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Sarah Alnaher, Rick Wolthusen, Farees Ahmad Khan & Muhammad Zeshan

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*[1]Sarah Alnaher, [2]Rick Wolthusen, [3]Farees Ahmad Khan & [4]Muhammad Zeshan

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Abstract

PANDAS/PANS is a burdening disorder that affects children, adolescents and caregivers. Despite numerous investigations to establish evidence-based interventions and clinical practices, more controversies and disagreements arise. This quantitative literature review established fundamental evidence regarding viral infections, bacterial infections, comorbidity, antibiotic therapy and immunotherapy. We conducted a qualitative and quantitative literature search on, Google Scholar and PubMed/Medline. The Boolean operators were used to combine search terms. An additional manual search was performed on the reference lists of the potential literature. The literature search was limited to English publications between 2014 to 2024. Results: Literature shows diverse aspects of PANDAS and PANS among children with OCD, adolescents, and other populations. The disease has been associated with bacterial and viral infections. We found a wealth of evidence on the controversial antibiotic therapy, comorbidities, immunotherapy and reports on infections. Proponents of bacterial and viral infections, alongside antibiotic therapy, emphasized the role of the infectious agents and the therapeutic effects of the antibacterial agents. Additionally, the importance of immunotherapy, NSAIDs and corticosteroids emerged, marking fundamental developments in the management of the disorder. Streptococcal and viral infections are risk factors of PANDAS/PANS, while immunotherapy, corticosteroids, NSAIDs, and antibiotic therapy produce positive clinical outcomes. However, this literature review established controversies on comorbidity, and antibiotic therapy as doctors disagree. However, we found that the authors agree that anxiety is a common comorbid disorder.

Keywords: *Immune-Brain Interface, PANS, PANDAS, Pediatric Neuropsychiatry, Neuroimmune Disorders*

1.0 Introduction

In 1998, PANDAS was first defined as a broad spectrum of complications and symptoms, stretching from featuring severe food consumption to OCD in children (Loffredo et al., 2020; Swedo, Leckman, & Rose, 2012). Since its discovery, PANDAS has been confusing and misunderstood in the medical fraternity. The disease would be broadly iterated PANS, evoking massive controversies and gaining significant attention (Hutanu et al., 2022; Wilbur et al., 2019). PANS/PANDAS' clinical phenotype and a subtype of OCD present exacerbated neuropsychiatric symptoms, i.e., moderate to severe OCD. It features multiple etiologies, like immunological and genetic, that occur without and with infections – *Streptococcus pyogenes*

(Orefici, Cardona, Cox, & Cunningham, 2016). Often, PANS' remarkable comorbid tics include visuomotor impairment, a decline in children's school performance, poor handwriting skills, poor quality of life and eating disorders.

One dimension of the clinical presentation of PANDAS/PANS regards streptococcal infection as a trigger. Theoretically, the nexus between group A streptococcal infections on the brain regards abnormal antibody-mediated response that produces abnormal neuropsychiatric outcomes in children without a history of comorbidities of such kind. Often, these changes induce obsessive compulsions, controllable speech, movements and behavioral attitudes (Hutanu et al., 2022). Remarkably, about 54.5% of global caregivers report speech disfluency among children with PANDAS/PANS, citing motor-related verbal blocks, high rates of speech, superfluous behavior, and vocal tics. PANS/PANDAS' association with streptococcal infections potentiated the hypothesis of autoimmune pathogenesis, resulting in cross-interaction between neuronal antigens and streptococcal antibodies, non-group A streptococcal infection recurrence susceptibilities, and immunomodulatory therapy responses. In the initial stage, the streptococcal-associated PANS/PANDAS is marked by urinary urgency, hyperactivity, declining school performance, deteriorating handwriting, separation anxiety, and impulsivity. Later episodes are marked by mood liability, inattention, oppositional behaviors, bedtime rituals and fears.

