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PANDAS AND PANS: PATHOGENESIS, DIAGNOSIS AND TREATMENT OF MYSTERIOUS DISEASES

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ABSTRACT

PANDAS and PANS are rare conditions characterized by rapidly developing neuropsychiatric symptoms such as OCD and tics. To diagnose PANDAS, it is necessary to establish its relationship with group A Streptococcus infection. PANS, on the other hand, includes cases of various etiologies. Despite decades of research, many aspects of these conditions remain unclear.

Aim: The aim of this paper is to review the latest research on the pathogenesis, diagnosis, and treatment of PANS and PANDAS.

Materials and methods: A literature review was conducted using the PubMed and Google Scholar databases, focusing on articles published between 1998 and 2026.

Results: Research indicates that neuroinflammation in the basal ganglia is the cause of PANDAS and PANS development. Specific brain structures and autoantibodies involved in this process have been identified. Despite this, diagnosis of these syndromes remains difficult, and treatment, including antibiotic therapy, psychiatric treatment, and immunomodulatory therapy, is based on limited scientific evidence.

Conclusions: Further research is necessary to expand our understanding of the causes of PANDAS and PANS and to enable more effective diagnosis and treatment of this syndrome.

KEYWORDS

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections, PANDAS, Pediatric Acute-onset Neuropsychiatric Syndrome, PANS, Neuroinflammation, Autoantibodies, Post-streptococcal Sequelae

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Introduction

Group A beta-hemolytic *Streptococcus* (GAS) is a common Gram-positive bacterium. Infections caused by it are extremely diverse, ranging from asymptomatic infections, pharyngitis, scarlet fever, and pyoderma, to serious invasive diseases such as sepsis, toxic shock syndrome, and necrotizing fasciitis. GAS can also cause post-infectious immunological complications. (Brouwer et al., 2023).

In 1998, Swedo et al. described a group of 50 children with streptococcal infection in whom they observed an abrupt onset of obsessive-compulsive disorder (OCD) and tics. It was accompanied by other neuropsychiatric symptoms such as emotional lability, separation anxiety, nighttime fears and bedtime rituals, cognitive deficits, oppositional behaviors, and motor hyperactivity. The disorder was characterized by a relapsing-remitting symptom pattern (Swedo et al., 1998). The newly discovered disease was defined as PANDAS, which is an abbreviation for Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections.

In subsequent years, researchers noted that similar symptoms also occurred in patients infected with other pathogens, such as *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, *Herpes simplex*, or the Varicella zoster virus, as well as in cases without a known infectious context. Therefore, they implemented the classification of PANS (Pediatric Acute-onset Neuropsychiatric Syndrome), which is broader than PANDAS and does not require knowledge of the etiology of the disorder (Swedo et al., 2012). PANDAS was therefore recognized as a subcategory of PANS.

Despite nearly 30 years of research on PANDAS, the pathophysiology of this disorder remains incompletely understood. There are also no universally accepted diagnostic criteria or treatment protocols. This unsatisfactory state of affairs is primarily due to difficulties in establishing causal and temporal links between infection and the onset of OCD and tics, as well as the clinical and immunological overlap between PANDAS and PANS, and other disorders such as Sydenham's chorea (SC). (Swedo et al., 2024).

Finding consensus is also hampered by the lack of large randomized trials and insufficient data on the actual effectiveness of antibiotics in children with this disease (La Bella et al., 2023). However, research is still underway that will hopefully shed light on controversial issues surrounding this disease and provide better patient care.

Methodology

Our work focuses on the pathogenesis, diagnosis, and treatment of PANS and PANDAS. We also considered issues related to the clinical presentation, epidemiology, and history of research on these diseases. We searched the PubMed and Google Scholar databases for articles published between 1998 and 2026. For our search, we used the terms "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections" and "pediatric acute-onset neuropsychiatric syndrome" in combination with "pathogenesis," "diagnostics," and "treatment." Our review included both original articles and review publications, as well as meta-analyses and case reports. We excluded articles not written in English.

Diagnostic criteria

The diagnostic criteria for PANDAS were first proposed by Swedo et al. in 1998. To make a diagnosis of PANDAS, patients had to meet all five criteria:

1. Presence of OCD and/or a tic disorder.
2. Pediatric onset – onset of symptoms between 3 years of age and the onset of puberty.
3. Episodic course of symptom severity – sudden onset of symptoms or dramatic exacerbations.
4. Association with GAS infection – confirmed presence of streptococci in the throat and/or presence of anti-GAS antibodies in the blood.
5. Association with neurological abnormalities – abnormal neurological test results during exacerbations. (Swedo et al., 1998).

In 2012, in connection with the description of a new disease entity, PANS, researchers proposed new criteria:

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 (Swedo et al., 2012).

According to the above criteria, PANS is a diagnosis of exclusion – this condition can only be diagnosed after ensuring that the symptoms presented have no other known cause. The differential diagnosis primarily includes other disorders with neuropsychiatric symptoms, such as Sydenham's chorea, Tourette syndrome, OCD, central nervous system vasculitis, autoimmune encephalitis, and neuropsychiatric lupus. (Dop et al., 2020).

