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PANDAS: Pediatric Autoimmune Neuropsychiatric Disorder Associated with Group A Streptococci – Pediatric Acute Neuropsychiatric Syndrome (PANS) A Comprehensive Review

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Abstract

Pediatric acute neuropsychiatric syndrome (PANS) and pediatric acute neuropsychiatric disorder associated with streptococcal infection (PANDAS), both are characterized by abrupt fluctuating episodes of obsessive-compulsive symptoms with other symptoms. These episodes are usually proceeded by infections with antigen mimicry speculated to be the cause of an immune dysregulation and inflammatory response. A cumulative data suggest that PANDAS is part of a systemic inflammatory response allowing anti-inflammatory drugs and immune modulator medications to be used for treatment with variable outcomes.

In this review we will shed light on documented facts about PANDAS and PANS aiming to raise awareness and improve management approach for affected children. This review synthesizes evidence from clinical studies, epidemiological data, and ongoing research to outline the historical context, pathogenesis, diagnostic criteria, differential diagnosis, treatment protocols, and controversies surrounding PANDAS and its broader counterpart PANS. We aim to emphasize evidence-based approaches while highlighting areas needing further investigation.

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Introduction

PANDAS represents abrupt-onset neuropsychiatric symptoms following group A beta hemolytic streptococcal (GAS) infections [1]. PANS and PANDAS are neurodevelopmental disorders characterized by sudden onset, often within 24 to 48 hours, of neuropsychiatric symptoms, such as obsessive–compulsive disorder (OCD), restricted eating, sensory changes, or tic disorders often with a relapsing remitting course [2]. PANS and PANDAS affect prepubertal children (typically ages 3–12 years), with symptoms causing significant impairment in daily functioning, school performance, and family life [3].

PANDAS falls under the broader umbrella of PANS, which includes non-GAS triggers, including common cold or COVID-19, metabolic changes, and environmental factors [4]. PANS is a broader syndrome of acute-onset neuropsychiatric symptoms from various triggers, including infections, environmental factors, or metabolic issues, serving as a diagnosis of exclusion without a specific trigger [4].

PANDAS originated in the 1990s at the National Institute of Mental Health (NIMH) by Swedo et al., based on observations of children with OCD/tics post-GAS infection, this was observed to be distinct from Sydenham chorea (SC), or St. Vitus' dance, which is a major manifestation of acute rheumatic fever (ARF) caused by autoimmune-mediated damage to the basal ganglia following GAS infection [5].

PANDAS was defined for the first time in 1998 by Swedo et al., based on a study of 50 patients with acute, sudden onset OCD, with or without tic disorder, who had previously developed GAS infection [6], it is hypothesized to involve an autoimmune response where antibodies targeting GAS cross-react with basal ganglia leading to inflammation with a great role of molecular mimicry [7].

Despite ongoing debates about its distinctiveness as a clinical entity [8], controversies regarding inconsistent autoantibody findings; some studies fail to distinguish PANDAS from non-GAS OCD/tics [9], recent emerging trials and biomarker research offer promise for improved diagnostics and

personalized interventions [10].

Pathogenesis

The pathophysiology of PANDAS involves an autoimmune response triggered by GAS infection. Antibodies produced against GAS epitopes may cross-react with proteins expressed in basal ganglia neurons, through molecular mimicry, a mechanism like Sydenham chorea (SC) [11].

Evidence includes elevated antineuronal antibodies in PANDAS versus controls; animal models show PANDAS-like behaviors post-GAS immunization and human sera from PANDAS patients bind rodent cholinergic interneurons [2]. Alternative models involve gut microbiota alterations linked to neuroinflammation and oxidative stress markers (NOX2, isoprostanes) are higher in patients with PANDAS [12].

Functional studies have pinpointed specific neuronal targets involved in PANDAS. Antibodies targeting dopamine (D1/D2) receptors, Lysoganglioside (lyso-GM1) receptors, beta-tubulin receptors, and dopamine 1 and 2 receptors (D1R, D2R) [13]. Animal models have shown that antibodies from GAS infections can cause neurological disorders by attacking cerebellar tissue and disrupting the blood brain barrier (BBB), leading to neuropsychiatric symptoms [14]. Recent research has shed light on the role of striatal cholinergic interneurons (CINs) in PANDAS. Immunoglobulin G (IgG) from PANDAS patients binds to CINs, inhibiting their activity. This inhibition has been associated with the development of repetitive behaviors like Tourette syndrome. Notably, PANDAS IgG does not bind to GABAergic interneurons or medium spiny neurons expressing D1R-D2R. In addition, Positron Emission Tomography (PET) scans and Magnetic Resonance Imaging (MRI) have revealed neuroinflammation in basal ganglia and the thalamic regions in PANDAS patients [15].

