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Treatment methods for Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections Syndrome: A literature review

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ABSTRACT

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a clinical syndrome of sudden onset occurring in children before puberty in which obsessive-compulsive symptoms and/or tics and other behavioural disorders are present following documented group A streptococcal (GAS) infection. PANDAS is a rare disease that is controversial with its diverse symptomatology and still-uncovered pathogenesis. The review presents different procedures of treatment, including pharmacological, non-pharmacological, and surgical procedures. PANDAS syndrome treatments are the subject of an increasing amount of research. Pharmacological therapies include penicillin and macrolide antibiotics, corticosteroids, and selective serotonin reuptake inhibitors. Cognitive-behavioural therapy, which has a proven effect in the treatment of obsessive-compulsive disorder (OCD), is also receiving increasing attention. Additionally, studies on intravenous immunoglobulin, plasma exchange, and plasmapheresis are underway. Treatment of PANDAS syndrome is developing all the time. More randomised trials are needed to establish precise diagnostic criteria and therapeutic recommendations for this disease entity.

Keywords: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS); tics; obsessive-compulsive disorder (OCD)

1. INTRODUCTION

Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) are currently defined as the sudden onset of obsessive-compulsive disorder and/or tics in pre-adolescent children with group A beta-haemolytic streptococcal (GAS) infection (La Bella et al., 2023). There is considerable

debate among rheumatologists and neurologists regarding this uncommon condition, whose pathophysiology, diagnosis, and treatment options are currently under investigation (La Bella et al., 2023). The first definition of this condition dates back to 1998, when Swedo described the first 50 cases of patients with obsessive-compulsive disorder of acute onset (Ruscio et al., 2010). The pathophysiology of PANDAS syndrome is based on molecular mimicry, indicating an autoimmune origin, and is comparable to that of Sydenham's chorea, a documented consequence of beta-haemolytic streptococcal infection (Xu et al., 2021). The epidemiology of the disease is not yet completely understood due to a lack of data. The condition is more common in men than in women, with a ratio of 2.6–4.7 to 1.

Patients who met all PANDAS criteria except for a proven group A streptococcal (GAS) infection were the focus of attention in 2012. In order to include this patient group, new criteria and the term Paediatric Acute-Start Neuropsychiatric Syndrome (PANS) were created (Trifiletti et al., 2022). Several PANDAS treatments are under investigation, including immunotherapy, pharmacotherapy, cognitive-behavioral therapy, and even surgery. This review aims to present the treatment of PANDAS syndrome using different methods.