The other dimension of clinical presentation regards autoimmune implications as a trigger. Many PANDAS patients report immune abnormalities, including pathologies of the basal ganglia, streptococcal-mediated anti-neuronal autoantibodies, alongside dopamine receptor autoantibodies (Murphy, Gerardi, & Parker-Athill, 2014; Rea, Guido, & Spalice, 2021). Three antibodies emerging in PANDAS studies include D2R, N-acetyl-beta-D-glucosamine, a streptococcal group-A carbohydrate antigen, and tubulin. In addition to reactivity within basal ganglia neurons, strong evidence from multiple studies established these autoantibodies among PANDAS/PANS' patients. PANDAS can be identified through movement and behavioral complications in infancy and adolescence, including orofacial movement complications induced by temporomandibular joint pains and otorhinolaryngologic symptoms.

Recently, substantial evidence associating streptococcal infections with autoimmune disturbance emerged. (Hutanu et al., 2022; Loffredo et al., 2020; Xu et al., 2021). Mothers are reported to be the main victims of this autoimmune disturbance. To elaborate on this rare finding, more studies on the dysregulation of cortico-basal ganglia circuits among women with PANDAS support autoimmune disturbance by bacterial infection. However, Xu et al. assert that PANDAS resulting from autoimmune actions against brain antigens, the post-infection production of antibodies targeting basal ganglia, remains unproven.

The propensity and typical diagnosis among children prompt the indication of treatments and interventions to remove antibodies and alleviate associated symptoms in adolescents and children. While multiple interventions have been proposed, clinicians and psychiatrists remain dissatisfied with the rationale of treatment as concerns and disputes over efficacy and safety issues arise. For instance, TPE has been recommended for adolescents and children with prolonged symptoms of PANS/PANDAS (Prus, Weidner, & Alquist, 2022). Likewise, mixed results emerged from antibiotic studies as treatments and prophylaxis for streptococcal-associated PANS/PANDAS.

Despite a wealth of evidence, there are still ensuing debates and controversies on PANDAS' pathology and mechanisms. The controversies regard conflicting evidence on autoantibody mechanisms and streptococcal infections. In this literature review, we synthesize current evidence on autoimmune-associated and streptococcal-associated PANDAS/PANS among children to draw knowledge, limitations and boundaries in symptomatology, etiology,

diagnosis and treatment. The review focuses on conflicting accounts of evidence presented on autoimmune implications, streptococcal infections, diagnosis and treatments.

2.0 Methodology

We conducted a qualitative and quantitative literature search on Google Scholar and PubMed/Medline to locate recent evidence on PANDAS and PANS's incidence and health outcomes. We adopted the Boolean operator "AND" to combine words with dissimilar meanings: (((PANDAS) AND (PANS)) AND (comorbidity) and ((pandas) AND (pans)) AND (symptoms). The literature search was limited to English publications between 2014 and 2024. We used a qualitative methodology to locate records reporting qualitative and quantitative data for comprehensive analysis.

The critique for eligible articles captured the most recent evidence on PANDAS and PANS. Fundamentally, we examined controversial themes to determine the current status of the topic among researchers, clinical evidence to ascertain the current clinical practices in diagnostics and management practices, and comorbidity. The multidimensional approach unveils evidence on directly and indirectly associated aspects of the disorder. We considered reviewing expert opinions from major psychiatric institutions. In this approach, we focused doctors' take on antibiotic therapy, and positions taken by institutions like the American Academy of Pediatrics, American Academy of Child and Adolescent Psychiatry, and the Journal of Child and Adolescent Psychopharmacology for evidence.