PANDAS requires a temporal link to GAS infection; this is considered controversial due to cases with subclinical infections [16]. PANS expand scope but is criticized for vagueness, sometimes viewed as idiopathic autoimmune encephalitis [3]. Both are clinical diagnoses without biomarkers, raising overuse concerns [17].

PANDAS is chronic disease that occurs with periods of exacerbation and remissions, with an average remission period of 3.3 years. It was observed that most children (approximately 72%) showed at least one exacerbation of PANDAS symptoms throughout the period of gradual remission. Episodes of exacerbation manifest suddenly and resolve gradually over a span of weeks to months. An extended duration of a streptococcal infection is linked to a worse clinical outcome. Untreated or unrecognized manifestations of PANDAS can also increase the risk of obsessive-compulsive manifestations and tics during adulthood [6].

Streptococcal infections may alter the gut microbiome, selecting strains associated with inflammation and immune response activation. This dysbiosis could impact the synthesis of brain metabolites, such as tyrosine and dopamine, influencing the behavioral changes in PANDAS [18].

Various theories involving regulatory T-cells, cytokines, immune-associated genes and immunoglobulins have been proposed to explain the immune dysregulation in PANDAS. These theories also require further validation to identify specific immune biomarkers associated with this complex clinical entity [6].

Patients with PANDAS exhibited higher levels of tumor necrosis factor-alpha and interleukin-17, both of which have been hypothesized to play a role in BBB permeability [19].

It has been hypothesized that specific subtypes of lymphocytes, T helper 17 (Th17) and Th17 derived cytokines [including interleukin (IL)-17] are involved in BBB leakage allowing the cross reaction of antistreptococcal antibodies to brain targets located in the basal ganglia through a process of molecular mimicry. Basal ganglia are involved in motor, cognitive and emotional functions, being implicated in the pathogenesis of OCD and tics [9].

Motor abnormalities observed in PANDAS patients have been related to higher titters of anti-basal ganglia antibodies compared to healthy controls. Although emerging data is revealing the mechanisms by which GABHS-specific Th17 cells and antineuronal antibodies cross the BBB [3], furthermore, it was assumed that a compromised mucosal secretion of IgA might predispose to the development of recurrent tonsillitis and autoimmune disorders [3].

PANS is triggered by a recent infection and or autoimmunity trigger (like SC, autoimmune encephalitis (AE), and Guillain-Barré syndrome). Not all cases of PANS are reported to be triggered by an infection, and no single microbe has been associated with its onset [20]. PANS is challenging from a clinical perspective, because it lacks disease-specific biomarkers, strong evidence for pathogenic causes, and consensus on treatment of clinical symptoms [21].

Some genetic studies indicate that both PANS and neuropsychiatric regression in autism spectrum disorder (ASD) are characterized by marked genetic heterogeneity. Nevertheless, the findings point toward a functional convergence on specific immune-related pathways, including inflammasome activation, Toll-like receptor signaling, and NF-κB–mediated inflammatory cascades. Disruption of these pathways may significantly alter immune regulation and contribute to pathological inflammatory responses [22].

Furthermore, the identification of genes involved in the DNA damage response (DDR) supports a potential role for the cGAS–STING pathway, a key inducer of type I interferon production and AIM2 inflammasome activation. This pathway is typically triggered by viral and bacterial DNA, as well as by damaged nuclear and mitochondrial DNA. Mutations in genes encoding regulators of these pathways may predispose individuals to maladaptive immune responses and/or neuroinflammation following infectious exposures that activate the same molecular mechanisms [23]. Importantly, these findings also suggest that specific genetic subgroups of individuals with ASD may be at increased risk of developing acute neuropsychiatric decompensation after infections. Further confirmation and deeper characterization of these genetic–immunological associations may have important translational implications for understanding and managing PANS and infection-associated regression in ASD [23].

