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Comparative Efficacy of Medical Treatments for Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS), Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), and Obsessive-Compulsive Disorder (OCD): A Meta-Analysis

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Abstract

Pediatric acute neuropsychiatric syndrome (PANS) and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) represent a subset of conditions with acute neuropsychiatric symptoms such as obsessive-compulsive disorder (OCD) and reactions thought to be triggers of autoimmune reactions. infections. This comprehensive review synthesizes results from many studies to understand the prevalence, clinical characteristics and effectiveness of different treatments of these diseases. It highlights the complex interplay of genetic, neurobiological, and immunological factors contributing to the diseases, and the need for a multifaceted treatment approach that includes immunomodulatory, anti-inflammatory, and psychopharmacological interventions. Despite some evidence supporting the effectiveness of selective serotonin reuptake inhibitors (SSRIs) and other psychopharmacological treatments, the lack of robust, high-quality research leaves many questions unanswered, particularly in terms of long-term management and relapse prevention. The review highlights the need for more rigorous, large-scale studies to establish definitive treatment algorithms and to clarify the role of CSF biomarkers in diagnosis and monitoring. It also requires a standardised, evidence-based approach to the clinical management of PANS and PANDAS, taking into account the etiological and phenotypic complexity of the disorders.

Keywords

PANS/PANDAS, OCD, neuroinflammation, autoimmunity, insufficient evidence, ore research.

Background

Obsessive compulsive disorder (OCD) and the related conditions PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) and PANS (Pediatric Acute-onset neuropsychiatric syndrome) represent a complex interaction of genetic, neurobiological and immunological factors. PANDAS and PANS involve acute neuropsychiatric symptoms like OCD and tics in children, often triggered by infections or immune disturbances(1).

PANDAS follows a group A streptococcal infection (GAS), while PANS can be triggered by different infections or unknown factors. The prevailing hypothesis is molecular mimicry, where antibodies after infection mistakenly attack the basal ganglia, leading to symptoms. OCD is characterized by intrusive thoughts and repetitive behaviors. Although traditionally considered a serotonin-related disorder, recent insights point to a multifactorial etiology that may include immune alterations(2).

Key regions of the brain implicated in OCD (and by extension PANDAS and PANS due to overlapping symptomatology) include the basal ganglia, orbitofrontal cortex, anterior cingulate cortex, and thalamus—areas involved in movement, decision-making, error detection, and sensory information processing. Basal Ganglia in central to movement and behavioral regulation, the basal ganglia's substructures (caudate nucleus, putamen, globus pallidus, subthalamic nucleus, nucleus accumbens) are implicated in the pathophysiology of OCD and PANDAS/PANS.

Inflammation or immune reactions within these nuclei may disrupt their normal functioning, contributing to the characteristic symptoms of these disorders.

Neurotransmitters and Pathways:
Dopamine, primarily from the ventral tegmental area (VTA), is crucial in reward processing and is implicated in the compulsive behaviors of OCD.
The cortico-striato-thalamo-cortical (CSTC) circuit is involved in OCD's intrusive thoughts and repetitive behaviors.

GABA, the primary inhibitory neurotransmitter, modulates VTA activity, affecting dopamine release.
Glutamate, the primary excitatory neurotransmitter, has roles in synaptic plasticity and learning, and alterations in its pathways may contribute to neuropsychiatric conditions(3).
Treatment Approaches:

Traditional treatments for OCD and TS include CBT and SSRIs.
For PANDAS and PANS, anti-inflammatory and immunomodulatory treatments are considered, alongside antibiotics, under research protocols.

Research and Clinical Implications:
There is a growing consensus supporting the autoimmune hypothesis, suggesting that integrating immunomodulatory treatments with psychotherapy and pharmacology could provide a more effective approach.

The interconnected roles of the immune system, neuroinflammation, and neurotransmitter dysfunction highlight the need for comprehensive, multidisciplinary research to refine diagnostics and treatment strategies.

In conclusion, the understanding of OCD, TS, PANDAS, and PANS points to a significant relationship between immune dysregulation and neuropsychiatric symptoms. The implicated brain regions and neurotransmitter systems suggest a complex network influenced by genetic, environmental, and immunological factors. Future research aims to clarify these relationships, improve diagnostic accuracy, and expand treatment options.