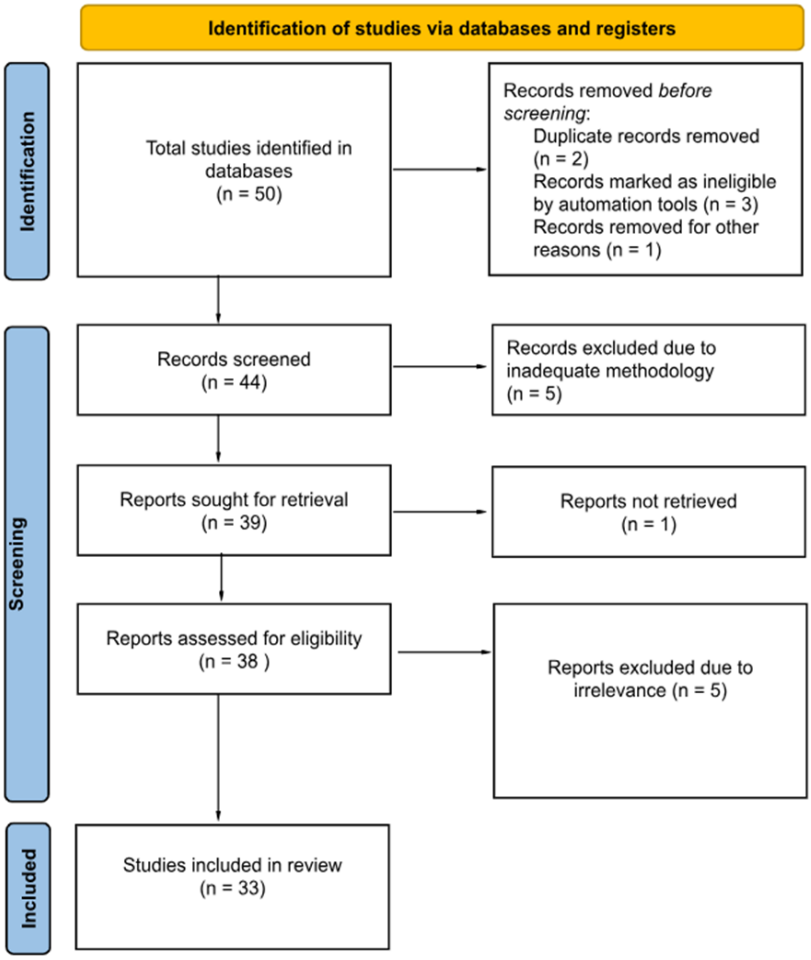

Figure 1 PRISMA flow chart diagram of the study selection process

2. REVIEW METHODS

The study duration was two months. The PubMed and Google Scholar databases were used to assess fifty papers using the following keywords: tonsillectomy, PANDAS Syndrome, tics, and cognitive-behavioral treatment. After removing 2 duplicates, 3 ineligible records, and 1 record removed for other reasons, 44 articles remained. After analyzing titles and methodology, we excluded 5 articles. Thirty-three articles were included in this article after research (Figure 1).

3. RESULTS & DISCUSSION

Pathogenesis

The Gram-positive bacterium known as Group A Streptococcus (GAS) frequently causes asymptomatic infections in people, but it can also induce septicemia, toxic shock-like syndrome, necrotizing fasciitis, pharyngitis, and purulent dermatitis. Immune responses may be triggered after infection (Brouwer et al., 2023). Children typically begin to show symptoms at an early age—around 6.3 years for tics and 7.4 years for OCD (Swedo et al., 1989). Researchers are leaning toward a hypothesis based on the phenomenon of molecular mimicry, in which antibodies produced against pathogens attack brain proteins (Cunningham et al., 2016). Brain imaging studies performed in PANDAS patients with microstructural abnormalities in the thalamus, basal ganglia, and amygdala suggest the validity of this thesis (Zheng et al., 2020). Enlargement of the striatum, caudate, putamen, basal ganglia, and globus pallidus, along with striatal interneuron dysregulation, microglial overactivation, and increased levels of antineuronal antibodies, are among the changes found in the central nervous system. Changes in the microbiota include the absence of certain bacterial families like Saccharibacteria, Turicibacteraceae, Tissierellaceae, Gemellaceae, Carnobacteriaceae (Bacilli class), Corynebacteriaceae, and Lachnospiraceae (Clostridia class), as well as increased levels of Bacteroidetes, Rikenellaceae, and Odoribacteriaceae, and decreased levels of Firmicutes and Actinobacteria. Furthermore, autoantibodies have been found to target calcium/calmodulin-dependent protein kinase II, tubulin, lysoganglioside, pyruvate kinase, and dopamine D1 and D2 receptors (Baj et al., 2020).

The results of whole-exome sequencing were presented in a study of 386 individuals with severe PANS in the United States and 10 instances in Europe. Mutations were found in 11 genes (PPM1D, SGCE, PLCG2, NLRC4, CACNA1B, SHANK3, CHK2, GRIN2A, RAG1, GABRG2 and SYNGAP1). These genes, which are mostly expressed at neural synapses, control microglia and peripheral immunological responses. The same neuronal genes have also been linked to myoclonus dystonia and autism spectrum disorders. In about half of the cases, the development of PANS overlapped with a pre-existing neurodevelopmental disorder, suggesting a likely genetic predisposition.

Treatment methods

Due to the lack of randomized trials, there are no specific guidelines for the treatment of PANDAS syndrome. Both non-pharmacological and pharmaceutical management are the cornerstones of PANDAS syndrome treatment. Non-pharmacological management involves the use of cognitive behavioural therapy and Parent Management Training (PMT). Antibiotics (penicillins, macrolides) are the mainstay of pharmacological treatment, although intravenous immunoglobulins, corticosteroids, and other substances also play a part (Figure 2), (Table 1).

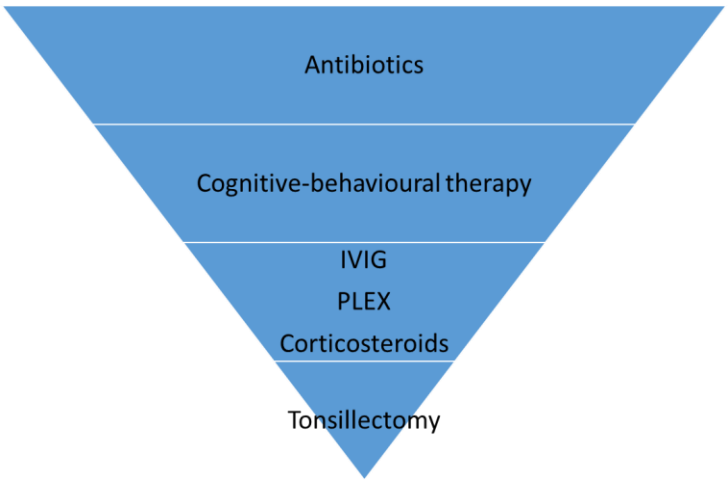

Figure 2. Treatment methods for PANDAS syndrome according to the hierarchy

Cognitive behavioural therapy

Two studies evaluated the effect of cognitive behavioural therapy on OCD symptoms occurring in patients with PANDAS syndrome. They showed a reduction in the severity of OCD symptoms. However, the lack of an active control trial and the small sample size

