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Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS): Current Concepts, Challenges, and Controversies

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Abstract

Introduction: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) constitute a controversial pediatric neuropsychiatric syndrome characterized by the acute onset of obsessive–compulsive disorder and/or tic disorders temporally associated with group A β-hemolytic streptococcal infection. Despite increasing clinical and research interest, the diagnosis and management of PANDAS remain challenging due to heterogeneous clinical presentation, absence of specific biomarkers, and lack of universally accepted diagnostic and therapeutic guidelines.

Materials and methods: This narrative review synthesizes current evidence regarding the definition, epidemiology, pathophysiology, clinical manifestations, and treatment strategies of PANDAS. A critical analysis of the literature was conducted to highlight diagnostic frameworks, proposed immune-mediated mechanisms, therapeutic approaches, and areas of

ongoing controversy, with particular attention to methodological limitations affecting clinical interpretation.

Conclusions: Available data support the concept of PANDAS as a post-infectious, immune-mediated neuropsychiatric condition involving basal ganglia dysfunction and neuroinflammatory processes; however, evidence remains inconsistent and insufficient to establish standardized diagnostic or treatment algorithms. Therapeutic interventions demonstrate variable efficacy, largely limited by heterogeneous study designs and small sample sizes. Continued interdisciplinary research focusing on refined phenotypic characterization, biomarker identification, and well-designed prospective studies is essential to clarify disease mechanisms and improve clinical management.

Keywords: PANDAS, PANS, obsessive–compulsive disorder, neuroimmunology, pediatric neuropsychiatry, streptococcal infection

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1. Introduction

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) constitute a controversial clinical entity first described by Swedo et al. in 1998. The syndrome was initially characterized as a sudden onset of obsessive–compulsive disorder (OCD) and/or tic disorders temporally associated with infection caused by Group A β-hemolytic Streptococcus (GAS). Despite more than two decades of clinical and experimental research, PANDAS remains a debated diagnosis due to the absence of specific biomarkers and universally accepted diagnostic guidelines.

PANDAS is conceptualized as a post-infectious autoimmune condition, sharing pathophysiological similarities with Sydenham's chorea, a well-established neurological complication of streptococcal infection. In both disorders, molecular mimicry between streptococcal antigens and neuronal tissue is thought to induce an autoimmune response affecting basal ganglia circuits, leading to neuropsychiatric and motor symptoms. (1–4)

1.1 Diagnostic criteria

Classic Diagnostic Criteria

The original working diagnostic criteria for PANDAS require the presence of all of the following features:

1. Presence of obsessive–compulsive disorder and/or a tic disorder;
2. Prepubertal onset of symptoms;
3. Acute onset with a relapsing–remitting course;
4. A clear temporal association between symptom onset or exacerbation and a GAS infection;
5. Presence of additional neurological abnormalities, particularly motor hyperactivity or choreiform movements. (2)

Diagnosis is based exclusively on clinical criteria and represents a diagnosis of exclusion, requiring careful differentiation from other psychiatric, neurological, and developmental disorders. No laboratory test or imaging modality currently allows for definitive confirmation of PANDAS, which significantly contributes to diagnostic uncertainty and ongoing controversy. (1,3,5)

1.2 PANDAS vs PANS

A key diagnostic requirement to diagnose PANDAS is a temporal association with Group A β-hemolytic Streptococcus infection, which significantly limits the applicability of this diagnosis in routine clinical practice, as many patients present after the window for microbiological or serological confirmation has passed.