Compared to the PANDAS criteria, the PANS criteria take into account neuropsychiatric disorders other than OCD and tics and do not specify the etiology of the disorder or the age of patients.

Epidemiology and clinical picture

The prevalence of PANDAS and PANS in the general population has not yet been accurately estimated due to the lack of large epidemiological studies. However, it is believed that approximately 5% of children with OCD meet the criteria for PANDAS. (Wald et al., 2023).

PANS and PANDAS are more common in boys than in girls (La Bella et al., 2023, Baj et al., 2020). This trend was already noticeable in the first study on PANDAS – three-quarters of the patients studied at that time were male (Swedo et al., 1998). This was confirmed by subsequent studies, such as a systematic review from 2022, which found 59.9% of patients were male (Cocuzza et al., 2022), and a cross-sectional study from 2024, in which the male-to-female ratio was 3.33:1 (Leonardi et al., 2024).

PANDAS and PANS symptoms most often appear during the prepubertal period. The average age of onset for tics is 6.3 years, and for OCD, 7.4 years (Swedo et al., 1998). The young age of PANDAS patients may be due to the fact that the immune response to pathogens is generally stronger in young children than in adolescents and adults (Grandinetti et al., 2024). Furthermore, children aged 5-12 years are more likely to develop PANDAS due to high exposure to GAS. The spread of infections among children is also facilitated by the fact that they are often asymptomatic (Esposito et al., 2014).

A characteristic feature of PANDAS, distinguishing it from other causes of OCD in children, is the rapid and abrupt onset of symptoms and the relapsing-remitting course of the disease. Symptoms peak 24-48 hours after onset (Swedo et al., 2015). Although the most common symptoms of PANDAS are OCD and tics, the most common symptoms observed in children were separation anxiety (92%), school issues (81%), and sleep disruptions (71%). However, the clinical picture of PANS and PANDAS is much broader. It includes 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, and repetitive behaviors (Swedo et al., 2015).

Among the initial symptoms of PANS, the most frequently observed were OCD (89%), anxiety (78%), and emotional lability (71%) (Gromark et al., 2019). Restrictive eating disorders can also be an initial symptom of PANS. They can take the form of an obsessive fear of contamination, sudden fear of swallowing, vomiting, or choking, perception of the appearance of food as unpleasant, or even body image distortions. Food restriction is often selective toward specific foods. In rare cases, children completely refuse to eat or drink (Toufexis et al., 2015).

In the study by Prosell et al., speech fluency disorders occurred in 54.5% of children diagnosed or suspected of having PANDAS or PANS. These disorders include higher speech rate, superfluous verbal

behavior, verbal blocks, and associated motor symptoms. The children participating in this study also had other verbal communication problems: stuttering, vocal tics, impaired articulation, reduced speech production and intelligibility, "baby talk" (a simplified, childish way of speaking) and mutistic behavior. (Prosell et al., 2022).

During PANS flares, children may be agitated, irritable, and aggressive, but also depressed or frightened. They experience involuntary, uncontrolled, and often mood-inconsistent episodes of laughing or crying. Memory impairment and, in the later stages of the disease, depression have also been reported (Swedo et al., 2012). Other symptoms found in children with PANS include auditory and visual hallucinations, including violent images, and suicidal and homicidal ideation. Patients have also been observed to have motor and phonic tics, behavioral regression, and extreme compulsions such as shoe licking and barking. (Grandinetti et al., 2024).

Physical examination may reveal dehydration or emaciation—consequences of restrictive eating disorders—as well as sequelae of compulsive symptoms, such as chapped hands from excessive washing or a red ring around the mouth from frequent lip licking. Due to the streptococcal etiology of PANDAS, patients may also experience pharyngitis or chorea similar to Sydenham's chorea (Grandinetti et al. 2024).

Sleep disturbances are common in children with PANS and PANDAS. They are present in up to 80% of patients, appear at the beginning of the disease and sometimes disappear during the course of the disease. The most frequently observed symptoms are parasomnias (nightmares, somnambulism and pavor nocturnus) as well as early or intermediate insomnia (difficulties in falling asleep or maintaining sleep), terminal insomnia (early awakenings), sleep movement disorders such as Periodic Limb Movement Disorder (PLMD) and REM sleep disorders such as REM Sleep Without Atony (RSWA). In a 2021 prospective study, polysomnography revealed sleep abnormalities in 73.9% of patients. 47% of them had ineffective sleep, 58.8% had fragmented sleep, 64.7% had RSWA, and 47.1% had PLMD. Among patients for whom respiratory parameters were available, 77.8% presented with snoring and 33% with obstructive sleep apnea syndrome (OSAS) (Gagliano et al., 2021).

