Abstract. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) are clinically characterized by the sudden onset of obsessive-compulsive manifestations, motor and verbal tics, as well as other behavioral symptoms in a group of children with B-hemolytic streptococcal infection. PANDAS are considered autoimmune diseases because the streptococcal infection and response can be demonstrated. The most frequent physiopathological mechanism is molecular mimicry: A foreign antigen shares sequence or structural similarities with self-antigens. A thorough review of the literature was carried out using the PubMed database and SCOPUS, searching for immunological, clinical and microbiological aspects, as well as the treatment of the PANDAS syndrome. The diagnosis is clinical and it requires a careful medical history and a thorough physical examination, while the treatment is complex. Untreated or unrecognized manifestations of PANDAS can increase the risk of obsessive-compulsive manifestations and tics during adulthood. Taking this into consideration, further studies are required to establish the best method of therapy.

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1. Introduction
PANDAS is the acronym for ‘pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections’. PANDAS is clinically characterized by sudden and major changes in personality, behavior and movement in a patient with streptococcal infection (e.g. pharyngitis, sinusitis and scarlet fever) (1). Research carried out identified other infectious causes which determine an auto-inflammatory reaction associated with neuropsychiatric manifestations, including Borrelia burgdorferi, mycoplasma pneumonia, herpes simplex or the varicella-zoster virus; these are called Pediatric acute-onset neuropsychiatric syndrome (PANS) (2).

PANDAS was first described in 1990 by a group of researchers who identified the sudden onset of some obsessive-compulsive manifestations, motor and verbal tics, as well as other behavioral disorders in a group of children with B-hemolytic streptococcal infection (1).

There are several risk factors for the onset of the PANDAS syndrome, such as repeated group A streptococcal infections and family history of autoimmune disease or rheumatic fever. It more frequently affects males and children with ages between 3 and 12 (1).

PANDAS is a rare condition and sometimes doctors fail to diagnose PANDAS due to some of the common symptoms associated with the disease. For this reason, and also because it is a relatively new disorder, it was considered necessary to conduct a review of this condition.

2. Methods
In the present review, a literature search in the Pubmed and Scopus databases was performed for the term ‘Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections’, in combination with ‘pathogenesis’, ‘symptoms’, ‘diagnosis’, ‘laboratory tests’, ‘treatment’ and ‘complications’ from 1996 to 2020. Inclusion criteria was represented by articles relevant to these searches.

Exclusion criteria was represented by studies written in other languages than English, letters to the editor, conference presentations, editorials, comments, opinions and articles without free access.
3. Results

PANDAS pathogenesis. PANDAS are considered an autoimmune disease because the streptococcal infection response can be demonstrated. The most frequent physiopathological mechanism is molecular mimicry: a foreign antigen shares sequence or structural similarities with self-antigens. Streptococcal infections are known to hide from the host immune system by mimicking host cells and cause the production of cross-reactive antibodies which cross the blood-brain barrier, bind to their host antigens in the basal lymph nodes and determine the onset of the neuropsychiatric symptoms (3,4).

Anti-neuronal autoantibodies react in the brain with certain specific antigens, including lysoganglioside (5,6), dopamine receptors (7), activation of the calcium-calmodulin dependent protein kinase II (CaMKII) in human neuronal cells (6) or tubulin (8).

Studies carried out on mice have revealed that human anti-brain autoantibodies induced by the streptococcal infection have as a target the dopamine D2 receptor (D2R) (7) and signal the CaMKII; the mice developed obsessive behaviors similarly to the PANDAS syndrome in human models (9,10).

Numerous studies have attempted to highlight the presence of a specific antibody in the brain of PANDAS patients, which would facilitate the accurate diagnosis of the PANDAS syndrome and would constitute the basis for a precise and tailored therapy (11,12,13). Unfortunately these studies were inconclusive, being unable to demonstrate the association between the recurrence of the symptoms and the presence of certain types of antibodies, several of them arousing suspicions with regard to the methodology used.

Autoantibodies that were initially characteristic for Sydenham's chorea, such as the D1 and D2 dopamine receptors, CaMKII-activity, β-tubulin and lysoganglioside-GM1 (lyso-GM1), are proposed as biomarkers for PANDAS (5,7,8,12,13). Both in patients with chorea and in patients with PANDAS syndrome, the CaMKII activity has been revealed to be increased by monoclonal antibodies and these antibodies bind to both an epitope in the GABHS cell wall and to lysoganglioside, implying molecular mimicry as a cause for the autoimmune process (6).

Thus, a panel of antibodies for the diagnosis and monitoring of the severity of symptoms called Cunningham, is currently marketed; however, it has poor specificity (specificity of only 10% for PANDAS and 6% for PANS); wide-ranging specificities (28-92%); variable negative predictive values (44-74%) (14).

