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REVIEW PAPER

PANDAS syndrome – pathophysiology, diagnostic challenges, and treatment approaches

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ABSTRACT

Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) represents a subset of pediatric acute-onset neuropsychiatric syndrome characterized by abrupt obsessive-compulsive and tic symptoms triggered by group A β-hemolytic streptococcus. Despite established diagnostic criteria, PANDAS remains controversial due to limited pathophysiological evidence and the absence of validated biomarkers. The most widely accepted hypothesis suggests molecular mimicry, with anti-neuronal autoantibodies causing immune-mediated damage to the basal ganglia. Diagnosis is essentially clinical, requiring exclusion of other infectious, inflammatory, or metabolic conditions. Treatment strategies are multidisciplinary and include antimicrobial therapy, psychiatric and behavioral interventions, and, in severe cases, immunomodulatory approaches such as corticosteroids, intravenous immunoglobulin, or plasma exchange. Given the relevance of this topic to the pediatric population, further research is required to clarify mechanisms, standardize diagnostic tools, and establish evidence-based treatment guidelines to optimize outcomes for affected children and their families.

KEY WORDS:

obsessive-compulsive disorder, PANDAS, PANS, pediatric autoimmune neuropsychiatric syndrome, group A β-hemolytic streptococcal infections.

INTRODUCTION

Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) is a subgroup of pediatric acute-onset neuropsychiatric syndrome (PANS) cases that are entirely associated with streptococcal infection. In 1894, Sir William Osler, in a publication titled "On chorea and choreiform affections", was the first one to note a set of peculiar and pervasive behaviours in children with Sydenham's chorea following streptococcal infections [1]. Later, in 1980, Swedo *et al*. provided the first comprehensive description of the first 50 cases of children with obsessive-compulsive disorder (OCD) or tic disorder diagnosis [2]. Researchers found that all children shared a similar clinical course of their disease, characterized by dramatic symptom exacerbation triggered by group A β-hemolytic streptococcus (GABHS) infection. The following diagnostic criteria for PANDAS were proposed and are summarized in Table 1 [2].

While the diagnostic criteria for PANS – an umbrella construct encompassing a wider spectrum of pediatric neuropsychiatric disorders, differs from those established for PANDAS, both syndromes share a distinctive clinical hallmark: the abrupt onset and rapid progression. Moreover, PANS and PANDAS are regarded as diagnoses of exclusion, implying that their symptomatology must not be more appropriately accounted for by an alternative disorder [3].

The review aims to synthesize available clinical and experimental evidence, highlight the challenges and limitations in establishing a reliable diagnosis, and provide

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TABLE 1. PANDAS diagnostic criteria [2]

Criteria	Description
Clinical symptoms	Presence of OCD, tic disorder, or both
Age of onset	Pediatric onset: from 3 years of age to the beginning of puberty
Course of illness	Episodic course with abrupt onset or dramatic symptom exacerbations. Symptoms decrease or resolve during exacerbations
Association with infection	Temporal relationship with group A β-hemolytic streptococcal infection
Neurological abnormalities	During exacerbations neurological abnormalities, most commonly motor hyperactivity or adventitious movements (involuntary movements)

OCD – obsessive-compulsive disorder

a critical assessment of the efficacy, safety, and applicability of both established and emerging therapeutic approaches, including pharmacological, immunological, surgical, and behavioral interventions.

MATERIAL AND METHODS

Relevant literature was obtained through a systematic search of the PubMed and Google Scholar biomedical databases. The search was conducted using key terms: "PANDAS", "Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection", "Pediatric Acute-Onset Neuropsychiatric Syndrome", "PANS and streptococcal infection", and "PANDAS treatment". The inclusion criteria covered full-text clinical studies, systematic reviews, narrative reviews, and relevant case reports addressing mainly the pathophysiology, diagnosis, or treatment of PANDAS. Initially, we gathered 156 articles; after screening, 41 articles were included in the present review. Additional references cited in relevant articles were also examined to capture further evidence and enhance the discussion.