Pathogenesis

A diagnosis of PANDAS requires a link between the onset of symptoms and a streptococcal infection (Swedo et al., 1998). The most common infections preceding the onset of PANDAS are sinusitis, pharyngitis, and bronchitis. It has not yet been determined whether any of these conditions is more likely to cause PANDAS. GAS infection can cause both onset and exacerbations. Patients with a history of multiple streptococcal infections have been observed to have a more severe course of PANDAS and more frequent relapses (Grandinetti et al., 2024).

Unlike PANDAS, the diagnosis of PANS does not require determining the cause of the patient's symptoms. There is evidence that, in addition to streptococci, PANS symptoms can be triggered by numerous other pathogens, including viruses (varicella zoster virus, Epstein-Barr virus, herpes simplex virus, Enterovirus, HIV, and SARS-CoV-2), bacteria (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Borrelia burgdorferi*), and protozoa (*Toxoplasma gondii*) (Grandinetti et al., 2024). Importantly, the etiology of PANS does not always have to be infectious. There are reports in the literature of PANS symptoms appearing in response to factors such as multiple food allergies, severe asthma, severe atopic eczema, celiac disease, post-infectious arthritis and IgA vasculitis (formerly known as Henoch-Schönlein purpura) (Gromark et al., 2018).

The pathogenesis of PANDAS and PANS remains incompletely understood, but molecular mimicry is believed to be the most important mechanism. This phenomenon involves antibodies directed against pathogens binding to human epitopes that are structurally similar to bacterial antigens (Rojas et al., 2018). According to this hypothesis, in PANDAS, antibodies cross the blood-brain barrier and bind to brain antigens, leading to inflammation in specific CNS structures, particularly the basal ganglia, and ultimately to neuropsychiatric disorders. Studies suggest a correlation between OCD and tics in children with PANDAS and elevated levels of autoantibodies (Cox et al., 2015). Therefore, PANDAS probably has a similar pathogenesis to another disease resulting from a streptococcal infection, whose autoimmune etiology is quite well understood – Sydenham's chorea (La Bella et al. 2023).

The pathophysiology of OCD and tic disorders is still a subject of research (Pauls et al., 2014), but these symptoms are believed to result, among other things, from impaired corticobasal ganglia circuitry (Bostan et al., 2018). In 2020, Xu et al. investigated whether such dysregulation also occurs in PANDAS, as a result of autoantibodies binding to structures in the basal ganglia. By exposing both mouse and human striatal tissue to IgG antibodies derived from the serum of children with PANDAS, they identified a neuronal population to which these antibodies exhibited high avidity: cholinergic interneurons of the striatum (CIN) (Xu et al., 2020).

It was observed that as PANDAS symptoms resolved after IVIG treatment, the strength of IgG binding to CIN significantly decreased (Frick et al., 2018). Xu et al. demonstrated that a similar phenomenon of IgG binding to CIN also occurs in patients with PANS who do not meet the strict criteria for PANDAS. However, they observed that in these patients, autoantibodies also tend to bind to other neuronal populations, such as PV interneurons and cholinergic septal neurons (Xu et al., 2024). Other studies have shown that inhibition of CIN function plays a role in the emergence of repetitive behavioral disorders in Tourette syndrome (Lenington et al., 2015; Kataoka et al., 2010). Additional evidence for the involvement of CIN disorders in the pathogenesis of OCD and tics was provided by studies in mice. Experimental depletion of CIN cells resulted in the emergence of repetitive behavioral pathology in these animals (Xu et al., 2015).

Research into the pathogenesis of PANDAS focuses not only on determining which brain regions are affected but also on identifying the specific epitopes against which autoantibodies are directed. Studies (Cox et al., 2015; Cunningham et al., 2016) suggest that they react with antigens such as lysoganglioside, dopamine receptors, CaMKII, and tubulin. Animal models may be useful to identify these antigens. In one such study, antibodies extracted from the serum of children with PANDAS were administered into the subarachnoid space of mice. Disruption of Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) activity was observed (Cunningham et al., 2016). This protein is responsible for behavioral control, learning and memory mechanisms, neuronal development, cortical excitability, and the synthesis and release of neurotransmitters. Increased CaMKII levels lead to increased dopamine release, which is associated with the development of tics and obsessive-compulsive disorder. Studies suggest that this increase is correlated with increased serum concentrations of specific antineuronal antibodies: anti-D1R and antilysoanglioside (Cox et al., 2015). CaMKII levels are significantly elevated in Sydenham's chorea, but not as significantly in PANDAS. This suggests that the pathophysiology of these diseases is closely intertwined, and the development of specific symptoms—isolated neuropsychiatric disorders in PANDAS and neuropsychiatric and movement disorders in Sydenham's chorea—depends on CaMKII levels (Cunningham et al., 2016).

