be developed.

#### VI. PRACTICAL SIGNIFICANCE

Currently, patients with PANDAS syndrome are monitored and treated with various other diagnoses such as Tourette's syndrome, chorea minor (Sydenham's chorea).

Our scientific work will help doctors - neurologists, pediatricians, cardio-rheumatologists, psychiatrists in diagnosing PANDAS syndrome and conduct the correct management tactics.

#### VII. LITERATURE REVIEW

##### Clinical picture and diagnosis of PANDAS syndrome in children.

Streptococcal infection caused by  $\beta$ -hemolytic group A streptococci is the most common bacterial infection that affects the human body today. Physicians of almost all specialties deal with this vast group of infectious diseases.

$\beta$ -hemolytic group A streptococcus (*Streptococcus pyogenes*) is a gram-positive, non-spore-forming, immobile microorganism. Grows on blood agar, has a pronounced hemolytic activity, catalase-negative, sensitive to bacitracin.

$\beta$ -hemolytic group A streptococcus (*Streptococcus pyogenes*) is a gram-positive, non-spore-forming, immobile microorganism. Grows on blood agar, has a pronounced hemolytic activity, catalase-negative, sensitive to bacitracin. It is found everywhere, often colonizes the skin and mucous membranes of a person. The main routes of transmission are airborne, contact and food. The pathogenesis of diseases is associated with the production of toxins: hemolysin, streptolysin, streptokinases A and B, deoxyribonuclease, hyaluronidase. The main nosiforms are superficial (tonsillitis, pharyngitis, impetigo, erysipelas), invasive (necrotizing fasciitis, myositis, meningitis, endocarditis, pneumonia, postpartum sepsis) and toxin-mediated infections (scarlet fever, toxic shock syndrome). The occurrence of neurological diseases in children, manifested by tics and obsessive-compulsive disorders, is also associated with streptococcal infection. In particular, various choreiform hyperkineses, tics, myoclonus and neurosis-like obsessive states in children associated with group A  $\beta$ -hemolytic streptococcus may appear. According to S. Svedo, such cases began to be designated as PANDAS syndrome (Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) - a childhood autoimmune neuropsychiatric disorder associated with streptococcal infection [6].

For 10 years, PANDAS syndrome was considered as related to rheumatic fever and especially chorea, which was confirmed by the association with infection caused by group A  $\beta$ -hemolytic streptococcus and the relative effectiveness of antirheumatic therapy. In connection with these circumstances, the proposed pathogenesis of this disease is an autoimmune reaction in which antibodies infect nerve cells [7]. In recent years, it has been suggested that some cases of Tourette's syndrome and obsessive-compulsive disorder (obsessive-compulsive syndrome) are associated with group A  $\beta$ -hemolytic streptococcus infection. Such cases are commonly referred to as Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection (PANDAS). Using this assumption is evidenced by: - identification of signs of a recent streptococcal infection or a high titer of anti-streptococcal antibodies at the time of the onset of hyperkineses or mental disorders or when they intensify;

- the presence of tics and obsessive-compulsive syndrome with small (rheumatic) chorea;

- frequent detection of markers of hypersensitivity to rheumatism (B-lymphocyte antigen D8 / 17) and antineuronal antibodies in patients with tics and obsessive-compulsive syndrome, including those who have never suffered from rheumatism or small cholesterol. It has been suggested that the autoimmune response against striatal antigens triggered by streptococcal infection can cause a wide range of disorders, from tics and chorea to obsessive-compulsive disorders and attention deficit hyperactivity disorder. All these disorders are based on dysfunction of certain frontostriatal neuronal circles. Moreover, the variety of clinical manifestations depends on the direction of autoantibodies against different antigens of the striatum. In particular, patients with tics show an increased level of antibodies against shell antigens, but not the caudate nucleus or globus pallidus [20, 22]. In some cases of acute obsessive-compulsive syndrome, MRI revealed an increase in the volume of the basal ganglia, which regressed after plasmapheresis (similar changes were previously noted in ChM). At the same time, PANDAS, unlike ChM, is not combined with any other manifestations of rheumatism (polyarthritis, rheumatic heart disease, rheumatic nodules, increased ESR). Unlike ChM patients, PANDAS patients have no positive family history of rheumatism. In this regard, it is assumed that, like previously described post-streptococcal reactive arthritis, PANDAS may be a non-rheumatic complication of streptococcal infection [23,29].

