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PANDAS and PANS: Pathophysiology, Diagnostics and Therapeutic Approaches in Pediatric Autoimmune Neuropsychiatric Disorders – a literature review

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ABSTRACT

Introduction and Purpose

PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) and PANS (pediatric acute-onset neuropsychiatric syndrome) are neuropsychiatric disorders that have been debated since their first descriptions. PANDAS is linked to Group A Streptococcus (GAS) infections and is characterized by the sudden onset of symptoms such as OCD and tics after GAS infection. PANS involves a broader spectrum of symptoms without a specific GAS trigger. Both conditions are under-researched, and diagnosing and treating them is challenging. This article summarizes the current knowledge on PANDAS and PANS, focusing on their etiology, diagnosis, and treatment.

Description of the State of Knowledge

PANDAS and PANS are marked by the sudden onset of OCD or severe food intake restrictions, alongside other neuropsychiatric symptoms. Clinical criteria for PANDAS were proposed in 1998, linking it to GAS infections, and in 2012, broader PANS criteria were introduced, expanding the possible causes. The pathophysiology remains unclear, with theories suggesting autoimmune processes or neuroinflammation. Diagnosis is complicated by symptom overlap with other disorders. Treatment often involves a multidisciplinary approach, including behavioral therapy and, in some cases, antibiotics for GAS infections. The effectiveness of immunomodulatory therapies remains debated.

Conclusions

PANDAS and PANS are complex disorders with sudden-onset symptoms, but diagnosing them is difficult due to unclear pathophysiology and overlapping symptoms. Further research is needed to better understand the underlying mechanisms and improve diagnostic and therapeutic approaches.

Keywords

PANDAS; PANS; Obsessive-Compulsive Disorder; Group A Streptococcus; Neuroinflammatory Disease

1. Introduction

Since the first description of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) was published in 1998 [1], controversies and the lack of clinical guidance have been challenging physicians, to whom parents, frightened by the acute onset of neuropsychiatric symptoms in their children, have addressed questions regarding the diagnosis and treatment of this entity. PANDAS, as a clinical entity, is characterized by an explosive onset of tics and obsessive-compulsive disorder (OCD) symptoms, and it is associated with group A beta-hemolytic streptococcus (GAS) infection. A broader definition, without the criterion of association with GAS infection, was published in 2012 [2] and it describes pediatric acute-onset neuropsychiatric syndrome (PANS). Although it is thought that PANDAS is a rare disorder [3], feelings of fear, frustration, and not being heard were reported by family members of children diagnosed with PANDAS [4]. This fact indicates that there is a need to explore the unknown etiology of this clinical entity and to work on defining a consensual, evidence-based diagnostic and therapeutic pathway.

2. Objective of the work

The aim of this study is to summarize the current knowledge of PANDAS and its broader version, PANS, including their etiology, risk factors, diagnosis, and treatment.

3. Matherials and methods

For this review article, databases such as PubMed and Google Scholar were searched. The search terms used to find relevant scientific papers included: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, pediatric acute-onset neuropsychiatric syndrome, PANS/PANDAS pathophysiology, and PANS/PANDAS treatment. Ultimately, 36 research articles were cited.

4. Description of the state of knowledge

1.

Definitions

Clinical criteria for PANDAS were proposed in 1998 for the first time. [1] [Table 1.] Patients suspected to be diagnosed with PANDAS had to meet all of the five criteria.

Criterion	Description
Presence of OCD and/or a tic disorder	satisfying lifetime diagnostic criteria (DSM-III-R or DSM-IV) for OCD or a tic disorder
Pediatric onset	symptoms presented for the firat time between age of 3 and the beginning of puberty
Episodic course of symptom severity	abrupt onset of symptoms or dramatic symptom exacerbations
Association with GAS infection	time relation to positive throat culture or elevated serum level of anti-GAS antibodies
Association with neurological abnormalities	abnormal results of neurological tests while presenting symptoms exacerbations

Table 1. 1998 PANDAS criteria.