PATHOPHYSIOLOGY

The exact biological mechanism by which GABHS causes PANDAS syndrome is yet to be uncovered. Several pathophysiologic pathways have been proposed in order to explain the correlation between streptococcal infection and PANDAS symptoms. Yet, there is not enough support for any of them. Currently, the most widely accepted hypothesis is that PANDAS syndrome develops as a result of molecular mimicry [4, 5]. It is a mechanism in which autoantibodies cross-react with the host's epitopes, inducing damage in different tissues. In PANDAS, the anti-neuronal autoantibodies specifically lead to immune-mediated damage of the basal ganglia, leading to neuropsychiatric presentations [6].

DIAGNOSIS

The clinical workup should focus on detailed medical history, including past and present symptoms, developmental history, and a comprehensive family history focused on inflammatory and autoimmune diseases, followed by a thorough somatic and neurological examination. The scheme might alter according to local practice, yet it should always focus on extracting the most valuable data to distinguish PANDAS from toher disorders in the differential diagnosis.. It is especially important to exclude specific infectious, inflammatory, and metabolic brain diseases before applying therapy that impacts the immune system [7].

Children at the age of three to puberty represent a critical group in which clinicians should be particularly vigilant for symptoms suggestive of PANDAS. The mean age at onset of PANDAS/PANS symptoms differs amongst different studies, but most commonly narrows down to the range of 5–8.6 years [8–10]. A higher prevalence of PANDAS syndrome has been observed in males [8–12].

Pharyngitis, the most common manifestation of strep infection in children, typically presents with the abrupt onset of sore throat, difficulty swallowing, pharyngeal erythema with or without exudates, fever, and tender anterior cervical lymphadenopathy, usually in the absence of cough or nasal congestion [13]. Clinical scoring systems such as the McIsaac score might serve as a helpful tool for clinicians to better identify GABHS cases. It is also essential to identify any other sites of infection.

Neurological examination should focus on evaluation of cognitive and motor abilities. Children with PANS generally have normal cognitive abilities, but their school performance may decline due to factors such as inattention, anxiety, OCD, or perfectionism [3]. Associated neurological findings may include motor or vocal tics, choreiform finger movements, sleep disturbances, and inattentiveness.

The following step of clinical work-up is to assess an ongoing GABHS infection. Group A β-hemolytic streptococcus is a Gram-positive, extracellular bacterium of spherical shape. It is one of the most frequent human pathogens. Group A β-hemolytic streptococcus causes a spectrum of diseases: from mild infections such as pharyngitis, scarlet fever, and impetigo to moderate conditions affecting skin like cellulitis and erysipelas, and severe forms including necrotizing fasciitis, streptococcal toxic shock syndrome, sepsis, pneumonia, and meningitis. Group A β-hemolytic streptococcus may also lead to post-infectious complications such as rheumatic

fever and post-streptococcal glomerulonephritis. Since most upper respiratory tract infections in the pediatric population are viral, a clinical diagnosis – even with the help of proper clinical scores, e.g. Centor score – is not sufficient for clinical studies. A throat swab for rapid testing or culture is required for assessment of a current GABHS infection [14]. The swab should be performed at the onset and during every exacerbation for an accurate PANDAS assessment, since the association between an infection and symptoms manifests not only during the initial symptoms, but with each aggravation. A positive swab devoid of clinical presentation might represent a coincidental colonization. Conversely, some streptococcal infections might be clinically unnoticed due to their mild course or even remain entirely asymptomatic. Antibodies antistreptolysin O and anti-DNase-B are GABHS-specific antibodies that develop after a strep infection [15]. To detect and monitor the infection, serial measures of antibody levels and a dynamic rise can be used. Unfortunately, there are no established standards for interpreting these results in the context of PANDAS diagnosis. Due to the lack of identifiable biomarkers or tests, the diagnosis remains essentially clinical.