hampered the results. Thus, it is likely that patients meeting PANDAS and PANS criteria may benefit from cognitive-behavioural therapy, but studies conducted to date do not conclusively prove this (Storch et al., 2006; Nadeau et al., 2015).

Another crucial component of assisting parents in dealing with their children's problematic behavior is parent management training, or PMT. Parents should learn how to resist their child's compulsive behavior because of the repetitive nature of the symptoms. Parents who experience ongoing stress as a result of their children's repeated symptoms also require psychological care (Guido et al., 2021). Parents and carers of children with PANDAS are more burdened by anxiety and depression (O'Dor et al., 2022).

CBT and low-dose selective serotonin reuptake inhibitors (SSRIs) have shown benefit, though severe cases may not fully respond. Experts recommend careful psychiatric assessment and cautious medication dosing due to sensitivity in these patients (Dop et al., 2021). CBT is also considered a low-risk, helpful option for managing symptoms and supporting families. But according to research like that done by Hesselmark et al., (2019), parents frequently express more satisfaction with therapies like intravenous immunoglobulin (IVIG) and antibiotics. CBT can also help parents cope with the psychological toll of the disorder.

A pilot study by Kleinsasser et al., (1999) found that group-based, trauma-focused CBT improved stress and depression symptoms in parents, promoting better coping and acceptance. Risperidone is among the most frequently used for this purpose, particularly to address choreiform movements and aggression. However, current support for its use is primarily based on case reports, with a lack of prospective studies or comprehensive reviews.

Antibiotics

Antibiotic therapy is one of the primary treatments for patients with PANDAS syndrome. Note that there are currently no established guidelines for antibiotic therapy for this disease due to the limited number of studies conducted. Thus, therapy needs to be customized for each patient and their family. Treatment has involved the use of a range of antibiotics, such as cephalosporins, macrolides, and penicillins (Sigra et al., 2018).

There is insufficient evidence on the effectiveness of antibiotic prophylaxis in preventing PANDAS. There was no difference in the prevention of infection or neuropsychiatric symptoms between the drug-taking group and the placebo group in a research study including a small number of patients who received penicillin prophylaxis (Murphy et al., 2017). However, patients with severe PANDAS syndrome and those who experience frequent symptom exacerbations may benefit from GAS prevention, according to some research. In such cases, the intramuscular administration of benzylpenicillin at a dose of 600,000 IU per month is recommended, as in the treatment of rheumatic fever (Murphy et al., 2015). Although azithromycin has also been suggested as a preventative measure, this suggestion is not supported because group A beta-haemolytic streptococci frequently exhibit macrolide resistance (O'Dwyer et al., 2013). Another study found that the occurrence of remission of neuropsychiatric symptoms during antibiotic treatment was more likely in children with PANDAS syndrome than in those without the disease (Murphy et al., 2012). To establish clear guidelines for the use of antibiotics and demonstrate their effectiveness in treating PANDAS syndrome, more randomized trials are required.

Immunomodulatory therapy and plasma exchange

According to specific research, people with PANDAS and those with tics of various infectious etiologies may benefit from immunomodulatory therapy, which includes both intravenous immunoglobulin administration and plasmapheresis (Perlmutter et al., 1999; Frankovich et al., 2017). The impact of IVIG and/or plasma exchange on the development of OCD symptoms in children with PANDAS has been assessed in two investigations. Regardless of the order of immunotherapy and placebo, both demonstrated behavioral improvements over the course of a year of follow-up. Thirty children who met PANDAS criteria and were on a preventative antibiotic participated in the first research. Three groups of children were formed: the first received IVIG for two days at a dose of 1g/kg/day, the second underwent plasma treatment with five to six exchanges over ten to twelve days, and the third received a placebo. After just one month of therapy, improvements in depressive, anxiety, and obsessive-compulsive symptoms were observed in the first two groups. Children who were initially in the placebo group received active therapy: two children with IVIG and eight children with plasmapheresis (PLEX). After a one-month follow-up, improvement in symptoms was noted in 8 children. A 1999 double-masked study evaluated the effect of IVIG and plasmapheresis in alleviating OCD symptoms in children with PANDAS. At the time, it demonstrated that IVIG reduced symptoms by 45% and plasmapheresis by 58%, respectively, while placebo infusion had no impact. The American Apheresis Society recognized plasmapheresis as the preferred treatment for PANDAS category I syndrome due to the findings of this study (Weinstein et al., 2008).