In 2012, a group of authors proposed new, broader criteria for an umbrella entity—PANS [Table 2], which includes the PANDAS subgroup of patients and encompasses those who do not meet the criterion of association with GAS infection [2] as observed symptoms do not always coincide with GAS infections. Additionally, tics are no longer considered the main criterion, and more specific neuropsychiatric symptoms are described in relation to the constellation of PANS signs. However, PANS is diagnosis of exclusion based on the clinical presentation.

1. **Unusually abrupt and dramatic onset of obsessive compulsive disorder (OCD) or severely restricted food intake**
2. **Concurrent, abrupt onset of additional severe neuropsychiatric symptoms from at least 2 of the following 7 categories:** • **Anxiety;** • **Emotional lability and/or depression;** • **Irritability, aggression, and/or severe oppositional behaviors;** • **Developmental regression;** • **Deterioration in school performance;** • **Sensory or motor abnormalities including heightened sensitivity to sensory stimuli, hallucinations, dysgraphia, and complex motor and/or**

	vocal tics; • **Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency**
3.	**Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette syndrome, or others.**

Table 2. 2012 PANS criteria.

The acuity of symptom onset is highlighted in both PANDAS and PANS definitions. Despite the fact that over a decade has passed since the PANS criteria were proposed, this entity is not listed in the DSM-V or ICD-11, which may lead to difficulties in diagnosing young patients who present with an abrupt onset of neuropsychiatric symptoms.

Pathophysiology

There is no strong evidence supporting any theory of PANDAS pathophysiology. Initially, it was theorized that the symptoms result from 'molecular mimicry' and the cross-reaction of anti-GAS antibodies with antigens in the basal ganglia, as part of a post-infection autoimmune process, similar to the etiology of Sydenham's chorea [5, 6], a typical post-streptococcal complication. Although this theory is based on the clinical similarity between PANS/PANDAS and Sydenham's chorea, there are studies that do not support the hypothesis that PANDAS symptoms result from antineuronal antibodies [7, 8]. In contrast, the most recent cohort studies show that specific antibodies against the human caudate nucleus and anti-neuronal antibodies are observed in children with OCD and PANDAS [9, 10]. Moreover, researchers have described cerebral microstructural differences in children with PANS in multiple brain structures: the thalamus, basal ganglia, and amygdala [11], which supports the theory of antibody cross-reaction with neuronal cell antigens. According to this theory, PANDAS could be described as an inflammatory brain disease.

In the context of the considered immunologic etiology of PANDAS/PANS, studies have been conducted that suggest a significant correlation between the discussed clinical symptoms and elevated anti-dopamine receptor (anti-D1R) and antilysoganglioside antineuronal antibodies in serum, concomitant with higher activation of CaMKII, a type of protein kinase that plays a critical role in various cellular processes in neuronal cells [12, 13]. Recent results from the work of Menendez, Chandra M, et al. demonstrate that a specific autoantibody obtained from PANDAS patients' sera targets D1R and is identified by the authors as a biomarker for PANS/PANDAS [14].

Furthermore, autoimmune processes are not the only factors considered to be involved in the pathophysiology of PANS/PANDAS. Kalinowski et al. explored the potential role of the C4 protein, a key component of the complement system, in this process, but the authors concluded that there was no difference in the number of copies of the C4A and C4B genes when comparing children with PANS/PANDAS to controls [15].

Recent research has also focused on the possible role of the gut microbiota, as streptococcal infections may lead to the selection of specific bacterial strains normally associated with gut inflammation and activation of the immune response [16].

Overall, the risk factors and biological mechanisms are not clearly defined, and there is a need for further research in this field.

Epidemiology and Clinical Presentation

There have been a few epidemiological and demographic studies on PANS/PANDAS. The exact prevalence of this condition remains unknown, but it is estimated that 5% of pediatric OCD patients meet the criteria for PANDAS [3], which seems to be a small percentage. However, large-scale epidemiological studies are needed to assess the actual incidence of PANS/PANDAS. Males are more frequently affected by PANS/PANDAS than females [1, 17], with the mean age of onset ranging from 6.3 to 7.4 years [1]. A recent cohort study from Italy assessed the median age of onset as 7 years old [17].