Currently, both in DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) and ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th Revision), PANDAS and PANS syndromes are not classified as distinct disorders. Nonetheless, they can be coded under "Obsessive-Compulsive and Related Disorder Due to Another Medical Condition (294.8) in DSM-5 and under "other specified immune disorders" (D89.89) in ICD-10.

TREATMENT OPTIONS

A multi-pronged approach to the treatment of PANS has been proposed. It is based on three complementary modes of intervention:

1) Antimicrobial treatment for moderate inflammation.
2) Managing symptoms with psychotherapy and psychoactive medications.
3) Alleviating disturbances in the immune system with immunomodulation.

ANTIMICROBIAL TREATMENT AND PROPHYLAXIS

In patients with upper respiratory tract GABHS infection confirmed by a positive microbiological test, primary antibiotic therapy is advised in order to minimize the risk of long-term sequelae such as rheumatic fever, PANDAS, post-streptococcal glomerulonephritis, or lingering symptoms of the infection itself.

First-line treatment includes oral penicillin, preferably in a form of suspension palatable for younger kids [5]. For patients with low compliance to treatment, suspected, or when there is no possibility of follow-up appointments, intramuscular penicillin can be given as an alternative option. In case of allergy to penicillin, azithromycin, or cephalosporins may be used. In a prospective study by Murphy and Pichichero, twelve children with the diagnosis of PANDAS were treated with antibiotics effective for GABHS eradication [16]. In all patients, therapy alleviated symptoms of OCD.

Group A β-hemolytic streptococcus infections are not only the primary etiological cause in the onset of PANDAS syndrome, but are also associated with severe symptom exacerbation in patients with an already established diagnosis [17]. Thus, the use of long-term penicillin prophylaxis for children with PANDAS could possibly prevent further neural injury. In one randomized double-blind study, twenty-three patients with PANDAS were treated with penicillin or azithromycin for 12 months [18]. Researchers noted a significant reduction in the frequency of streptococcal infection rates and a decrease in neuropsychiatric symptom exacerbations. However, insufficient evidence of effectiveness, the chance of antibiotic resistance, and other conceivable side effects of long-term use of antimicrobial therapy in children restrict the use of antimicrobial prophylaxis. To limit the exposure to multiple antibiotics over a long period of time, currently available guidelines only recommend long-term prophylaxis for a selected group of patients. These include children experiencing numerous GABHS-associated neuropsychiatric exacerbations and the most severely affected children.

PSYCHOTHERAPY AND PSYCHIATRIC MEDICATIONS

A compilation of interventions applied ought to be custom fitted to each patient's symptoms and situation and later adjusted during the course of the disease. To guarantee the best symptom control and minimize neural harm, psychotherapy and psychopharmacologic interventions should be applied as soon as the diagnosis of PANDAS is made. The prompt start of treatment is especially important since a proper amount of time is needed before these treatments develop their full effect. For medications, often the benefits are not seen before 2–3 months after an optimum dosage has been achieved; treatment has to be held for around 12–16 sessions to show positive effects [19]. Selective serotonin reuptake inhibitors (SSRIs) are first-line medication for treating PANDAS-related OCD [20]. It is recommended that the pharmacotherapy should be started with an introductory low dose, later gradually increased in a minimum of 14-day-long intervals, and carefully monitored [21]. At the beginning of treatment, to help with aggression and anxiety, benzodiazepines might be helpful [21]. Some of the side effects of psychotropic medication described in the literature include: hyperactivity, mania, disinhibited behavior, worsening OCD behavior, aggression, irritability, agitation, and suicidality. Since some of these symptoms resemble the symptoms

of the PANDAS disorder itself, it is critical to discriminate between the two. Of important note, the use of medication is limited to drugs registered for treating OCD in children.