Considering that certain studies have not demonstrated any correlation between the levels of cytokines and clinical exacerbation (15) some researchers have suggested the possibility that PANDAS may represent a heterogeneous immune dysregulation syndrome that involves a large variety of possible alterations of the regulatory T cells, immunoglobulins, cytokines, cerebrospinal fluid (CSF) oligoglionic bands, and immune-associated genes (16).

The results of a recent study revealed an increase in anti-neuronal autoantibody titers and the activity of CaMKII pathway in human neuronal cells in the acute phase of PANDAS (17). The autoantibody titers decreased during improvement.

Clinical picture. The onset of the symptoms is approximately four to six weeks after a streptococcal infection and includes behaviors similar to the obsessive-compulsive disorder (OCD) and Tourette's syndrome. Symptoms can interfere with schooling and rapidly become debilitating (11).

The psychological symptoms may include repetitive, obsessive-compulsive behaviors, separation anxiety, fear, and panic attacks, incessant screaming, irritability, frequent mood changes, emotional and developmental regression, visual or auditory hallucinations, depression and suicidal thoughts.

The physical symptoms may include tics and uncommon movements, sensitivity to light, sound and touch, deterioration of motor abilities (handwriting), hyperactivity or the inability to concentrate, memory problems, sleep disorders, refusal to eat, which may lead to weight loss, joint pain, frequent urinating and enuresis and nearing a catatonic state.

Symptoms become more severe and usually reach a maximum within 2-3 days, unlike other childhood psychiatric diseases that develop gradually (11).

Diagnosis. The diagnosis for the PANDAS syndrome is clinical and it requires a careful medical history and a thorough physical examination.

Diagnosis criteria. The diagnosis criteria are the following: i) The presence of OCDs, ADHD-like symptoms or tics; ii) the onset of the symptoms between the ages of 3 and 12; iii) sudden onset of the symptoms or worsening of the existing symptoms for a short period of time; iv) temporal association between streptococcal infection and the onset-exacerbation of the symptoms, confirmed by culture or the presence of anti-streptococcal antibodies; and v) association with neurological anomalies, especially hyperactivity, choreiform motor movements, bedwetting, anxiety, emotional lability, developmental regression or mood changes (18). By definition, PANDAS is a diagnosis of exclusion, after eliminating all other possibilities.

Paraclinical investigation. Since there is no biomarker for the establishment of a diagnosis, there was a consensus regarding the laboratory tests suitable in the case of a patient with OCDs: Complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein, metabolic panel, urine analysis, pharyngeal swab and anti-streptococcal antibodies (11,19). Neither the pharyngeal swab, nor the anti-streptococcal antibodies represent a marker for PANDAS syndrome, because the positive results do not differentiate between the state of carrier and acute infection, they only indicate exposure to the streptococcal infection (20).

Children with psychiatric and neurological signs, with attention deficit, orientation disorders, convulsions, new tics, sudden onset of sleep disorders or anomalies identified during the physical or neurological examination require the analysis of the CSF and neuroimaging exams (21).

As far as the antibody panel for the diagnosis goes, it is not suitable for patients with mild or moderate forms of the disease, given its poor specificity; a positive test does not establish the diagnosis of PANDAS syndrome, and a negative test does not provide new information (14). Furthermore, inexact tests represent an additional stress factor for the child and the family (22).
Differential diagnosis is performed with other disorders that include psychiatric manifestations: Sydenham's chorea (a movement disorder associated with rheumatic fever, also caused by Streptococcus), Tourette's syndrome, OCD, central nervous system vasculitis, autoimmune encephalitis and neuropsychiatric lupus (3,6,9).

Treatment. The treatment of PANDAS involves approaching both the physical and psychiatric symptoms. Treatment must reduce the OCDS, the tics or other behaviors that could interfere with day to day living and school.

The treatment of the streptococcal infection is performed with antibiotics: Amoxicillin, penicillin, azithromycin and cephalosporins (23,24). It is assumed that certain anti-streptococcal antibiotics administered also have a neuroprotective effect. Thus, according to a study led by Murphy et al., the therapy with cefdinir, a β-lactam, produced notable improvements to the tics evaluated with the Yale Global Tic Severity Scale (YGTSS) and to the obsessive-compulsive type symptoms evaluated with the Children's Yale-Brown Scale (CY-BOCS) (25). However, the overall differences in the groups were not significant. Testing and treatment of carriers are also necessary.

Treatment of the psychiatric symptoms. The psychiatric symptoms can begin to improve upon the start of the antibiotic treatment. The OCD and other psychiatric symptoms are generally treated with the cognitive behavioral therapy (26). Usually, OCD also responds well to selective serotonin reuptake inhibitors, a type of antidepressants (fluoxetine, fluvoxamine, sertraline, paroxetine) prescribed in small doses that can be gradually increased if necessary (27).