To overcome these limitations, the broader category of PANS was introduced. PANS emphasizes a dramatic and acute onset of obsessive–compulsive symptoms or severe restrictive eating, accompanied by additional neuropsychiatric manifestations such as anxiety, behavioral regression, cognitive deterioration, sensory or motor abnormalities, or somatic symptoms. Importantly, PANS criteria are etiologically non-specific and do not require confirmation of a preceding streptococcal infection, allowing for a wider range of potential infectious and non-infectious triggers

Although PANDAS and PANS share clinical features and a similar relapsing–remitting course, they should not be regarded as a hierarchical relationship. Instead, they represent intersecting diagnostic frameworks capturing overlapping patient populations. Some children meet criteria for both syndromes, whereas others fulfill only one set of criteria depending on symptom profile and documented triggers. This overlap highlights the conceptual and practical challenges in distinguishing between these entities and supports the view that PANDAS and PANS lie on a neuroimmune spectrum rather than constituting clearly separable disorders. (6–9)

Table.1. Comparison of PANDAS and PANS

Feature	**PANDAS**	**PANS**
Full name	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections	Pediatric Acute-Onset Neuropsychiatric Syndrome
Key symptom	Abrupt onset of OCD and/or tics	Abrupt onset of OCD or restrictive eating
Required trigger	Group A streptococcal infection	Not specified
Etiological concept	Infection-specific	Etiologically non-specific
Age of onset	Childhood (prepubertal)	Childhood
Course	Relapsing–remitting	Relapsing–remitting

Feature	PANDAS	PANS
Clinical scope	Narrower, research-oriented	Broader, clinically oriented
Relationship	Overlaps with PANS	Overlaps with PANDAS

2. Epidemiology

The epidemiology of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections remains poorly defined. Although PANDAS is generally regarded as a rare condition, its true prevalence and incidence are unknown. Available estimates are hindered by the absence of objective diagnostic biomarkers, reliance on clinical criteria, and substantial symptom overlap with common pediatric neuropsychiatric disorders, leading to probable underdiagnosis and inconsistent reporting across clinical settings. (1,2,10,11)

PANDAS most commonly manifests in early childhood, with symptom onset typically occurring between 3 years of age and puberty. This age distribution corresponds to periods of increased exposure to Group A streptococcal infections in daycare and school environments. Children presenting with tic-predominant symptoms tend to develop clinical manifestations at a younger age than those whose presentation is dominated by obsessive–compulsive symptoms. (1,2,12–14)

A consistent male predominance has been reported across observational studies. Male-to-female ratios exceeding 2:1 have been described, suggesting a possible sex-related susceptibility. The reasons for this disparity remain unclear but may reflect differences in immune response, neurodevelopmental vulnerability, or healthcare-seeking behavior. (1,9,14)

Efforts to estimate disease frequency are further complicated by the high baseline prevalence of both streptococcal infections and obsessive–compulsive or tic disorders in the pediatric population. Additionally, asymptomatic streptococcal carriage and difficulties in documenting a clear temporal relationship between infection and neuropsychiatric symptom onset obscure causal inference. Population-based studies indicate an increased risk of obsessive–compulsive and tic disorders following streptococcal infections, yet similar associations have been observed after non-streptococcal infections, suggesting that immune activation rather than a pathogen-specific effect may contribute to symptom development in susceptible children. (1,10,15)

Overall, the lack of standardized diagnostic criteria and prospective epidemiological studies limits accurate assessment of the true burden of PANDAS. Improved case definitions and large, population-based investigations are required to clarify its prevalence and natural history. (5,11,14)

3. Pathophysiology

PANDAS is conceptualized as a post-infectious, immune-mediated neuropsychiatric syndrome in which symptom onset or exacerbations follow infection with Group A β-hemolytic Streptococcus, most commonly *Streptococcus pyogenes*. Rather than direct central nervous system invasion, the prevailing model assumes that streptococcal infection initiates a systemic immune response that, in susceptible individuals, leads to downstream neuropsychiatric effects through immune-mediated mechanisms.