Possible PANDAS criteria are:

- 1) The presence of tics and (or) signs of obsessive-compulsive syndrome;
- 2) Onset in childhood (from 3 years to puberty);
- 3) A sudden onset of symptoms or a wave-like course with sharp exacerbations and subsequent complete or partial remissions;The appearance or a sharp increase in these symptoms after a recent infection of group A beta-hemolytic streptococcus;
- 5) The presence of other neurological disorders, including hyperactivity or choreiform movements during an exacerbation (with obvious chorea, the diagnosis is ChM, not PANDAS) [53,54]. Streptococcal infection often occurs in childhood, so the relationship between infection and the onset (increase) of symptoms can only be established with long-term observation of the patient. According to S.E.Swedoetal criteria. (1998), should be documented at least 2 episodes of worsening of the condition that occurred shortly after the transferred infection. Streptococcal infection should be confirmed by bacteriological examination of nasopharyngeal lavage and serological tests (increased titer of antistreptolysin O and / or antideoxyribonuclease B) [55]. S.E.

Swedo et al. (1998) presented a series of 50 patients with PANDAS diagnosed according to these criteria. However, the reality of PANDAS still cannot be considered proven, and the sensitivity and specificity of its criteria require special studies [53,54].

Patients diagnosed with PANDAS described in the literature often responded poorly to standard therapy for tics or obsessive-compulsive syndrome, but noted rapid improvement with treatment with penicillin, plasmapheresis, corticosteroids, or IV immunoglobulin. The positive effect of plasmapheresis and IV immunoglobulin in the form of a persistent reduction in hyperkinesia and obsessive-compulsive syndrome has been proven in a small number of PANDAS patients in double-blind trials. However, in the absence of generally accepted diagnostic criteria for PANDAS and strict indications for immunotherapy, these methods cannot be recommended for wide clinical use in patients with tics and obsessive-compulsive syndrome. The question of the advisability of long-term prophylactic use of antibiotics (as after ChM) remains unresolved [54]

PANDAS syndrome has been known for over a decade, but we still do not know what exactly is the mechanism of the effect of streptococcus on the human brain. This is to be found out by scientists at the American National Institute of Mental Health, who announced the launch of the PANDAS research project in NewScientist on March 28, 20

It is very likely that in some cases in children and adolescents, the same antibodies attack the basal ganglia and lead to a neuropsychiatric disorder called PANDAS syndrome. The Institute of Mental Health will monitor cases of the disease, improve the diagnostic and treatment procedures. It is suggested that intravenous infusion of human immunoglobulins may prove to be a highly successful therapy for PANDAS, as it has proven to be effective in the treatment of other autoimmune diseases.

In the medical world, there is also an opinion that the likelihood of PANDAS disease is much higher for those children whose immune system is already weakened, and therefore fails in the form of an autoimmune reaction in case of streptococcal infection [8,53,54].

The PANDAS syndrome is described as a manifestation of persistent streptococcal infection, which is immunopathologically associated with brain structures and causes autoimmune cerebral vasculopathy with a predominant lesion of

the cortical-subcortical structures and striatum. In the treatment of such children, it is recommended to use antibacterial, anticonvulsant and antirheumatic drugs both during an exacerbation and during relapses [45].

In recent years, it has been suggested that various choreiform hyperkineses, tics, myoclonias and neurosis-like obsessive states in children with group A  $\beta$ -hemolytic streptococcus (BGSGA) are related. Similar cases, as suggested by S.E. Swedo, L. Klesling (1994), commonly referred to as "Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS syndrome)

The characteristic features of PANDAS are: 1) neurological disorders (hypermotility, tics, choreiform hyperkineses, myoclonus); 2) obsessive-compulsive disorders (obsessive thoughts and ritual actions) in combination with tics; 3) onset of the disease from 5 to 14 years old; 4) acute onset and relapsing-remitting course; 5) connection with BGSGA-infection of the nasopharynx (chronic tonsillitis), confirmed by microbiological (isolation of the pathogen in a smear from the pharynx) and serological methods (increased titers of antistreptolysin-O and anti-DNase B); 6) identification of markers of hypersensitivity to rheumatism (antigens of B-lymphocytes D8 / 17) and anti-neuronal antibodies; 7) absence of polyarthritis, carditis, annular erythema and rheumatic nodules; 8) rapid regression of neuropsychiatric symptoms with adequate antibacterial therapy of BGSHA infection of the nasopharynx; 9) the absence of organic lesions of the basal ganglia and cortical structures in clinical studies and neuroimaging (MRI, CT); 10) changes in the EEG, including convulsive readiness, often spike waves identified during the recording of nocturnal sleep [55,58].