Another evidence supporting the close connection between PANDAS and Sydenham's chorea is that antibodies against the dopamine receptors D1R and D2R have been detected in patients with each disease (Chain et al., 2020). However, anti-D1R antibodies have been shown to be significantly more common in children with PANDAS, while anti-D2R antibodies are more characteristic of Sydenham's chorea. In the latter, the anti-D2R/D1R antibody ratio has even been shown to be correlated with the severity of neuropsychiatric symptoms (Ben-Pazi et al., 2013). Activation of different dopamine receptors may explain why two distinct GAS sequelae produce different symptoms, even though both are associated with autoimmune encephalitis – anti-D1R antibodies can cause OCD and tics, while anti-D2R antibodies can cause chorea (Menendez et al., 2024). It is worth noting that increased levels of anti-D2R antibodies were also detected in patients with PANDAS, who, in addition to the characteristic symptoms of this disease, also exhibited movement disorders similar to those seen in Sydenham's chorea (Cox et al., 2013). These observations may be useful in differentiating these two conditions.

Despite accumulating evidence that molecular mimicry plays a key role in the pathogenesis of PANDAS, this issue remains controversial, as some studies have yielded conflicting results. In 2011, Brilot et al. examined the surface binding of IgG antibodies from the serum of children with Sydenham's chorea, Tourette's syndrome, and PANDAS to antigens of live neuronal cell lines. Cell surface IgG binding was present in patients with Sydenham's chorea, but patients with PANDAS and Tourette's syndrome showed no differences from controls (Brilot et al., 2011). Other studies have also failed to identify autoantibodies specific to these diseases (Morris et al., 2009; Morris-Berry et al., 2013).

In addition to autoantibody activity, immune dysregulation may contribute to the development of PANDAS symptoms. Leonardi et al. conducted a study comparing immunological parameters of children with PANDAS with a control group. Although they did not find congenital immune disorders in any of the patients, they detected elevated levels of TNF-alpha and IL-17 and decreased levels of complement components C3 and C4 in children with PANDAS. TNF-alpha and IL-17 are proinflammatory cytokines, so researchers speculate that there is a correlation between their elevated levels and the persistence of neuropsychiatric symptoms in PANDAS patients (Leonardi et al., 2024).

The exact cause of the decreased C4 levels in PANDAS patients remains unknown. It has been proposed that it results from a reduced number of copies of the gene encoding this protein. This suggests that children with low numbers of copies of the C4 gene have a greater genetic susceptibility to PANDAS. However, studies have not demonstrated this association. No differences in gene copy number were found between children with PANDAS and healthy children (Kalinowski et al., 2023).

Magnetic resonance imaging (MRI) is a valuable tool that can provide information about which brain structures are affected in PANDAS and PANS. The appearance of brain inflammation is associated with an increase in the volume of affected structures (Giedd et al., 2000), a decrease in cerebral blood flow (CBF) (Sankar et al., 2018), and an increase in the diffusion of water molecules in the extracellular fluid, as reflected by the actual diffusion coefficient (ADC) (Vendhan et al., 2016).

Zheng et al. demonstrated that ADC was significantly higher in specific brain structures of children with PANS than in healthy children. This difference was most noticeable in the thalamus, caudate nucleus, putamen, globus pallidus, and amygdala (Zheng et al., 2020). Increased ADC in these specific structures is not surprising, given the symptoms of PANS: inflammation in the basal ganglia may contribute to motor disorders and obsessive-compulsive symptoms (Teixeira et al., 2014), and in the amygdala to mood disorders and emotional lability (Mehta et al., 2018). Lesions in the thalamus, on the other hand, may disrupt connections between different parts of the brain (Pelzer et al., 2017) and affect the sleep-wake rhythm (Jan et al., 2009). In the present study, CBF was also higher in children with PANS, but this difference did not reach statistical significance (Zheng et al., 2020).

Other studies have also observed increased volume of the caudate nucleus, putamen, and globus pallidus in children with PANDAS, which may also indicate the presence of inflammation in these structures (Giedd et al., 2000). Interestingly, Zheng et al. found no significant differences in the volume of individual brain regions between children with PANS and the control group (Zheng et al., 2020).

Results suggesting the involvement of the basal ganglia in the development of PANDAS have also been obtained using positron emission tomography (PET) imaging. This study demonstrated elevated binding potential values in the caudate and lenticular nuclei of PANDAS patients. This value is a measure of the binding of a radioactive substance to receptors in cells, and its elevated levels suggest activated microglia-mediated neuroinflammation in these brain regions (Kumar et al., 2015).

Evidence from neuropsychological testing and polysomnography also supports impaired basal ganglia function in children with PANDAS. Patients demonstrated poorer performance on tasks related to neurocognitive and executive functioning, visuospatial memory, and fine motor speed (Lewin et al., 2011). Rapid eye movement (REM) sleep motor disinhibition was observed in 80% of PANDAS patients undergoing polysomnography. This disorder can occur as a result of damage to the basal ganglia and is characterized by excessive movement, hand stereotypies, moaning, laughing, or the continuation of periodic limb movements during sleep (PLMS) into REM sleep (Gaughan et al., 2016).