A central pathogenic hypothesis involves molecular mimicry, whereby antibodies generated against streptococcal antigens cross-react with neuronal targets. Several candidate autoantibodies have been proposed, including antibodies directed against dopamine receptors (D1 and D2), lysoganglioside GM1, and tubulin. These antibodies are thought to influence intracellular signaling pathways involved in dopaminergic neurotransmission, potentially contributing to the abrupt onset of obsessive-compulsive symptoms and motor phenomena. However, findings across studies remain heterogeneous, and the specificity and reproducibility of these antibodies have not been consistently demonstrated, which contributes to ongoing debate regarding their pathogenic significance. (16,17)

The proposed immune-mediated effects appear to converge on basal ganglia circuits, consistent with the characteristic clinical phenotype dominated by tics and compulsive behaviors. Dysregulation of cortico–striato–thalamo–cortical pathways is considered a key neurobiological substrate, and experimental data suggest that immune factors may preferentially affect striatal neuronal populations, including cholinergic interneurons. Such disturbances in basal ganglia function provide a plausible link between peripheral immune activation and central neuropsychiatric manifestations. (18,19)

In addition to antibody-mediated mechanisms, increasing attention has been directed toward neuroinflammatory processes and blood–brain barrier dysfunction. Experimental and translational studies suggest that pro-inflammatory immune pathways, including Th17-related mechanisms, may facilitate immune cell migration into the central nervous system and promote inflammatory changes within basal ganglia structures. Microglial activation and altered synaptic signaling have been proposed as downstream consequences, further supporting an inflammatory contribution to symptom development. (17,19)

Beyond classical immune models, emerging evidence points to a potential role of systemic inflammation and oxidative stress in modulating disease expression. Peripheral markers associated with increased gut permeability, endotoxemia, and oxidative pathways have been

reported in some cohorts, suggesting that immune amplification outside the central nervous system may indirectly influence neuroinflammatory processes. While these findings remain preliminary and require confirmation in larger, longitudinal studies, they highlight the multifactorial nature of immune dysregulation in PANDAS. (18,19)

Conceptually, the pathophysiological framework of PANDAS shares notable similarities with Sydenham's chorea, a well-established post-streptococcal neuroimmune disorder. Both conditions are characterized by antecedent streptococcal infection, involvement of basal ganglia circuitry, and immune-mediated mechanisms affecting motor and behavioral function. Sydenham's chorea is often regarded as a prototypical example of post-infectious autoimmune basal ganglia disease, whereas PANDAS represents a more heterogeneous and less clearly defined clinical entity. (1,17)

4. Clinical presentation

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections present with a heterogeneous constellation of neuropsychiatric and neurological symptoms, characterized by an abrupt onset and episodic course. The clinical picture extends beyond isolated obsessive–compulsive symptoms and reflects a broader disturbance of behavioral, emotional, and motor functioning. (2,3,11)

The core manifestations include the sudden appearance or rapid worsening of obsessive–compulsive behaviors and/or tic disorders in previously healthy children. Obsessive–compulsive symptoms often emerge dramatically and interfere significantly with daily functioning, while tics may be motor or vocal and fluctuate in severity. In many patients, obsessive–compulsive symptoms and tics coexist, further complicating clinical assessment and differential diagnosis. (2,3,13)

In addition to these hallmark features, children with PANDAS frequently exhibit a range of associated neuropsychiatric symptoms. These include marked anxiety, emotional lability, irritability, impulsivity, oppositional behaviors, and mood changes. Cognitive and behavioral regression, such as deterioration in academic performance or handwriting, is commonly reported. Sleep disturbances, including insomnia and parasomnias, as well as somatic complaints and enuresis, are also frequently observed, contributing to functional impairment. (3,9,13)

Neurological manifestations represent another important component of the syndrome. Besides tics, patients may display motor hyperactivity, clumsiness, or choreiform movements,

suggesting involvement of basal ganglia circuits. These motor features, although often subtle, support the hypothesis of subcortical dysfunction and overlap with other post-streptococcal movement disorders. (2,3,11)

The clinical course of PANDAS is typically episodic and relapsing–remitting, with symptom exacerbations often temporally associated with infectious episodes. Periods of partial or complete remission may occur between flares, although residual symptoms can persist. The severity and combination of symptoms vary considerably between individuals, underscoring the phenotypic heterogeneity of the disorder. (3,9,13)