In the clinic of the disease in children aged 7 to 15 years

complaints of hyperactivity, choreiform and tic-like hyperkineses were observed, including generalized tic (Gilles de la Tourette's syndrome), emotional lability, absent-mindedness, impaired attention, difficulty falling asleep, obsessive anxious thoughts (obsessions), fear of being left alone, the desire to perform repetitive compulsive ritual actions ( ), blinking, stereotypical tilting of the head to the shoulder, sniffing, biting nails, clapping, shrugging. All children had a fear of being examined by a doctor, procedures, and when examined using diagnostic devices. All patients from the age of 5-7 years were followed up by a pediatric neurologist or psychiatrist for obsessive-compulsive movement neurosis, "functional" hyperkineses, and generalized tics [53,54].

Diagnostic criteria for PANDAS syndrome [8,53]:

- 1) the presence of obsessive-compulsive disorders and / or tics;
- 2) childhood debut: symptoms appear between 3 years of age and puberty;
- 3) paroxysmal type of the course of the disease, characterized by a sudden onset or a sharp increase in symptoms. Often the appearance of symptoms or their exacerbation can be associated with a certain day or week. Symptoms are usually significantly reduced, and sometimes completely disappear between episodes of exacerbation;
- 4) connection with streptococcal infection - exacerbation should be associated with the detection of streptococcus in the nasopharynx and / or with an increase in the titer of antibodies to streptococcus;
- 5) connection with neurological disorders. During an exacerbation, changes in the neurological status are found in patients. The most common are hyperactivity and hyperkineses (including choreiform).

## REFERENCES

- [1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders 4th ed. — Washington (DC): American Psychiatric Association, 1994.
- [2] Castillo, M.L. Sydenham's chorea: MRI and proton spectroscopy / M. Castillo, L. Kwok, A. Arbelaez // *Neuroradiology*. — 1999. — Vol. 41. — P. 943—945.
- [3] Church, A.J. et al. Anti-basal ganglia antibodies in acute and persistent Sydenham's chorea // *Neurology*. — 2002 (2 of 2). — P. 227—231.
- [4] Dale, R.C. Autoimmunity and the basal ganglia: new insights into old diseases // *J. Med.* — 2003. — Vol. 96. — P. 183—191.

- [5] Eapen, V. Adult-Onset tic disorders / V. Eapen, A.J. Lees et al. // *Movement Disorders*. — 2002. — Vol. 17, № 4. — P. 735—740. — 35)
- [6] Fedoseeva, I. The content of noradrenaline in blood serum in children with tic disorders / I. Fedoseeva, T. Poponnikova, L. Galaganova // *Europ J Neurol*. — 2010. — Vol. 17, suppl. 3. — P. 520.
- [7] Fernandez-Alvarez E. Transient movement disorders in children / *J. Neurol.* — 1998. — Vol. 245. — P. 1—5.
- [8] Harvey S., Singer Serial Immune Markers Do Not Correlate With Clinical Exacerbations in Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections // *Pediatrics*. — 2008. — vol.121(1). — P.198-1205.
- [9] Jancovic, J. Tics and Tourette's Syndrome / In: [E. Tolosa, W.C.Coller, O.S.Gershanik (Eds)] *Differential Diagnosis and treatment of movement disorders*. — Butterworth- Heinemann,1998. — P. 99—107.
- [10] Kofman O. Paroxysmal sneezing. *Can Med Assoc J* 1964;91(11):618.
- [11] Kurlan, R. *Handbook of Tourette's Syndrome and Related Tic and Behavioral Disorders (Neurological Disease and Therapy)*. — 2005. — P. 325—329.
- [12] Macerollo A., Martino D. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): an evolving concept. *Tremor Other Hyperkinet Mov (NY)*. 2013.
- [13] Murphy M.L., Pichichero M.E. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Arch Pediatr Adolesc Med* 2002;156(4):356–61.
- [14] Perlmutter S.J., Leitman S.F., Garvey M.A. et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive- compulsive disorder and tic disorders in childhood. *Lancet* 1999;354(9185):1153–8.
- [15] Pringsheim, T., Davenport W.J. , Lang A. // *Tics Current Opinion in Neurology*. — 2003. — Vol.16. — P. 523—527.
- [16] Rampello L. Tic disorders: from pathophysiology to treatment / L. Rampello, A..Alvano, G. Battaglia et al. // *J. Neurol.* — 2006.— Vol. 253, —P. 1—15.
- [17] Roger Kurlan et al. Streptococcal Infection and Exacerbations of Childhood Tics and Obsessive-Compulsive Symptoms: A Prospective Blinded Cohort Study. *Pediatrics* 2008;121;1188-1197.
- [18] Sanchez-Carpintero, R. A preliminary study of the frequency of anti-basal ganglia antibodies and streptococcal infection in attention deficit/hyperactivity