A crucial aspect of the patient's history is the acuity and relapsing-remitting course of the disease [18]. Moreover, the cardinal symptoms and comorbidities included in the PANS criteria reach peak severity within 24-48 hours of onset [18]. This characteristic disease course appears to differentiate PANS/PANDAS patients from other pediatric cases of OCD and tics.

As both the PANS and PANDAS criteria state, there are many possible constellations of clinical symptoms that patients may present at onset. The most frequently reported symptoms are separation anxiety (92%), followed closely by school issues (81%) and sleep problems (71%). Moreover, children may present behavioral regression, aggressiveness, hyperactivity, dysgraphia, mydriasis, tics, urinary symptoms (frequency or enuresis), increased sensory sensitivity and restricted food intake. OCD symptoms include intrusive thoughts, phobias/contamination fears, unfounded fears, repetitive behaviors [17, 18].

Diagnostics

One of the main challenges in diagnosing PANS/PANDAS is that, according to the criteria, the discussed medical entity is defined as a diagnosis of exclusion, and the physician's task is to rule out many diseases that may explain the reported symptoms and their acute onset. The fact that there are many psychiatric or neuropsychiatric diseases characterized by clusters of symptoms overlapping with the PANS/PANDAS criteria can also be challenging when evaluating a patient suspected of having PANS/PANDAS. However, based on studies conducted, there is a list of key points to follow in order to recognize children with PANS/PANDAS.

Patient Medical History and Family History

As a basic diagnostic tool, the patient’s medical history should be thoroughly assessed, including signs and symptoms characteristic not only of PANS but also of other medical disorders that must be excluded. Diseases considered as differential diagnoses for children with PANS/PANDAS include OCD, anorexia nervosa, avoidant/restrictive food intake disorder, Tourette syndrome, transient tic disorder, bipolar disorder, Sydenham’s chorea, autoimmune encephalitis, systemic autoimmune diseases, and Wilson’s disease [19]. Therefore, it is crucial to screen the patient’s history for symptoms indicating any of these disorders and also for any previous mental health issues. Children with a history of preexisting mental health disorders suspected of having PANS may present symptoms related to those conditions, and misinterpreting them as a presentation of a new acute-onset syndrome like PANS/PANDAS may lead to misdiagnosis. Moreover, many comorbidities have been found to coincide with PANS. Youth with PANS often have comorbid anxiety, emotional lability, and report a low quality of life [20]. Therefore, it is essential to evaluate the clinical course of the symptoms presented, including duration, severity, impact on normal life functioning, and acuity of onset [19]. The history of upper respiratory infections, particularly GAS infections, is also important, and antibiotic treatments for symptomatic pharyngitis should be noted [21]. Medical records from the primary care physician or the school nurse may also be helpful, as they may reveal prior neuropsychiatric or neurodevelopmental disorders [21].

Moreover, screening of the patient’s family history should also be performed, as first-degree relatives of PANS patients have increased rates of tic disorders, OCD, acute rheumatic fever, and maternal autoimmune disorders [19, 22, 23], which may indicate that PANS/PANDAS patients have an inherited vulnerability to develop such symptoms. However, genetic risk factors are not well defined.

Neurologic Examination

PANS/PANDAS patients do not present neurological abnormalities on examination, except for motor or vocal tics and choreiform movements, particularly piano-playing movements of the fingers when the child has their arms and hands extended and eyes closed [1]. These movements may be elicited with a Romberg test [19]. If more organized choreiform movements, affecting the entire body including the face and tongue, are present, the diagnosis of Sydenham's chorea or autoimmune encephalitis should be considered [19].

Psychiatric Evaluation

A comprehensive evaluation by an experienced pediatric psychiatrist or psychologist is needed to recognize all present and prior psychiatric disorders and to differentiate PANS/PANDAS from other entities. If this is not possible, the assessment by the primary care pediatrician should be performed, focusing at least on the PANS-related signs and symptoms [19].