3.0 Results

To many, PANDAS is caused by infections. However, controversies on infection-related incidences regard insufficient evidence (Swedo et al., 2012). A retrospective study established that streptococcal infections alter neuronal cell stimulation and anti-neuronal autoantibody (Shimasaki et al., 2020). While supporting Shimasaki et al.'s report, Hutanu et al. and Rea et al.'s study reported that Children diagnosed with streptococcal infections and their parents reported new onset of neuropsychiatric symptoms like anxiety and depression. The effect of immune-infectious interplay and OCD emerges through OCD's symptomatology, which usually occurs in 1% to 10% among PANDAS associated with streptococcal infections (Nazeer, Latif, Mondal, Azeem, & Greydanus, 2020). Despite its association with anti-DNase B antibody titers and positive anti-streptolysin O since 1998, PANDAS was not listed in DSM-V as an independent neuropsychiatric disorder up until 2013. While emphasizing the influence of neuroinflammation in PANDAS and PANS, Vreeland et al. reported that group Aa streptococci provoke acute-onset OCD. Animal models indicated anti-neuronal autoantibodies and basal ganglia changes (Vreeland et al., 2023).

Additional evidence of viral infections has emerged in recent years. Investigations on PANDAS/PANS revealed the influence of COVID-19, with strong evidence indicating that COVID-19 infection impacts setbacks and higher frequencies of symptom flares, especially following COVID-19 vaccination (LaRusso & Abadia, 2023). According to LaRusso and Abadia, children with OCD and COVID-19 infection displayed coercive behaviors toward their caregivers. Cumulatively, these events affected caregivers' mental health negatively, creating further health burdens and broken relationships (O'Dor et al., 2024). Consequently, the caregivers expressed dissatisfaction. This evidence asserted exacerbated and new symptomatology, including mood liability, anxiety, and OCD, among children suspected to have or been diagnosed with COVID-19.

Sudden and rapid onset of OCD, where children develop unusual behaviors or thoughts, mark PANDAS and PANS. Often, doctors consider decreased eating, compulsiveness and obsessive behavior as indicators of PANS in children (Psychiatry, 2023). The American Academy of

Child and Adolescent Psychiatry contends that infections, or any other agents that activate immune functions, are triggers of PANS. More so, unlike PANS, PANDAS is attributed to streptococcal infections, drawing the nexus between the disorder with immunity and prost-infection production of antibodies.

The association of PANDAS with streptococcal infections and multiple comorbidities necessitate better clinical practices and treatment approaches. These comorbidities define the clinical differences among children with OCD. Proponents of comorbidity cite tics in PANS, and associate them with symptoms like suicidality, behavioral regression, anxiety, and depression (Orefici et al., 2016). At the same time, other proponents associated PANDAS/PANS with other comorbid neurological and neuropsychiatric disorders, including bedtime rituals, nighttime fears, emotional liability, and separation anxiety (Hesselmark & Bejerot, 2019; Swedo et al., 2012). Another multicenter study revealed that these disorders feature multiple comorbidities, including school issues, separation anxiety, urinary symptoms, sleep disruptions, among other complications (Swedo et al., 2015), eating, oppositional defiant, panic, and personality disorders, alongside social phobia, suicidality and bipolar disorder. Despite varied incidence, studies by Orefici et al., Hesselmark and Bejerot, Swedo et al. 2012, and Swedo et al., 2015 reported anxiety as a common comorbid disorder.

Further, the controversies surrounding PANDAS and PANS stretch to interventions against the bacteria infections. The *American Academy of Child and Adolescent Psychiatry* and the *American Academy of Pediatrics* reported diverse opinions on diagnosis and treatment among psychiatrists and doctors. For instance, Dr. Brick recommended antibiotic therapy for PANDAS associated with streptococcal infections irrespective of negative streptococcal throat culture (Pupillo, 2017). Antibiotic therapy focuses on prophylaxis for children recovering from multiple streptococcal-associated neuropsychiatric exacerbations or immunotherapy. Rae, Guide, and Spalice supported antibiotic therapy by citing the regulation of the immune system through immunomodulatory actions and counters neuroinflammation. Proponents of antibiotic therapy recommend combined therapy with corticosteroids, NSAIDs, therapeutic plasma exchange or IVIG when symptoms persist. On the other hand, Dr. Fisher opposed antibiotic therapy, and requested for more evidence on the effectiveness and safety.