Epidemiology

PANDAS Symptoms are most frequently observed between the age of 3 and puberty. The early onset of PANDAS is associated with the highest rate of GAS exposure during early childhood. The onset of PANDAS after puberty is possible, nevertheless, it forms a minor percentage of cases [24]. Early-onset OCD is associated with high familial load [25].

Mean onset is 6.3 years for tics and 7.4 years for OCD; with male:

female ratio of 2.6:1 (4.7:1 under 8 years) [26]. This sex imbalance suggests potential biological or immunological susceptibility factors that warrant further investigation [4].

Prevalence is rare, with estimates ranging from 1 in 11,765 children [27] in population-based studies to higher rates (up to 40%) in OCD/tic cohorts, though data are limited due to diagnostic challenges [26]. Higher in families with rheumatic fever history [27]. Association with GAS: Case-control studies show 2–3x higher GAS risk pre-onset; prospective data mixed—some link repeated GAS to exacerbations, others find no causality due to high background rates [28].

Geographically, PANS has been documented across multiple countries, indicating a global distribution rather than a region-specific disorder [4].

Exacerbations of PANDAS symptoms are observed in 30% of cases due to GAS infections; 20% are because of non-streptococcal illnesses and approximately half of the cases are because of a non-identified factor [24] Infection triggers which initiated PANS/PANDAS were reported as GAS (66.8%), viral (e.g., common cold, measles) (14.2%), mycoplasma pneumoniae (7.5%), other bacterial infection (7.1%), Lyme disease (Borrelia Burgdorferi) (4.3%) or COVID-19 infections [29].

Clinical Features

The onset of the symptoms is four to six weeks following GAS infection [6]. Children with PANDAS commonly present with abrupt or sudden-onset (within 24–48 hours) OCD, often characterized by the rapid development of intense, debilitating symptoms, such as severe contamination fears, Common compulsions include excessive hand washing, perfectionism, and food restriction due to contamination fears or choking concerns, sometimes exacerbated by body image distortions [30]. Elevated anti-streptococcal antibody levels are associated with increased severity of OCD [31].

Psychiatric comorbidities include ADHD (≈40%), oppositional defiant disorder (≈40%), and depression (≈36%). Anxiety disorders are frequent, including separation anxiety, generalized anxiety, phobias, panic attacks, and night fears with a "sawtooth" course (abrupt exacerbations followed by partial or full remission) [32].

Emotional lability, agitation, impulsivity, irritability, aggression, oppositional behaviors, self-harm, and suicidal tendencies are reported. These symptoms often impair academic performance in up to 81% of affected children [31].

Sensory abnormalities such as hyperacusis, tactile sensitivity, and visual/auditory hallucinations are common, alongside speech disfluency, selective mutism, and behavioral regression [31].

Motor abnormalities predominantly consist of tics, choreiform movements, dysarthria, dyskinesia, nail biting, skin pinching, and hair pulling. Subtle finger and toe movements (“piano playing” movements) are characteristic [33].

Somatic and systemic manifestations include sleep disturbances, urinary symptoms (urgency, frequency, nocturnal enuresis), joint pain, skin lesions, systolic murmurs, and echocardiographic abnormalities [33]. Otolaryngological symptoms such as sinusitis, otitis, tonsillar enlargement, and pharyngitis are observed in 67.7% of patients, with an elevated risk of rheumatic fever. These manifestations are sudden, severe, and significantly impair daily functioning [6].

Sudden onset of PANDAS/PANS symptoms known as flare, Flares were classified based on the timing, severity, and evolution of neuropsychiatric symptoms relative to each patient’s baseline level of functioning. An initial flare was defined as the first recorded episode of symptom exacerbation, marking the earliest observable departure from the patient’s baseline. Subsequent flares refer to any later episodes of symptom escalation following the initial flare [34].

Each flare was further characterized by its onset pattern: acute or hyperacute flares were defined by a rapid emergence of symptoms over a short period, whereas less severe or gradually developing symptom episodes were classified as subacute flares. The resolution of a flare was determined through clinician and parent agreement, identifying either partial recovery (residual symptoms persist) or full recovery (return to baseline functioning) [34].

To avoid ambiguity in longitudinal assessment, the term relapse was avoided, as it can complicate flare counting. Instead, all episodes were referred to as either initial or subsequent flares, and flare series were used to describe notable exacerbations or the emergence of new symptoms occurring during an ongoing flare. This framework allowed systematic documentation of symptom dynamics and recovery intervals in the absence of definitive biological markers [10].