Infectious Disease Evaluation

Despite the fact that GAS infection is debated as the trigger for PANDAS, routine testing, including pharyngeal swabs and antistreptococcal antibodies, is not recommended in all cases of acute-onset neuropsychiatric symptoms consistent with PANS. The American Academy of Pediatrics states that there is a lack of empirical evidence supporting the benefit of universal GAS testing and subsequent antibiotic treatment in positive patients, outweighing the potential harms [21]. Moreover, a positive result for anti-GAS antibodies indicates exposure to GAS but does not distinguish a new acute infection from a chronic carrier state lasting for years [24]. Therefore, only children with pharyngitis consistent with streptococcal infection are recommended to be tested for GAS [21].

Neuroimaging

Brain MRI results of PANS/PANDAS patients reveal enlargement of the basal ganglia structures (e.g., caudate nuclei, putamen, and globus pallidus) [24, 25]. Furthermore, PET scans have demonstrated increased activation of microglial cells, which are associated with neuroinflammation, in the bilateral caudate nuclei and bilateral lentiform nuclei in youth with PANDAS [26]. However, there is no clear neuroimaging diagnostic protocol for PANS/PANDAS. MRI results may be helpful in distinguishing PANS/PANDAS from other neuropsychiatric disorders, such as autoimmune encephalitis, when more specific symptoms are reported [21].

Treatment

As PANS/PANDAS is a multisymptomatic condition, the treatment recommendations must also be comprehensive. Three main subgroups of interventions can be specified: 1) psychiatric and behavioral interventions for OCD, other types of anxiety, tics, or food intake disorders; 2) antibiotic treatment for GAS infection; and 3) anti-inflammatory and immunomodulatory therapies for presumed underlying neuroinflammation and autoimmune problems [27].

Psychiatric and Behavioral Interventions

Psychiatric, physical therapy/occupational therapy, and traditional symptom-managing interventions are recommended for the treatment of psychiatric and behavioral problems in PANS/PANDAS patients [27]. It is important to start these interventions early in the course of symptoms in children with PANS, as other considered antibiotic or immunomodulatory medications take time to begin working [21]. OCD is one of the most important issues related to PANS/PANDAS [17, 18]. Cognitive Behavioral Therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) are the first-line treatments for OCD symptoms in children. Both of these treatment methods are helpful, although the combination of CBT and SSRIs is more effective than using either of them alone [29]. To help children with separation anxiety return to normal daily activities and regular sleeping patterns, parent training should be offered. Moreover, CBT may also be helpful [28]. In most cases of PANS/PANDAS, motor or vocal tics are not treated. However, if tics interfere with the child's functioning, comprehensive behavioral intervention for tics (CBIT) may be considered as a treatment [30]. Sleep disturbances, which are common in children with PANS/PANDAS, require the application of good sleep hygiene principles as the first line of treatment. Occasionally, melatonin may be recommended if behavioral interventions fail to improve sleep [28]. An unusually abrupt and dramatic onset of severely restricted food intake is one of the cardinal symptoms of PANS [2]. This is related to OCD symptoms in PANS patients, as children with PANS often report fears of food contamination, poisoning, vomiting, or choking, leading to restrictions in food intake [31]. In cases of avoidant/restrictive food intake disorder (ARFID), there are two main interventions that may be helpful. Firstly, an assessment of vital signs, electrocardiogram (ECG), electrolytes, and body weight should be performed to identify PANS/PANDAS patients who may require hospitalization and nutritional therapy. Exposure and response prevention (ERP) – a specific type of CBT – involves gradual exposure to foods and associated discomfort while guiding patients to resist compulsive behaviors, such as food restriction, that relieve their anxiety. ERP is the second intervention that should be considered

and is generally recommended in OCD treatment, as it exposes patients to situations that trigger their anxiety or discomfort [28].