Tonsillectomy

One possible therapy option for kids with PANDAS is tonsillectomy. Some case reports have even shown a reduction in symptom severity in children after tonsillectomy, but this has not been proven in larger studies (Alexander et al., 2011; Damesh et al., 2015). There was a retrospective study comparing the severity of OCD symptoms and streptococcal antibody titres in 20 patients with PANDAS syndrome after tonsillectomy with a group of 23 patients with PANDAS without tonsillectomy. This study revealed no distinctions between the two groups (Murphy et al., 2013). In another retrospective analysis, 120 patients were included, of whom 56 underwent tonsil removal surgery. At two years of follow-up, there was no difference in the reduction of neuropsychiatric symptoms, streptococcal antibody titres, or recurrence episodes between individuals who had surgery and those who did not (Pavone et al., 2014). The evidence supporting tonsillectomy as a treatment for PANDAS syndrome is insufficient to draw firm conclusions.

Corticosteroids and NSAIDs

The effectiveness of corticosteroids in treating PANDAS in children has not yet been adequately established. The usefulness of oral corticosteroids administered for brief periods of time (4–5 days) or for longer periods of time (5 days–8 weeks) in controlling symptom flares in patients with PANS or PANDAS was examined by Brown et al., (2017). According to their findings, corticosteroid medication, especially when given shortly after symptom onset, shortened the duration of flares and first episodes. Longer courses of steroids showed a more lasting improvement in symptoms. However, the authors emphasized the need for randomized, double-anonymized, placebo-controlled trials to evaluate this treatment. The same research team also studied the impact of non-steroidal anti-inflammatory drugs (NSAIDs)—including Naproxen, Ibuprofen, Sulindac, and Celecoxib—on symptom flares. They found that NSAID use significantly decreased flare duration, even when used preventatively as part of ongoing maintenance therapy. Furthermore, additional research is needed on this topic.

The observational study assessed 403 illness exacerbations in 98 patients. With an average duration of 11.4 weeks, patients whose exacerbations were not treated with corticosteroids had a longer duration than those whose exacerbations were treated with corticosteroids. In patients taking corticosteroids, the duration of exacerbations was reduced by 3.5 weeks (Brown et al., 2017).

Table 1. Summary of treatment methods

Therapy	Benefits	Limitations
Antibiotics	Reduction in OCD symptoms	No defined guidelines for antibiotic therapy; limited number of studies
Cognitive-behavioural therapy	Reduction in the severity of OCD symptoms; decrease of stress and depression symptoms in parents	Lack of prospective studies or comprehensive reviews
Tonsillectomy	Reduction in symptom severity	Insufficient evidence to draw firm conclusions
IVIG	Improvement in depressive, anxiety, and obsessive-compulsive symptoms	More research is required on this subject
Corticosteroids	Decrease in flare and first episodes duration	
NSAIDs	Significant decrease in flare duration	

4. CONCLUSION

Although there is ample evidence of PANDAS syndrome for many, the diagnosis remains controversial. Making the diagnosis requires a thorough patient and family history, psychiatric evaluation, physical examination, and multiple laboratory tests. PANDAS continues to be poorly understood. It is challenging to develop specific management recommendations because the current research on therapeutic options for this condition is limited in scope and has stringent exclusion criteria. To further understand the pathophysiology of PANDAS disease and create evidence-based treatments, further study is required.

PANDAS syndrome is a relatively new disease entity that needs to undergo numerous investigations. The diagnosis remains a controversial topic despite many studies confirming its existence. More randomised studies on treatments for PANDAS syndrome are required. Due to the wide variety of symptoms associated with PANDAS, it is challenging to develop precise diagnostic criteria and management recommendations. Because PANDAS symptoms can vary greatly, it is challenging to create accurate diagnostic standards and treatment guidelines. Due to the lack of precise criteria, it is also difficult to differentiate this disease entity from others with similar symptoms and course. Treatment of PANDAS syndrome is mainly based on controlling the streptococcal infection with antibiotics, but also using psychological therapy to reduce OCD symptoms and tics. There is a growing body of research into the use of immunomodulatory treatment, which has the potential to mitigate neuropsychiatric symptoms in paediatric patients with PANDAS.

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Conflict of interest

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Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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