Children with pediatric acute-onset neuropsychiatric syndrome (PANS) frequently exhibit systemic autoimmune and inflammatory manifestations in addition to neuropsychiatric symptoms. Approximately one-third of patients demonstrating at least one marker of autoimmunity, immune dysregulation or inflammation, or vasculopathy exhibited evidence of overlapping immune involvement, with markers spanning two or more immunological subcategories. Musculoskeletal involvement was particularly prominent, with a substantial proportion of patients developing inflammatory arthritis during follow-up [35].

By 14 years of age, the cumulative incidence of arthritis reached 28.3%, while other autoimmune conditions occurred less frequently. Arthritis typically manifested in early adolescence and was most classified as enthesitis-related arthritis (ERA) or spondylo arthritis (SpA), with a notable subset of patients fulfilling criteria for both. Psoriatic arthritis was observed in a smaller proportion of cases, and a subset of patients with arthritis developed additional autoimmune disorders, highlighting the multi systemic nature of immune involvement in PANS [36].

Clinical joint examinations commonly revealed tenderness of the distal interphalangeal joints and axial skeletal structures, including the spinous processes. Imaging findings among affected patients frequently demonstrated joint effusions, synovitis, and capsular thickening, whereas such abnormalities were absent in patients without clinically diagnosed arthritis. Extra-articular features, including nail pitting and psoriasis, were observed in a minority of patients, further supporting an association between PANS and autoimmune rheumatologic phenotypes [35].

Diagnostic Criteria

PANS diagnostic criteria: Abrupt and dramatic onset of OCD or severely restricted food intake with abrupt onset of additional severe neuropsychiatric symptoms from at least 2 of the following 7 categories:

1. Anxiety.
2. Emotional lability and/or depression.

3. Irritability, aggression, and/or severe oppositional behaviors.
4. Developmental regression.
5. Deterioration in school performance.
6. Sensory or motor abnormalities include heightened sensitivity to sensory stimuli, hallucinations, dysgraphia, and complex motor and/or vocal tics.
7. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency that are not better explained by a known neurologic or medical disorder [4].

PANDAS' diagnostic criteria:

1. OCD and/or tic disorder.
2. Prepubertal onset of symptoms (3 years to puberty).
3. Episodic course characterized by acute, severe onset and dramatic symptom exacerbations.
4. Temporal relationship between GAS infection, symptom onset, and exacerbations.
5. Association with neurologic abnormalities (hyperactivity, choreiform movements) [20].

Diagnostic Process

Start with high index of suspicion in cases with abrupt onset of OCD or motor tics associated with underlying anxiety or increasing urinary frequency [37]**.** Clinical evaluation using throat or skin culture, rapid antigen detection test (RADT, it is advisable to confirm negative results with culture); Antistreptolysin O (ASO) and anti-DNase B titers (rise over 4–6 weeks and confirms recent GAS infection) [9].

Preliminary diagnosis will be probable PANDAS in case of abrupt onset of symptoms with recent GAS infection and showed antibiotic response [38]. This should be followed by monitoring these cases with repeat cultures or serology in cases of remissions to exclude carriage status [39].

Management and Treatment Protocols

Multidisciplinary approach covering treatment of GAS infection, managing neuropsychiatric symptoms, and immunotherapy was highlighted in many management protocols [40].

For mild cases, symptomatic treatment with anti-inflammatory agent like ibuprofen 10 mg/kg/dose every 8 hours for 5 to 14 days or a short course of oral steroids (prednisone 2 mg/kg/day for 5 days), this provides faster resolution (flares shorten 2.6–4 weeks) vs. watchful waiting [4].

In moderate to severe cases, first line therapy with antibiotics (Amoxicillin: 500 mg 3 times daily for 10 days (or 50 mg/kg/dose once daily, maximum 1000 mg/day for 10 days or Azithromycin: 12 mg/kg/day, maximum 500 mg once daily for 3-5 days or Cefadroxil 30 mg/kg/day for 10 days [41]. Second line therapy with steroids or Intravenous Immunoglobulin (IVIG) (1 g/kg/day for 2 days) [42]. IVIG was found to be superior to placebo in RCTs (45–58% symptom reduction at 1 month) and better than steroids for severe cases [43, 44].