Antibiotic Treatment for GAS Infection

As GAS infection is considered a trigger for PANS/PANDAS, various antibiotics have been used to treat PANS/PANDAS symptoms in children. However, the results of conducted studies are inconclusive, and the evidence for the effectiveness of antibiotic prophylaxis is limited [32, 33]. The American Academy of Pediatrics states that only patients with an abrupt onset of PANS/PANDAS symptoms and concomitant pharyngitis should be tested for GAS using a throat culture, a rapid antigen detection test, or a nucleic acid amplification test. If the result is positive, the patient should be treated with the appropriate antibiotics for a 10-day course (usually amoxicillin) [21]. Chronic secondary antimicrobial prophylaxis for streptococcal infections in specific patient groups has been suggested by some authors [33]. However, there is no clear evidence of its clinical effects, and no guidelines define the duration of this prophylaxis. Therefore, larger-scale studies are needed on this topic.

Anti-inflammatory and Immunomodulatory Therapies

Neuroinflammation is postulated to play a key role in the pathophysiology of PANS/PANDAS. Immune abnormalities have been documented in over 80% of PANS patients [20, 34]. Depending on the severity of PANS symptoms, different immunomodulatory therapies have been suggested by some specialists. In patients with mild PANS symptoms that persist over time, nonsteroidal anti-inflammatory drugs (NSAIDs) and/or short bursts of oral corticosteroids may be helpful. For moderate-to-severe PANS, oral or intravenous corticosteroids may be considered; however, intravenous immunoglobulin (IVIG) is often the preferred treatment for these patients. For more severe or chronic presentations, prolonged corticosteroid courses (with tapering) or repeated high-dose corticosteroids may be indicated. For PANS with extreme or life-threatening impairment, therapeutic plasma exchange (TPE) is the first-line therapy, either alone or in combination with IVIG, high-dose intravenous corticosteroids, and/or rituximab [35]. However, opposing arguments can also be found. A systematic review from 2018 showed that the evidence for the use of NSAIDs, steroids, IVIG, and TPE was inconclusive [32]. Moreover, a 2016 randomized controlled trial (RCT) failed to demonstrate the superiority of IVIG over placebo in patients diagnosed with PANS [36]. Therefore, the APA does not recommend the use of aggressive immunomodulatory therapies, given the lack of clear evidence of underlying CNS inflammation or autoimmunity in many children diagnosed with PANS [21]. It is important to remember the potential risks of aggressive therapies and the need for an individualized

approach to children with PANS, as they may present various symptom constellations that require evaluation by specialists.

5. Conclusions

In conclusion, the diagnosis and treatment of PANDAS and its broader counterpart, PANS, continue to be a challenge for both pediatricians and patients' relatives. Well-established diagnostic criteria are not defined, and the pathophysiology of these medical entities is not clearly understood. Although the association between PANS/PANDAS and immune or autoimmune responses is an area of active research, definitive evidence supporting the neuroinflammation theory remains limited. Additionally, biological markers for PANS/PANDAS are not yet known. The proposed theories, such as molecular mimicry and the role of streptococcal infections, offer potential frameworks for understanding these disorders, but further studies are needed to verify these hypotheses.

The clinical presentation of PANS/PANDAS is complex, with a broad spectrum of symptoms and comorbidities. The sudden and dramatic onset of neuropsychiatric symptoms distinguishes this disorder, but its overlap with other psychiatric and neurodevelopmental conditions complicates diagnosis. Effective treatment strategies must address not only the psychiatric and behavioral symptoms but also incorporate immunomodulatory therapies when indicated. However, despite promising interventions such as immunotherapy, there is insufficient evidence to definitively recommend these treatments for all patients. Moreover, the potential risks must be considered, as well as the need for individualized treatment plans.

As we look ahead, it is clear that further research is essential to better understand the underlying mechanisms of PANS/PANDAS, define diagnostic criteria, and evaluate the efficacy of current and emerging treatments. Clinicians must maintain a cautious approach, adjusting interventions to the severity of symptoms and the individual needs of each patient.

Disclosure:

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