Recently, research has increasingly focused on the function of the gut microbiota and its interaction with various structures of the human body, including the brain. The composition of the microbiota can influence human behavior and various brain functions through a network of interconnections known as the gut-brain axis (Carabotti et al., 2015). Analysis of the gut microbiota composition in children with PANDAS and PANS revealed that it differs from that of controls. The authors suggest that streptococcal infections may modify the gut microbiota by selecting specific bacterial strains that contribute to the development of a systemic immune response, increase intestinal permeability, and facilitate the production of autoantibodies. In PANDAS, such gut-derived immune activation can lead to disruption of the blood-brain barrier and, consequently, neuroinflammation (Shaik et al., 2026). This condition can persist even after the pathogen has been eliminated from the body. Moreover, these changes may have an indirect impact on brain function by reducing the production of substances involved in the metabolism of D-alanine, tyrosine, short-chain fatty acids or the dopamine pathway (Quagliariello et al., 2018).

As with many other diseases, genetic predisposition may increase the likelihood of developing PANS or PANDAS. Whole-exome sequencing was performed in patients with severe PANS, identifying 11 genes with mutations (*PPM1D*, *SGCE*, *PLCG2*, *NLRC4*, *CACNA1B*, *SHANK3*, *CHK2*, *GRIN2A*, *RAG1*, *GABRG2*, and *SYNGAP1*). These genes can be divided into two groups. Some are responsible for regulating the peripheral immune response and microglia, while others are responsible for the function of neuronal synapses. Mutations in some of these genes have also been identified in patients with autism spectrum disorder and myoclonic dystonia. Genetic predisposition as a cause of PANS is also suggested by the fact that 50% of the patients studied had other neurodevelopmental disorders (Trifiletti et al., 2022).

Interestingly, many of the identified genes are expressed in the intestine. The *PPM1D* gene has a protective effect on oxidation stress-induced gut permeability (Oshima et al., 2007), and mutations in the *NLRC4* gene influence the development of inflammatory bowel disease (Pellegrini et al., 2020). These findings, along with the previously mentioned distinct microbiota composition in children with PANDAS, strongly

suggest that disruption of the gut-brain axis plays an important role in the pathogenesis of PANDAS and PANS, as well as other autoimmune diseases and neuropsychiatric disorders (Trifiletti et al., 2022).

Analysis of the medical history of children with PANDAS revealed that first-degree relatives had a higher incidence of OCD, tics, and rheumatic fever than the general population, suggesting that susceptibility to non-suppurative post-streptococcal complications may be hereditary (Swedo et al., 1998). An increased incidence of autoimmune diseases has also been found in close relatives of patients. This trend is particularly evident in mothers of children with PANDAS (Murphy et al., 2012), with 20% of them reporting a diagnosis of a serious autoimmune disease such as multiple sclerosis, Crohn's disease, PANS, lupus, rheumatoid arthritis, or thyroid disease (Calaprice et al., 2017).

Diagnostics

As mentioned above, a diagnosis of PANDAS requires establishing a relationship between the disease and a streptococcal infection. This can be done by detecting the presence of GAS in the throat or other infected area of the body: nasal cavity, skin, anal or vaginal area – a rapid antigen test and bacterial cultures are used for this purpose. Another method involves detecting GAS-specific antibodies in the blood, such as antistreptolysin O (ASO) or antideoxyribonuclease B (anti-DNase B) (Delice et al., 2015). Their peak concentration in the blood occurs after the streptococcal infection, occurring after 3-5 weeks and 6-8 weeks, respectively (Esposito et al., 2014). Studies have shown that PANDAS flares are correlated with a sudden and dramatic increase in antistreptococcal antibody titers, whereas the decline in titers during remission is much slower (Murphy et al., 2012).

Unlike many other autoimmune diseases, no biomarkers have yet been identified that are pathognomonic for PANDAS. However, several candidates have been proposed: autoantibodies against dopamine D1R and D2R receptors, beta-tubulin, lysoganglioside GaM1, and CAMKII kinase activity. These analytes were used in the Cunningham Panel, a commercially available set of assays designed for the diagnosis and monitoring of PANS and PANDAS. However, the effectiveness of this panel in detecting PANS and PANDAS is highly questionable. In a 2017 study, all 13 PANDAS patients tested had at least one positive value on the Cunningham Panel (sensitivity 100%), however, 34 out of 38 non-PANDAS cases also had at least one positive value on the panel (specificity 11%). Similar results were obtained for 20 PANS patients: eighteen of them (sensitivity 90%) had at least one positive value. At the same time, 29 out of 31 non-PANS cases (specificity 6%) also had at least one positive value. No individual result or composite score had a diagnostic odds ratio > 1, meaning the Cunningham Panel was no better than chance in detecting PANDAS or PANS in these samples (Hesselmarm et al., 2017). In response to these results, a manufacturer-affiliated evaluation was created, which demonstrated correlations between Cunningham Panel test results and symptoms in already diagnosed patients (Shimasaki et al., 2020). However, this study design does not assess diagnostic accuracy in an unselected group of patients, so Hesselmarm et al.'s conclusions have not been effectively challenged (Cesaroni et al., 2026). The usefulness of the Cunningham Panel therefore requires further research, but at this time, it is not a recommended diagnostic method (Board of Directors, 2025).