PANDAS' management ranges from prophylactic measures, both short- and long-term interventions, to addressing the onset of flares (Brown et al., 2017). A wealth of literature demonstrates NSAIDs' effectiveness in managing residual neuropsychiatric symptoms by shortening the onset of flares within 30 days of administration. Brown et al.'s study revealed that 10 mg/Kg of naproxen, BD, and 10 mg/kg of ibuprofen administered 6 to 8 hours reduced the onset of flares to about 2.6 weeks, as compared to 12.2 weeks without NSAID treatment. This therapeutic approach is beneficial for children with remitting, relapsing or new onset neuropsychiatric symptoms. Clinically, NSAIDs are ideal for managing shorter flares among children with neuroinflammations associated with streptococcal infections in PANDAS.

Investigations on PANDAS/PANS management stretched to COVID-19-infected children to strike a risk-benefit balance between the benefits of autoimmune encephalitis and streptococcal infection-associated PANDAS/PANS. Strong evidence of COVID-19 infection setbacks and higher frequencies of symptom flares among PANDAS/PANS was higher following COVID-19 vaccination (LaRusso & Abadia, 2023). Often, children with OCD display coercive behaviors toward their caregivers. Cumulatively, these events affected caregivers' mental health negatively, creating further health burdens and broken relationships (O'Dor et al., 2024). Through these phenomena, the COVID-19 pandemic introduced a new dilemma in the research and development of effective interventions against PANDAS/PANS. A study by O'Dor et al. reported exacerbated and new symptomatology, including mood liability, anxiety, and OCD,

among children suspected to have or been diagnosed with COVID-19. Because of the broken relationships and the mental health burden, most caregivers' express dissatisfaction with their practice.

Literature shows standardized immunomodulatory therapy guidelines for mild, moderate-to-severe, and life-threatening or severe PANS (Frankovich et al., 2017). The specification of treatment guidelines for every stage of disease severity demonstrates the therapeutic developments emerging from recent research and studies. To begin with, in combination with cognitive behavioral therapy, "tincture of time" has been suggested as the first-line therapy for mildly impairing PANS. However, short-acting orally administered corticosteroids and NSAIDs when symptoms persist. Frankovich et al.'s study found that intravenous or oral corticosteroids. In contrast, repeated administration of high doses of corticosteroids or prolonged administration is effective for moderate-to-severe PANS and chronic or severe presentations, respectively. Further, the treatment guidelines distinguished the treatment of life-threatening impairment through TPE. As a first-line intervention for extreme PANS, TPE can be used as monotherapy or combined therapy with rituximab and/or high doses of intravenous corticosteroids and IVIG.

4.0 Discussion

Today, PANDAS and PANS remains a point of concern in psychiatry due to the severe health implications. The current interventions, including antibiotic therapy, psychopharmacologic interventions and psychotherapy, directly influence the clinical practices, research and policymaking frameworks (Psychiatry, 2023; Margo Thienemann et al., 2017). Yet, the present literature review unveils controversial accounts of the roles of infections, comorbidities, treatments for PANDAS and immunotherapy for PANS.

This literature review found strong evidence supporting the role of infections on PANDAS. Bacterial and viral infections trigger immune responses, resulting in neuroinflammation and neuropsychiatric symptoms. Specifically, group A streptococcal infections and the COVID-19 pandemic were associated with exacerbated symptoms of PANDAS (Nazeer et al., 2020; Shimasaki et al., 2020; Vreeland et al., 2023). In recent years, advanced diagnoses have been performed to obtain more evidence on the role of infections in PANDAS. One study supported these findings by asserting that streptococcal infections trigger a disordered immune response, resulting in the acute onset of symptoms (Sørensen et al., 2018). Orefici et al. supported this argument by asserting that PANS is less associated with bacterial infections as compared to PANDAS. Additionally, the literature emphasized that COVID-19 enhanced mood liability, tics, and OCD among PANDAS/PANS patients. Nonetheless, the literature begs questions on effective interventions to eradicate infections to prevent the provocation of neuroinflammation and associated immune responses.