Some severe cases of PANDAS may not respond to drugs and behavioral therapy (28). In such cases, the treatment guidelines drawn up by the members of the PANS Research Consortium in 2017, recommend immunomodulating therapies, individually or in combinations: Corticosteroids, intravenous immunoglobulin, plasmapheresis, mycophenolate or rituximab (29,30). Corticosteroids (prednisone) are administered to improve OCD symptoms, but they can worsen the tics. In numerous cases, the manifestations reappear upon the interruption of the steroid treatment; therefore, at present, steroids are not usually recommended for the treatment of PANDAS. Studies are controversial as far as these immune system modulators are concerned, numerous researchers claim that some of these studies are incorrectly carried out, full of prejudice, while others bring poor proof for the use of these toxic drugs (29). Taking this into consideration, further studies are necessary to establish the best treatment method for these patients.

Prognosis. Although children fully recover, there are patients who develop persistent neuropsychiatric symptoms or present worsened symptoms after each streptococcal infection. We cannot foresee which children will be affected or how severe these symptoms will be. Untreated or unrecognized manifestations of PANDAS can increase the risk of having obsessive-compulsive manifestations and tics during adulthood. Comorbid tics are associated with deterioration of handwriting skills and decline in school performance, visual and motor impairment, sleep disruption, eating disorders, separation anxiety and poor quality of life compared to children without tics (25).

4. Conclusions

Although there are over 20 years of research of the PANDAS syndrome, there is still a stringent need to a better definition of clinical manifestations, precise biological markers and neuroimaging tests in order to establish a therapeutic protocol following correctly drawn.

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Competing interests

The authors declare that they have no competing interests.

References

1. Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, Lougee L, Dow S, Zamkoff J and Dubbert BK: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: Clinical description of the first 50 cases. Am J Psychiatry 155: 264-271, 1998.
2. Swedo SE, Leckman JF and Rose NR: From research subgroup to clinical syndrome: Modifying the PANDAS criteria to describe PANS (pediatric acute-onset neuropsychiatric syndrome). Pediatr Therapeut 2: 1-8, 2012.
3. Kirvan CA, Swedo SE, Kurahara D and Cunningham MW: Streptococcal mimicry and antibody-mediated cell signaling in the pathogenesis of Sydenham's chorea. Autoimmunity 39: 21-29, 2006.
4. Siloşi CA, Siloşi I, Pădureanu V, Bogdan M, Mogoantă ŞȘ, Ciurea ME, Cojocaru M, Boldeanu L, Averămescu CS, Boldeanu MV and Popa DG: Sepsis and identification of reliable biomarkers for postoperative period prognosis. Rom J Morphol Embryol 59: 77-91, 2018.
antibodies and movement disorders associated with streptococcal infection. Pediatrics 121: 1198-1205, 2008.

11. Cunningham MW, Miller V, Swedo SE, Mutch PJ: Cefdinir for recent-onset pediatric neuropsychiatric disorders. JIMMU 69: 2209-2212, 2018.

12. Murphy TK, Parker-Athill EC, Lewin AB, Storch EA and Mutch PJ: Cefdinir for recent-onset pediatric neuropsychiatric disorders: A pilot randomized trial. J Child Adolesc Psychopharmacol 25: 57-64, 2015.

13. Albu CV, Padureanu V, Boldeanu MV, Bumbea AM, Enescu AS, Niculescu EC, Dop D, Diaconu R, Stepan AE, Gheonea C and Enescu A: Vascular neurocognitive disorders and the vascular risk factors. J Mind Med Sci 5: 7-15, 2018.

14. Franklin ME, Sayta J, Freeman JB, Khanna M, Compton S, Almirall D, Moore P, Choate-Summers M, Garcia A, Edson AL, et al: Cognitive behaviour therapy augmentation of pharmacotherapy in pediatric obsessive-compulsive disorder: The pediatric OCD treatment study II (POTS II) randomized controlled trial. JAMA 306: 1224-1232, 2011.

15. Swedo SE, Franklin J and Murphy TK: Overview of treatment of pediatric acute-onset neuropsychiatric syndrome. J Child Adolesc Psychopharmacol 27: 562-565, 2017.

16. Sigra S, Hesselmark E and Bejerot S: Treatment of PANS and PANS: A systematic review. Neurosci Biobehav Rev 86: 51-65, 2018.

17. Franklin J, Swedo S, Murphy T, Dale RC, Agalliu D, Williams K, Daines M, Mady Hornig M, Chugani H, Brewer S, et al: Clinical management of pediatric acute-onset neuropsychiatric syndrome: Part II-use of immunomodulatory therapies. J Child Adolesc Psychopharmacol 27: 574-593, 2017.

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