Taken together, the symptom profile of PANDAS reflects a multidimensional neuropsychiatric syndrome rather than a narrowly defined anxiety or tic disorder. Recognition of the full spectrum of clinical manifestations is essential for appropriate diagnostic consideration and highlights the challenges inherent in differentiating PANDAS from other pediatric neuropsychiatric conditions. (9,11)

Table.2. Comparison of primary pediatric OCD and OCD associated with PANDAS (2,13,20,21)

Feature	**Primary pediatric OCD**	**OCD associated with PANDAS**
Onset	Gradual, insidious	Abrupt, acute (hours–days)
Trigger	No identifiable infectious trigger	Often temporally associated with GAS infection
Symptom severity at onset	Mild to moderate	Severe at presentation
Core symptoms	Obsessions and compulsions	Obsessions and compulsions
Insight	Often preserved	Frequently reduced, especially early
Associated neuropsychiatric symptoms	Limited	Common (anxiety, emotional lability, regression, enuresis)
Tic comorbidity	Possible	Frequent
Clinical course	Chronic, fluctuating	Episodic, relapsing–remitting

Feature	Primary pediatric OCD	OCD associated with PANDAS
Proposed pathophysiology	Neurodevelopmental / CSTC dysfunction	Post-infectious, immune-mediated, basal ganglia involvement

5. Treatment

5.1 Pharmacological and immunomodulatory treatment strategies

Management of PANDAS differs from standard OCD treatment due to its suspected post-infectious autoimmune background. In addition to cognitive-behavioral therapy and psychopharmacology, antibiotics and immunomodulatory interventions have been investigated. Antimicrobial treatment aims to eradicate streptococcal infection and possibly reduce neuropsychiatric exacerbations; however, clinical studies report heterogeneous and generally modest effects, limited by small sample sizes and methodological bias. (22)

Antibiotic therapy is commonly employed in PANDAS both during acute symptom exacerbations and as a preventive strategy against recurrent streptococcal infections. Although observational studies and parental reports indicate clinical improvement in a subset of patients, randomized trials have produced inconsistent results, particularly with regard to long-term prophylaxis. Variability in antibiotic selection, dosing regimens, and treatment duration limits the generalizability of available findings. In line with the proposed autoimmune pathophysiology, immunomodulatory therapies such as intravenous immunoglobulin and plasma exchange have been reserved for severe or treatment-resistant cases, with some studies reporting reductions in obsessive–compulsive symptoms and tics. However, the supporting evidence is limited, largely derived from small clinical trials and case series, while corticosteroids and nonsteroidal anti-inflammatory drugs appear to provide only transient or variable benefit. Recent expert consensus recommends a stepwise, individualized approach to PANDAS management, emphasizing standard psychiatric care as first-line treatment, with antimicrobial or immunomodulatory interventions considered selectively in patients with evidence of infection or immune dysregulation. Despite its distinct etiological framework, PANDAS shares core clinical features with primary obsessive–compulsive disorder; therefore, cognitive-behavioral therapy with exposure and response prevention and cautious use of selective serotonin reuptake inhibitors remain central to symptom management, although these

interventions primarily target clinical manifestations rather than underlying immune mechanisms. (22–24)

5.2 Challenges in the Treatment of PANS/PANDAS

Despite the range of therapeutic strategies described above, the management of PANS/PANDAS is limited by significant methodological and clinical challenges. Available studies demonstrate heterogeneous and often inconsistent treatment responses, with pooled analyses failing to show clear superiority of any single intervention. Interpretation of outcomes is constrained by small sample sizes, non-uniform diagnostic criteria, variability in treatment timing and modalities, and the absence of validated biomarkers for predicting therapeutic response. Furthermore, the predominance of low-evidence study designs and heterogeneous outcome measures hampers comparability across studies and precludes the development of standardized, evidence-based treatment algorithms. (25)