Divergent opinions emerged from the *American Academy of Pediatrics,* the *Journal of Child and Adolescent Psychopharmacology, Common Sense Media,* and the *American Academy of Child and Adolescent Psychiatry* on the potential clinical outcomes of antibiotic therapy. A case in point is the effectiveness and the rationale for antibiotic therapy against group A streptococcal infections (M. Thienemann et al., 2017). Characteristically, Dr. Brick recommended antibiotic therapy, while Dr. Fisher disputed the intervention, calling for further investigations for more evidence. This evidence addresses the gap of a guideline in antibiotic therapy in PANDAS and PANS.

Interestingly, the adverse effects of the disease do not only affect patients but also caregivers. Negative impact on caregivers' mental health, increased health burden, and dissatisfaction could impact overall practice (O'Dor et al., 2024), especially among caregivers tending to

COVID-19 patients with PANDAS/PANS. This argument spells the health burden of PANDAS/PANS in two phases: health and social issues. For instance, O'Dor et al. reported massive broken social ties among caregivers tending to children with PANDAS/PANS. This phenomenon embodies one dimension of dissatisfaction among a section of the caregivers. PANDAS/PANS children with COVID-19 were found with new symptoms that implicate additional health burdens among them. Subsequently, the burden befalls their caregivers, implicating health burdens and dissatisfaction with professional roles.

A wealth of knowledge emerged on NSAID and corticosteroid management of the disorders. Many investigations do not point to a particular rejection of NSAID interventions against PANDAS/PANS. The rationale of NSAIDs and corticosteroids in PANDAS/PANS aligns with the need to address inflammation, with therapeutic effects unfolding in multiple dimensions. The prophylactic rationale of NSAD and corticosteroid administration is short- and long-term for mild, moderate-to-severe, and life-threatening PANDAS and PANS (Frankovich et al., 2017; Nazeer et al., 2020). Particularly, NSAIDs reduced symptoms within a short period. While endorsing the clinical benefits of corticosteroids and NSAIDs in PANDAS/PANS, multiple studies assert low adverse effects and high efficacy among COVID-19 patients (AGRAWAL, MOSCOTE-SALAZAR, & KENI, 2019; Amponsah, Tagoe, Adams, & Bugyei, 2022). This study found a similar alignment with immunomodulatory intervention against PANS. Strong evidence supported the effectiveness of this intervention, marking a significant clinical milestone in management and clinical practices.

The abrupt onset of new tics triggers concerns about effective responses to patients, especially in low-income, middle-income countries and inaccessible parts of the world (Schön & Well-being, 2023). Since 1998, more studies revealed more evidence of the disease. Yet, unresolved therapeutic approaches, including immunotherapy, psychoactive interventions and antibiotics, emerge in the evidence (Hutanu et al., 2022; Prosell, Norman, Sand, & McAllister, 2022). Of course, the studies report conflicting outcomes of therapeutic approaches, symptomatology, and diagnostic approaches that differ in opinions regarding clinical practices. Therefore, more evidence is required to establish a rational and standard pharmacological intervention.

Literature suggests additional interventions for PANDAS and PANS patients. For instance, Thienemann et al. strongly indicated that psychotherapy, psychopharmacologic interventions and behavioral therapy could be simultaneously implemented to improve patients' quality of life. The simultaneous interventions aim at clearing bacterial infections, modulating the immune system, and reducing inflammations (Margo Thienemann et al., 2017). Thienemann et al. and Frankovich et al. added that benzodiazepines are ideal first-line for PANDAS/PANS for children with aggressive and agitative behaviors, insomnia, anxiety and ADHD, tics, depression, psychosis, and pain. However, individualized treatments match exacerbating symptoms, especially where an augmentation of symptom-specific pharmacologic and behavioral interventions is needed. Individualized care addresses interpersonal differences in treatment response, clinical outcomes and adverse effects. Supportive and educative therapies are pillars of the tailored interventions, which is beneficial to parents as they can monitor and partake in care activities.