COGNITIVE BEHAVIORAL THERAPY

Cognitive behavioral therapy (CBT), especially exposure/response prevention and parent management training, is a form of therapy with evidence-based effectiveness for pediatric OCD [20]. The latter includes encouraging families not to participate in behaviors accommodating the child's avoidance and rituals, positively reinforcing desired behaviors, setting clear limits, expectations, and consequences, and establishing reward systems. In one study, seven children with the diagnosis of PANDAS (six out of seven were already started on SSRIs before the study) undertook a 3-week CBT program [22]. After the final session, six children displayed symptom improvement; remission was noted in three children in a follow-up assessment three months post-therapy. In another study, eight out of eleven children with PANDAS-related OCD who were incomplete responders to antibiotics, after completing CBT therapy, presented reduced symptom severity [23]. In another study, authors recognized a significant relief in OCD symptoms in a one-year follow-up after CBT therapy [8].

IMMUNOMODULATORY TREATMENT

Immunomodulatory treatment is usually reserved for children with severe symptoms or a chronic course of the disease. Before initiating immunotherapy, it is recommended that clinicians should pursue a complete differential diagnosis work-up to make sure the symptoms are not caused by any other disease, in which case the therapy could disadvantage the patient [7]. Immunomodulatory treatment comprises: non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, intravenous immunoglobulin (IVIG), and total plasma exchange (TPE).

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Several research studies have proved NSAIDs efficacy. In a retrospective study by Spartz *et al*., it was observed that in a group of patients trailed on patients who received NSAIDs treatment, approximately one-third of the patients experienced improvement in some or all PANS symptoms [24]. Moreover, in one-third of the patients, symptom exacerbation was observed following the withdrawal of NSAID therapy. In another study conducted by Brown *et al*. in patients treated with NSAIDs, exacerbations were shorter and milder compared to those untreated [25]. The primary course of NSAIDs therapy should last for 6 weeks, followed by a probationary discontinuation period [7]. In case of a flare-up, medications can be restarted and continued for longer than 6 weeks.

CORTICOSTEROIDS

A brief course of oral or intravenous corticosteroids given during the first few days after the initial onset of symptoms might be another beneficial treatment option. The recommended initial dose for prednisone is 1–2 mg/kg/day, given in one dose in the morning or divided to twice daily [7]. According to a study by Brown *et al*., corticosteroid treatment almost halved the duration of flares compared to children who were not treated with corticosteroids [26]. However, long-term corticosteroids, although often providing successful symptom relief, might lead to permanent toxicities. Additionally, a group of patients displaying signs such as anxiety, rage, irritability, depression, emotional lability, and insomnia should be generally excluded from corticosteroid therapy, as it might aggravate those symptoms.

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin alone or in combination with corticosteroids is a preferred treatment option for moderate-to-severe PANDAS. A recent study by Frankovich/Melamed *et al*. presented data showing a decrease in monocyte and dendritic cell levels post-IVIG treatment, reinforcing the concept of PANS as an inflammatory disease [27]. A double-blind, placebo-controlled investigation showed that IVIG and TPE were both effective in reducing OCD symptoms in PANDAS patients (by 45% and 58%, respectively) [28]. In another study, twelve children who had failed prior therapies benefited from IVIG administration [29]. Another study evaluated the outcome of six consecutive IVIG infusions in a group of 21 children with moderate-to-severe PANS. The results showed a statistically significant improvement in psychometric measures following the treatment, with the effects maintained for at least 8 weeks [30]. Conversely, TPE and IVIG have not demonstrated efficacy in the management of non-PANDAS OCD and tic disorders [6, 7].

The suggested induction dose of IVIG is 1.5–2 g/kg (with the maximum dose of 70 g) and 1–2 g/kg for subsequent dosing [7]. However, clear guidelines on repetitive use of IVIG in PANDAS have not yet been researched and established. Headache, including migraines, was the main complaint reported after IVIG administration. Pain typically develops 6–72 hours after the infusion and can last up to 7 days. Aseptic meningitis is another commonly described side effect of IVIG. It is recommended that, before IVIG application, accurate measures should be taken to minimize the side effects; these might include the use of anti-inflammatory and anti-nausea medication, adequate hydration, and dividing the total dose of IVIG into smaller doses.