In severe or refractory cases, first line includes IVIG with 5-7 plasma exchange (PEX) sessions and second line therapy with Rituximab 375 mg/m² weekly for 2–4 weeks [45]. Combination of PEX and IVIG yields 70–80% improvement and is considered superior to monotherapy [38].

Psychotropics (start low and go slow). SSRIs (Fluoxetine 2.5–5 mg/day) and increase up to 40 mg/day guided by clinical response. Benzodiazepines (Lorazepam 0.25–0.5 mg/dose) [42]. Atypical antipsychotics (Risperidone 0.125–1 mg/day) for severe OCD [46].

Prophylaxis: Preventive antibiotics (Amoxicillin 250 mg twice daily or Azithromycin (5 mg/kg daily) for 10 days and up to 3 weeks), were found to be effective in RCTs with fewer exacerbations; reduces GAS infection rate (OR 0.28) *vs.* none [38].

GAS infection is considered a high disease burden with negative effects on children and adolescents, there has been several trials to develop an effective preventive vaccine for GAS, different technologies have been tried, focusing on M protein, non-M protein antigens as potential candidates, however, there is no advancement beyond phase 2 clinical tails, which makes it a long wait till we can have commercially available vaccine [47].

Discussion

The clinical presentation of PANS and PANDAS challenges traditional psychiatric symptomatology by shifting the focus from purely behavioral origins to a complex neuroimmunological dysfunction. Molecular mimicry, with current evidence strongly suggests that antibodies produced against GAS cross-react with basal ganglia proteins, specifically targeting dopamine D1/D2 receptors and striatal CINs. This cross-reactivity, likely mediated by Th17-driven BBB permeability, triggers localized neuroinflammation cascade disrupting the motor and emotional circuits responsible for the sudden onset of OCD symptoms and tics.

Emerging evidence regarding antineuronal antibodies (such as anti-D1R and anti-D2R) and gut-brain axis dysbiosis offers promising diagnostic potential. The distinction between PANDAS and the broader PANS is vital, as it expands the diagnostic lens to include non-streptococcal triggers like COVID-19 or metabolic stressors, ensuring that cases without a clear GAS link are not overlooked. Emerging data indicate that streptococcal infections can cause gut dysbiosis, potentially influencing neuroinflammation through the synthesis of metabolites like tyrosine and dopamine.

Ultimately, effective management necessitates a tripartite therapeutic approach that addresses various triggers, the dysregulated immune system, and the psychiatric symptoms simultaneously. While antimicrobials and immunomodulators show variable success, they represent a critical shift toward treating the underlying cause rather than just the behavioral manifestations. Future research must prioritize large-scale randomized controlled trials to standardize these interventions and validate biomarkers, moving the field toward a more precise, evidence-based standard of care. The primary role of antibiotic prophylaxis, such as penicillin or azithromycin, is to eliminate the persistent or recurrent GAS antigenic stimulus, to reduce the continuous activation of Th17 cells and the subsequent production of pro-inflammatory cytokines like IL-17. This reduction in the peripheral inflammatory load allows the BBB's tight junction proteins to stabilize, "closing the gate" against further autoantibody infiltration. Furthermore, some antibiotics, particularly macrolides, may possess secondary immunomodulatory properties that directly dampen the systemic cytokine storm.

Conclusion

PANS and PANDAS represent a complex frontier in pediatric neuroimmunology, characterized by a distinct, abrupt-onset clinical profile that necessitates early recognition and a multidisciplinary management approach. The lack of definitive, universally accepted biomarkers remains a significant hurdle, often leading to diagnostic delays or over-reliance on exclusion-based clinical judgment.

Many studies are limited by small sample sizes and a lack of randomized controlled trials (RCTs). Future research must prioritize identifying longitudinal biomarkers to distinguish active inflammation from permanent neurological injury, ensuring that children receive targeted rather than broad-spectrum treatments. There is still room for future research to overcome diagnostic vagueness, integrate neuroimmunology in formulating diagnostic panels as well as clinical biomarkers to allow early detection and intervention to improve outcome further. Longitudinal studies and randomized controlled trials are imperative to validate emerging biomarkers and standardize therapeutic protocols.

By bridging the gap between immunology and child psychiatry, clinicians can move toward a more personalized, evidence-based model of care that reduces long-term neuropsychiatric morbidity and improves the quality of life for affected children and their families.

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