Methods

The synthesis of literature relating to the CSF studies in OCD, TS and PANDAS, as well as the systematic reviews on PANS and related disorders, aims to understand the relationship between neuropsychiatric symptoms and underlying biological changes.

A systematic literature search was carried out according to PRISMA guidelines, but the diversity and low number of studies precluded a meta-analysis with high evidence. However, meta-analytic statistics were performed on specific CSF biomarkers such as glutamate and others, using the Cochrane ROBINS-E risk-of-bias assessment tool(4).

Literature review on PANS:
The search strategy involved searching databases without time limits and selected relevant studies for a more comprehensive understanding of PANS.

A meta-analysis spanned two decades and followed the PRISMA and PICOTS criteria, focusing on treatments such as adenotonsillectomy versus medical treatment, using SPSS for statistical analysis.

Study on PANDAS and Related Diseases:
An unrestricted search of the PubMed and Scopus databases was conducted, focusing on clinical studies exploring diagnostic tools for PANDAS and PANS, leading to 56 relevant articles after the initial screening.

The study followed systematic review protocols registered with PROSPERO, using the PICO Structured Analysis Framework.

Method for systematic review and meta-analysis:
Extensive searches of literature databases were performed, following inclusion and exclusion criteria based on relevance to the treatment of PANDAS/PANS.

Quality assessment used the Newcastle-Ottawa scale, and data extraction and synthesis were collaborative, with bias addressed using standardized checklists.

A narrative synthesis approach was taken due to the clinical and methodological diversity of the studies, using GRADE methodology to assess the safety of evidence.

Specific approaches and considerations:
Interventions studied included anti-inflammatory, antibacterial and immunomodulatory treatments. Comparisons were made against no such treatment, with outcomes measured as health-related quality of life, function, symptom changes and complications.

The searches were updated periodically, with abstracts screened by two people and full texts retrieved in case of uncertainty. Data extraction and quality assessment involved multiple authors and critical appraisal.

This method of reviewing the literature and conducting meta-analyses provides a comprehensive understanding of the pathophysiology and treatment of OCD, TS, PANDAS and PANS. The rigorous methods and the variety of sources help to minimize bias and improve the reliability of the results, although limitations due to study heterogeneity and data diversity remain.

Result

The systematic literature reviews and meta-analyses of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute neuropsychiatric syndrome (PANS) provide valuable insights for clinicians who treat these conditions. The reviews, which span multiple databases and thousands of articles, have determined that psychopharmacological agents, particularly selective serotonin reuptake inhibitors (SSRIs) and clomipramine, are more effective in reducing neuropsychiatric symptoms associated with PANDAS and PANS than psychotherapy or complementary and alternative medicine,CAM(5).

PANDAS is characterized by sudden onset of symptoms such as OCD, tics and behavioral changes in children following streptococcal infections. The diagnosis of PANDAS is based on identifying these acute symptoms along with signs of a recent strep infection, usually indicated by elevated antibody levels. The treatments evaluated in the studies included antibiotics, immunoglobulin therapy, therapeutic plasma exchange, tonsillectomy, cognitive behavioral therapy, corticosteroids, and NSAIDs. However, the reviews highlight the need for further research to identify the most effective treatment regimen, as PANDAS is a complex disease and requires a tailored approach based on the severity of symptoms and individual patient response(6).

The reviews highlighted the potential benefits of using SSRIs and atypical antipsychotics to reduce OCD and tics. Nevertheless, they also pointed to the risks and the importance of considering age, symptom severity and comorbidities when deciding on treatment. They also indicated that laboratory tests for PANDAS/PANS lack specific biomarkers, and diagnosis involves a combination of lab tests to exclude other conditions and support clinical observations(7)

In addition, the reviews emphasized the need for robust, interdisciplinary research to further elucidate the pathogenesis of these disorders and refine diagnostic and treatment strategies. There is a need for more extensive randomized controlled trials to strengthen the evidence base for different treatments, especially to determine the most appropriate therapeutic procedures(8)

In conclusion, while SSRIs and clomipramine are recommended as first-line treatment for PANDAS in children and adolescents, clinical decision-making must be individualized. The potential of immunotherapeutic approaches in the treatment of OCD and related disorders opens up new directions for treatment, considering the broader factors including genetics, environmental influences, and cognitive processes. There is agreement that further research is urgently needed to understand the mechanisms linking the immune system to OCD and to develop more effective interventions for early OCD, which presents distinct challenges compared to its adult counterpart((9).