In addition to analytes specifically associated with PANDAS or PANS, other laboratory parameters may be helpful in diagnosis. Blood tests should be performed not only at the onset of the disease but also later, especially during exacerbations (Frankovich et al., 2015). In a 5-year prospective follow-up study of 34 PANDAS patients, 78% of patients had abnormal blood counts, 74% had altered protein phoresis, 72% had reduced complement, 19% had TPO antibody elevation, 15% had TSH abnormalities, 11% had low T4, 7% had ANA positivity, 4% had low IgG, and 41% had IgG subclass deficiency. IL-1 beta was increased in 36%, IL-10 in 20%, and TNF-alpha in 19% of cases (Gromark et al., 2022).

Treatment

The treatment of PANDAS and PANS is based on three complementary modes of intervention: causal treatment, i.e., combating the microorganisms causing the disease, treatment of psychiatric symptoms (medications acting on the CNS, psychotherapy, supportive interventions), and treatment of immune system disorders through immunomodulatory and anti-inflammatory therapies (Swedo et al., 2017).

The primary treatment for PANDAS is antibiotics (La Bella et al., 2023). In clinical practice, beta-lactam antibiotics and the macrolides azithromycin and clarithromycin are used. However, there are no universally recognized antibiotic treatment guidelines, and the evidence for the effectiveness of specific antibiotics is equivocal, primarily due to the small number of studies. To date, only one (Wilbur et al., 2018) randomized, double-blind, placebo-controlled study has been published. In this study, 31 children received

either azithromycin or placebo for 4 weeks. The researchers observed a significant reduction in OCD symptoms in the drug-treated group. Other neuropsychiatric outcomes did not differ between the study and control groups (Murphy et al., 2017).

The choice of antibiotic depends mainly on the physician's experience, the patient's and/or caregiver's preferences, and data from non-randomized studies (La Bella et al., 2023). Typically, the treatment for streptococcal pharyngitis is amoxicillin at a dose of 50 mg/kg 2-3 times daily for 6-10 days (Grandinetti et al., 2024). This treatment is also recommended when there is no evidence of a relationship between PANS symptoms and streptococcal infection, as negative test results do not completely rule out the existence of an underlying source of infection (Cooperstock et al., 2017). An alternative to amoxicillin treatment may be azithromycin, whose advantages include ease of administration, activity against *Mycoplasma pneumoniae*, and possible immunomodulatory effects (Obregon et al., 2012). Unfortunately, the drawback of this antibiotic is the increasing bacterial resistance and the associated complications in patients (Silva-Costa et al., 2015). Patients with PANDAS usually experience rapid improvement after antibiotic administration (Falcini et al., 2013), but up to 50% of them may experience a relapse within 3 years.

While antibiotic therapy is an established treatment for the active phase of the disease, the effectiveness of antibiotic prophylaxis for PANDAS has not yet been proven and the evidence appears to be mutually exclusive. Studies in a small group of patients given a prophylactic dose of penicillin V showed no differences from placebo (Garvey et al., 1999). However, in another study, annual prophylaxis with penicillin V resulted in a 95% reduction in the incidence of GAS infections and a 75% reduction in the number of neuropsychiatric exacerbations. The same study found that azithromycin is also effective in the prevention of PANDAS - after its use, the number of infections decreased by 95% and the number of neuropsychiatric exacerbations by 56% (Snider et al., 2005). Lepri et al. also observed that long-term antibiotic prophylaxis resulted in significant benefits in reducing neurological symptoms in the majority of patients with PANDAS and PANS (Lepri et al., 2019). However, the inconclusive research results do not mean that antibiotic prophylaxis is of no importance in the treatment of PANDAS. Cooperstock et al. recommend its use in children with the most severe symptoms and/or multiple neuropsychiatric exacerbations. Its aim is to prevent the recurrence of poorly tolerated and debilitating symptoms and to reduce the risk of long-term complications of the disease (Cooperstock et al., 2017).

Psychological, behavioral, and psychopharmacological therapies are also important components of treatment for patients with PANDAS. These therapies can improve overall functioning and reduce specific symptoms. Cognitive behavioral therapy and low doses of SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) are used to treat OCD in PANDAS (Franklin et al., 2011).

Cognitive behavioral therapy (CBT) is an evidence-based treatment for OCD. However, few authors have described its use in patients whose disorder has an autoimmune etiology (Sigra et al., 2018). In a 2006 study by Storch et al., a significant reduction in obsessive-compulsive symptoms was observed in children with PANDAS who received this treatment. However, the significance of this evidence is limited by the small sample size (7 patients) and the lack of a control group (Storch et al., 2006). Similar limitations are associated with the 2015 study by Nadeau et al., which additionally had a high dropout rate – only 6 patients were evaluated at follow-ups ranging from 1 to 4 months. The improvement in the patients' condition may also have been influenced by the fact that they underwent antibiotic therapy in parallel with CBT (Nadeau et al., 2015).