TOTAL PLASMA EXCHANGE

Total plasma exchange therapy provides the biggest symptom relief and is reserved for extreme cases of PANDAS. Children with life-threatening PANDAS should be admitted to the hospital and continuously monitored. The recommended schedule for TPE consists of five single-volume exchanges within 7–10 days [28, 31]. One retrospective study investigated patients' responses to one TPE course in a group of sixteen adolescents and adults [32]. Over half of the patients experienced symptom improvement after the therapy. Adverse events associated with TPE encompass catheter-related infections, thrombotic episodes, anemia, syncope, psychogenic non-epileptic seizures, and amplified pain responses. Although TPE represents an important therapeutic modality, further large-scale clinical studies with appropriately designed study and control groups are necessary to better understand the potential applications, benefits, and risks associated with this form of therapy.

GUT-BRAIN-AXIS TARGETED THERAPIES

The human gastrointestinal tract hosts a complex community of bacteria, viruses, protozoa, archaea, and fungi known as the gut microbiota. Emerging evidence suggests gut dysbiosis may fuel systemic and neuroinflammation, potentially impacting neural function *via* immune-mediated pathways. Recent studies found that patients with PANDAS syndrome might have an altered gut microbiome, which may directly affect their behavioral and neuropsychiatric symptoms [33, 34]. Targeting the gut-brain axis creates new avenues for treatment beyond the three primary approaches. These therapies include the use of vitamin D and probiotics, which will be explained in more detail in the following text. Other gut-brain targeted strategies for the treatment of PANDAS include magnesium, Omega-3, anti-microbial herbs, and supplements supporting gut health.

Vitamin D plays a major role as an immunomodulatory and neuroprotective agent. Thus, it has a potential role as a determining factor in both proneness to acquiring streptococcal infection and developing pathological autoimmune response. In a case-control study by Çelık *et al*., vitamin D deficiency was significantly more common amongst children with PANDAS compared to the control group [35]. In another study, 25-(OH)-vitamin D levels were checked in a group of children and adolescents with PANDAS syndrome and compared to a control group; PANDAS patients presented reduced values of 25-(OH)D [36]. Currently available data support the hypothesis that there is a distinct correlation between vitamin D metabolism and PANDAS, but more studies are needed to further explore this subject.

Probiotics are live microorganisms, usually bacteria, that, when administered in adequate amounts, may provide benefits to their host. The administration of probiotics has the potential to modulate the gut microbiome and, consequently, may influence neuropsychiatric symptoms. Some studies have shown benefits in depression, anxiety, and autism spectrum disorder [37–39]. It is important to note that these studies are limited by reliance on anecdotal evidence, small sample groups, short treatment durations, and heterogeneous probiotic strains.

TONSILLECTOMY

Tonsillectomy is a commonly used mode of treatment for recurrent pharyngitis. Thus, it was also studied as a possible prevention method for developing PANDAS syndrome or preventing later exacerbations. In a retrospective medical chart review by Demesh *et al*., a group of children with unsatisfactory response to antibiotics experienced significant symptom relief after tonsillectomy [40]. In another case study, two siblings presenting with recurrent pharyngitis and behavioral changes (OCD and tics) underwent tonsillectomy; both children remained free of OCD and tics after the surgery [41]. Unfortunately, this anecdotal evidence is too scarce to provide a strong evidential baseline for creating treatment guidelines.

CONCLUSIONS

Although diagnostic criteria have already been defined, PANDAS remains a controversial entity in the medical world. Further studies are vital for providing a clear pathophysiology mechanism description, evaluating comprehensive diagnostic algorithms, and standardized treatment guidelines. Until ready, clinicians are encouraged to consider PANDAS in the differential diagnosis of children who present with an acute onset of obsessive-compulsive symptoms. A multi-disciplinary approach should be applied to provide holistic care tailored to each patient's case complexity. The interdisciplinary team should consist of both physicians and psychologists, as well as other medical healthcare professionals. Given the impact PANDAS has on both the patients and their family, establishing a deep level of understanding of this syndrome should be a priority among clinicians and researchers.

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