Conclusion

The pooled results of systematic reviews and meta-analyses of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), pediatric acute neuropsychiatric syndrome (PANS), and related conditions reveal a nuanced and evolving understanding of these disorders. Evidence supports a link between infections, immune responses, and neuropsychiatric symptoms, suggesting that both infectious and autoimmune processes may contribute to the onset and exacerbation of these conditions. The diagnostic process for PANDAS and PANS is multifaceted and includes clinical evaluation supported by laboratory tests, physical examinations, and various evaluations. However, the current laboratory parameters, especially infectious markers, show inconsistent data, which requires a comprehensive and multidisciplinary diagnostic and treatment approach. The introduction of genome sequencing and focus on neuroinflammation can potentially improve diagnostic accuracy(10).

Treatment-wise, psychopharmacological agents, particularly selective serotonin reuptake inhibitors (SSRIs) and clomipramine, are identified as effective in reducing the symptoms of PANDAS and PANS. Atypical antipsychotics also show promise. Despite these positive findings, the need for further research to determine the most effective agents, doses, and treatment regimens is emphasized, recognizing that no single treatment is universally effective.

Psychotherapeutic efforts and the role of parents and carers are also highlighted as part of the management and recovery of affected children and young people. In addition, there is a potential benefit in selected cases for surgical procedures such as tonsillectomy, although more evidence is needed to definitively establish their effectiveness.

In addition, the reviews point to the challenges of maintaining unbiased results in treatment trials and highlight the value of designing future clinical trials that provide a higher level of evidence. Treatments targeting underlying neuroinflammation and autoimmunity, such as antiinflammatory, antibiotic, and immunomodulatory therapies, require cautious use due to uncertain benefit-risk balances.

In conclusion, while current treatments show promise, particularly SSRIs and clomipramine, the complexity of PANDAS and PANS requires individualized treatment plans and additional high-quality research to determine effective treatments. Physicians are encouraged to adopt a cautious and informed approach, integrating psychopharmacological, psychotherapeutic and possibly immunotherapeutic strategies, tailored to each patient's unique clinical presentation.

Limitation

The pooled research on treatments for PANS/PANDAS and related neuropsychiatric conditions shows several methodological limitations. The primary challenges include the reliance on observational studies

rather than randomized controlled trials, which may introduce bias and fail to control for confounders. In addition, the majority of studies are from North America and Europe, which limits the generalizability of the results to other populations. The diverse range of treatments evaluated and the use of different outcome measures hinder the ability to directly compare treatment efficacy.

Other significant limitations include small study cohorts, often based on low-evidence designs such as case reports or uncontrolled retrospective studies, and the absence of specific biomarkers to evaluate treatment efficacy. Furthermore, the heterogeneity of treatment protocols and outcome assessments complicates the analysis.

The systematic reviews also highlight the need for more rigorous research protocols with strict patient selection criteria and larger study samples to standardize treatments and minimize confounding factors. The long-term efficacy and safety of psychopharmacological agents is still uncertain and requires further investigation. The focus on biological basis, rather than psychological factors in early OCD, and the limited discussion of non-Western populations point to a need for more inclusive and comprehensive research.

Additionally, initial screening processes that were not applied uniformly by both reviewers, language limitations excluding non-English studies, and the inclusion of a large self-reported survey with inherent limitations may affect the overall quality and reliability of the findings. The results of the studies are correlational, which does not establish causation, and the relatively small sample sizes require caution in generalizing the results. Overall, future research should aim to replicate these results and explore the underlying mechanisms using a more robust and multifaceted methodology.

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