Like cognitive behavioral therapy, SSRIs are commonly used to treat OCD, and there is ample scientific evidence to support their effectiveness. However, there have been no systematic studies of SSRIs in the treatment of OCD in PANDAS and PANS. Although the use of these medications has been reported in numerous case reports, assessing their effectiveness is hampered by the fact that they were not used as a mainstay of treatment for PANDAS in any of the studies and were used concurrently with other psychiatric or immunomodulatory medications. (Sigra et al., 2018).

In addition to causal treatment, immunomodulatory therapy plays a role in the treatment of PANDAS, which is due to the neuroinflammatory nature of the disease. Various immunomodulatory therapies are used, including NSAIDs, corticosteroids, IVIG, plasmapheresis, and rituximab (Frankovich et al., 2017). However, as with other PANDAS treatment options, the evidence for their effectiveness is equivocal.

The effectiveness of IVIG in treating PANDAS has been described in numerous case reports (Sigra et al., 2018). Surveys show that patients themselves rate this therapy quite highly – 49% considered it very effective, and 25% considered it somewhat effective (Calaprice et al., 2017). Despite this, the scientific evidence supporting its use in treating PANDAS is not very impressive. In 2016, Williams et al. conducted a randomized controlled trial examining the effectiveness of IVIG treatment compared to placebo. The study did not demonstrate superiority of this method (Williams et al., 2016). These results contradict an older RCT

from 1999, which suggested that IVIG was more effective than placebo (Perlmutter et al., 1999). It is worth noting that the majority of patients receiving IVIG in the 2016 study eventually recovered with this therapy. However, this occurred not in the double-blind phase, but only in the subsequent open-label phase. The authors did not identify a factor that would increase the efficacy of IVIG in the treatment of PANDAS, but they did observe that elevated baseline levels of calcium calmodulin-dependent protein kinase II (CaMKII) and antinuclear antibodies (ANA) in serum correlated with a good response to treatment (Williams et al., 2016).

The effectiveness of plasmapheresis in treating PANDAS is also poorly documented. The only controlled trial examining the effects of this therapy was the open-label placebo-controlled trial by Perlmutter et al. in 1999, which showed significant improvement in patients treated with plasmapheresis (Perlmutter et al., 1999). Similar findings were reported in a retrospective case series of 40 patients at Georgetown University Hospital. Plasmapheresis resulted in a 78% reduction in symptom severity during follow-up (Latimer et al., 2015).

Nonsteroidal anti-inflammatory drugs, commonly used for the symptomatic treatment of pain and inflammation, are also used in the treatment of PANDAS and PANS. Brown et al. retrospectively analyzed a group of 218 patients from the PANS clinic operating within the Stanford PANS Program. They observed that exacerbations in patients treated with NSAIDs lasted an average of 4 weeks shorter than in patients not taking these medications (Brown et al., 2017). Other researchers reported a case series based on the same sample and assessed the effectiveness of NSAID treatment. They considered patients as responders if their condition improved after adding an NSAID or worsened after removing it. According to their evaluation, NSAID treatment was effective in 42% of patients (Spartz et al., 2017).

The Stanford PANS clinic also conducted an observational study examining the effectiveness of oral corticosteroids in alleviating PANS flare-ups. Researchers observed that flare-ups in patients not receiving steroids lasted an average of 11.4 weeks, which is 3.5 weeks longer than in those receiving these medications. Corticosteroid therapy was more effective when administered early in the disease course and for a longer period of time. Unfortunately, as many as 44% of patients receiving this treatment experienced side effects, most commonly exacerbation of psychiatric symptoms, such as tics (Brown et al. 2017). Corticosteroid use is also associated with a high risk of relapse.

Some authors have advocated for surgical removal of the tonsils—tonsillectomy and adenoidectomy—as a treatment and prevention option for PANDAS. This would eliminate the most common cause of the syndrome, streptococcal pharyngitis. Evidence for the effectiveness of such interventions is very limited. Murphy et al. retrospectively found that the severity of neuropsychiatric symptoms and the presence of anti-streptococcal antibodies did not differ in patients with prior adenoidectomy and/or tonsillectomy compared to controls (Murphy et al., 2013). Similar conclusions were reached in a 2014 prospective study of 120 children with PANDAS, 56 of whom underwent surgery and 64 served as controls. Again, no significant improvement was observed in symptom progression, streptococcal and neuronal antibody levels, or the severity of neuropsychiatric symptoms (Pavone et al., 2014). Therefore, it seems that surgical treatment can be recommended only in those children with PANDAS who have standard indications for tonsillectomy, such as sleep apnea or chronic inflammation (Baugh et al., 2011).

Given the postulated role of gut microbiota in the pathogenesis of PANDAS, questions arise about the clinical significance of this information and the potential use of probiotics in the treatment of this disease. However, to date, no studies have provided evidence that any probiotics modulate neuropsychiatric symptoms in PANDAS. (Cooperstock et al., 2017).

Discussion

In the nearly thirty years since the first reports of PANDAS, numerous studies have been published on this syndrome. The description of the related disorder PANS allowed researchers to expand their attention to cases in which sudden-onset neuropsychiatric symptoms occurred in children without a clear history of streptococcal infections. However, many controversies surrounding PANDAS and PANS remain unanswered, and new discoveries have also raised new questions.