6. Controversies and Current Perspectives

The diagnosis and management of PANDAS remain highly controversial, and to date no universally accepted, evidence-based clinical guidelines have been established. Divergent positions among medical specialties contribute substantially to this lack of consensus. Pediatric neurologists and immunologists are more likely to emphasize inflammatory and immune-mediated mechanisms, supporting targeted diagnostic investigations and, in selected cases, immunomodulatory or antimicrobial treatment. In contrast, child psychiatrists often conceptualize PANDAS-related symptoms within the broader spectrum of obsessive–compulsive and tic disorders, highlighting phenotypic overlap with primary OCD and prioritizing standard psychiatric interventions. Criticism of the PANDAS construct focuses on inconsistent diagnostic criteria, the high background prevalence of streptococcal infections in childhood, difficulties in establishing a causal temporal relationship between infection and symptom onset, and the absence of robust biomarkers or large randomized controlled trials. Skeptics argue that observed symptom exacerbations may reflect nonspecific stress responses or natural fluctuations of neuropsychiatric disorders rather than a distinct autoimmune entity. Consequently, PANDAS has been variably framed as a discrete diagnosis, a subtype within the broader PANS spectrum, or a heuristic model for studying immune-related neuropsychiatric phenomena. Current research directions aim to refine phenotypic definitions, identify reliable immunological or neurobiological markers, clarify the role of environmental and stress-related

triggers, and conduct methodologically rigorous studies capable of resolving ongoing debates and informing future clinical recommendations. (1,17,26–28)

7. Discussion

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) remain a highly debated entity in pediatric neuropsychiatry. Although increasing evidence suggests that immune-mediated mechanisms may contribute to acute-onset neuropsychiatric symptoms in a subset of patients, the disorder is best conceptualized as part of a broader neuroimmune spectrum rather than a clearly defined nosological category.

Proposed pathophysiological mechanisms, including molecular mimicry, basal ganglia dysfunction, and neuroinflammatory processes, provide a plausible biological framework; however, no immunological marker has demonstrated sufficient specificity or reproducibility to support routine diagnostic use. The absence of validated biomarkers, combined with overlapping clinical features and the high prevalence of streptococcal infections in childhood, continues to challenge diagnostic certainty and causal inference.

Therapeutic strategies for PANDAS reflect this uncertainty. Antibiotics, immunomodulatory interventions, and standard psychiatric treatments have been applied with heterogeneous and generally modest outcomes. Methodological limitations of existing studies—including small sample sizes, non-uniform diagnostic criteria, and variable outcome measures—preclude the formulation of standardized, evidence-based treatment algorithms, reinforcing the need for individualized and multidisciplinary management.

Ongoing controversy is further shaped by differing perspectives among pediatric neurology, immunology, and child psychiatry, which influence both clinical practice and research priorities. Future investigations should focus on refined phenotypic characterization, longitudinal designs, and biomarker discovery to identify clinically meaningful subgroups and guide targeted interventions.

8. Cocnlusions

PANDAS represents a complex and controversial pediatric neuropsychiatric condition situated at the intersection of immunology, neurology, and psychiatry. Although a post-infectious, immune-mediated contribution to symptom development is supported by experimental and clinical observations, current evidence remains insufficient to establish definitive diagnostic criteria or standardized treatment algorithms.

The heterogeneity of clinical presentation, lack of validated biomarkers, and methodological limitations of existing studies continue to impede consensus regarding disease classification and management. Therapeutic interventions demonstrate variable efficacy, emphasizing the need for individualized, multidisciplinary care focused on symptom severity, functional impairment, and comorbidities.

Advancing the field will require well-designed prospective studies, improved phenotypic stratification, and collaborative research efforts aimed at clarifying pathophysiological mechanisms. Such approaches are essential

to improve diagnostic accuracy, optimize treatment strategies, and ultimately enhance outcomes for children affected by acute-onset neuropsychiatric syndromes within the PANDAS/PANS spectrum.

Disclosure

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Formal analysis: MW, KDW, BC

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