Recent years have provided evidence that the long-proposed concept of molecular mimicry as the primary pathophysiology of PANDAS and PANS is likely correct. Researchers have established that neuroinflammation in PANDAS involves the basal ganglia (Zheng et al., 2020; Kumar et al., 2014) and identified areas where autoantibodies bind (Xu et al., 2020).

The identification of autoantibodies present in patients has led to the discovery of links between PANDAS and Sydenham's chorea (Menendez et al., 2024; Chain et al., 2020; Cunningham et al., 2016). The evidence supporting the presence of neuroinflammation in these two autoimmune conditions is largely complementary. This includes not only similar autoantibody profiles but also imaging data showing changes in the basal ganglia and observable data on the effectiveness of immunomodulation (Vreeland et al., 2023). These connections create scope for further research. There are also reports of associations between these diseases and other neuropsychiatric disorders, such as Tourette syndrome (Hsu et al., 2021).

Another interesting issue that has recently attracted researchers' attention is the role of gut microbiota in the development of autoimmune diseases such as PANDAS and PANS. Changes in gut microbiota can affect intestinal barrier permeability, immune system homeostasis, and contribute to the development of neuroimmune diseases (Matera et al., 2025). A growing body of research (Quagliarello et al., 2018; Shaik et al., 2026) indicates that the composition of gut microbiota in patients differs significantly from that of healthy individuals.

Genetic analysis shows that the tendency to develop PANDAS and PANS may be hereditary (Trifiletti et al., 2022). Identifying the genes responsible for the development of these diseases may allow for the identification of risk groups and more effective prevention in the future.

Despite these advances, diagnosing PANDAS and PANS remains challenging. Laboratory biomarkers for these diseases have not yet been identified. Neither the Cunningham panel nor other tests such as ASO or anti-DNase B antibodies have proven particularly useful in this task (Hesselmark et al., 2017, Cesaroni et al., 2026). MRI and PET scans appear more promising, revealing brain structures affected by the disease process (Zheng et al., 2020; Kumar et al., 2014). However, neuroimaging has so far been used primarily to rule out structural, demyelinating, or inflammatory diseases rather than to confirm PANDAS (Cesaroni et al., 2026).

Studies have provided limited evidence for the effectiveness of PANDAS and PANS treatment with methods such as antibiotics, psychotherapy, SSRIs, IVIG, and plasmapheresis (Murphy et al., 2017; Snider et al., 2005, Storch et al., 2006, Nadeau et al. 2015, Perlmutter et al., 2019). A clinical report from the American Academy of Pediatrics indicated cognitive behavioral therapy and SSRIs as first-line treatment and recommended caution in the use of invasive immunotherapies such as IVIG or plasmapheresis (Board of Directors, 2025). Currently, there is no strong scientific evidence to support any treatment for patients with PANDAS, and each case should be considered individually (Sigra et al., 2018). However, this is not due to the ineffectiveness of these methods, but primarily to the lack of randomized trials.

An individualized approach to the treatment of patients with PANS and PANDAS also requires consideration of the psychological context. Cesaroni et al. point out that explaining the occurrence of tics and OCD as a consequence of an infectious disease may be perceived as more emotionally acceptable than a neurobiological or genetic model. An infectious cause of symptoms assumes a specific cause that can be treated in a specific way, for example, with antibiotics. Accepting that a child's neuropsychiatric symptoms stem from developmental disorders, often occurring in families, with a relapsing-remitting course and limited pharmacotherapeutic options may be psychologically more difficult for patients and their families to accept. This may also contribute to physicians misdiagnosing PANDAS and PANS when other causes of tics and OCD are present (Cesaroni et al. 2026).

Conclusions

Research into the pathogenesis, diagnosis, and treatment of PANDAS and PANS is enabling a growing understanding of these diseases and improving patient care. However, further research is necessary in each of these areas.

Evidence points to an autoimmune and neuroinflammatory pathophysiology of PANDAS and PANS. Recent years have seen the identification of brain structures involved in the disease process (Xu et al., 2020). Autoantibodies in patients have also been identified, and links between PANDAS and PANS and Sydenham's chorea have been discovered (Menendez et al., 2024). However, many questions remain unclear.

Diagnosing PANDAS and PANS is hampered by the lack of sufficiently sensitive and specific biomarkers. This is despite the expanding knowledge of the autoantibodies characteristic of these conditions. However, their usefulness in diagnosing and monitoring the disease remains limited. A similar situation applies to imaging methods such as MRI and PET (Cesaroni et al., 2026).

The small number of randomized controlled trials makes the treatment of PANS and PANS-related illnesses difficult and dependent on the physician's experience and the specific characteristics of individual

patients (Sigra et al., 2018). This issue is further complicated by the fact that the results of the few studies are contradictory.

Despite our expanding understanding of PANS and PANDAS, they remain exceptionally mysterious diseases. Many years of research and hard work by scientists and physicians are still needed to change this state of affairs.

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