Further, psychotherapy is indicated against OCD (Rea et al., 2021), to alleviate the neuropsychiatric symptoms. Psychotherapy's efficacy against OCD in PANDAS/PANS has been asserted in multiple studies and supported by many authors (Franklin, Eken, & Osterlund, 2023). Specifically, psychotherapy alleviates compulsivity among patients. To complement the above-described interventions, antipsychotics have been investigated. However, the rationale of the indication remains unclear, posing the need for extensive studies.

Fundamentally, although PANS is an iterated version of PANDAS (Hutanu et al., 2022; Wilbur et al., 2019), the stark differences are quite clear. The convergence points to PANDAS-PANS' differences regarding infections. Unlike PANS, PANDAS is associated with streptococcal infections. Previous investigations reported group A streptococcal infections in PANDAS but not PANS. Other differentiating elements PANDAS, and PANS, differ across the studies. For instance, PANS are characterized by aggressivity, irritability and food restriction. In contrast, PANDAS is marked by higher levels of anti-DNAse B and anti-streptolysin O. Additionally, PANDAS can be easily identified through movement and behavioral disorders like orofacial movement diseases induced by temporomandibular joint, and the presence of otorhinolaryngologic symptoms presenting in adolescence and infancy (Cocuzza et al., 2019). The broad categorization of behavioral and movement identified of PANDAS impacts present clinical practice by expanding the scope of physical examination.

A recent study supported this difference by asserting unreported symptoms of PANDAS and PANS. Language impairment, poor speech production, and impaired articulation have been reported as unreported symptoms of PANDAS/PANS (Prosell et al., 2022), posing the need for further investigations on evidence-based interventions. The emergence of diverse symptoms and unreported signs supports the need for further investigations to unveil all symptoms. Also, it casts the need for scientific evidence to establish the grounds for the emergence of diverse symptomatology.

5.0 Conclusions and Recommendations for Future Studies

Since it was first defined, PANDAS/PANS remains a burdening psychiatric illness among children and adolescents. Researchers have studied multidimensional aspects of the disease, from pathophysiology to treatments. Yet, many controversies and aspects remain unresolved, especially symptomatology and treatment. This review uncovered interesting evidence of controversial interventions and symptoms available in existing evidence.

Our literature review established important points of agreement and disagreement on PANDAS and PANS. Firstly, we found that researchers agree that infections, including bacterial and viral infections. While some authors argued that streptococcal infections cause PANDAS, others argued that PANS is not associated with streptococcal infections. In connection to viral infections, some studies endorsed antibiotic therapy, whereas others reported a backlash on the rationale of antibiotic indication for PANDAS/PANS patients. While some doctors endorse antibiotic therapy, others reject it, asking for advanced studies for a rational indication. Bacterial eradication addresses the resulting immunomodulatory outcomes, hence alleviation of symptoms. The evidence categorically exposed discord among psychiatrists, with Dr. Brick and Dr. Fisher conflicting on the rationale of antibiotic therapy. Dr. Fisher's demand for more evidence disputed Dr. Brick's recommendation for antibiotic therapy, suggesting a strong acknowledgement of gaps or issues with antibiotic therapy. These standard treatment guidelines are ideal for harmonizing treatment gaps. Additionally, the treatment guidelines should include interventions for caregivers who suffer the severity of PANDAS/PANS as they deliver care. Combined therapy is recommended to achieve the synergistic effects needed to achieve more results. By combining antibiotics with immune modulators, corticosteroids and NSAIDs, better results are achieved in terms of reduced symptomatology.

Secondly, another sect of researchers asserted that viral infections caused PANDAS and PANS

Thirdly, we found divergent reports regarding comorbid conditions with PANS and PANDAS, setting the ground for stark differences among researchers. Researchers reported different comorbidities, including suicidality, behavioral regression, anxiety, and depression. In contrast, other authors reported bedtime rituals, nighttime fears, emotional liability, and

separation anxiety, school issues, separation anxiety, urinary symptoms, sleep disruptions, among other complications. The varied incidence of these comorbidities evokes controversies and debates, with the exception of anxiety disorders, which most researchers agree on.

Additional investigations are ideal for addressing the crisis surrounding interventions for children in underserved and inaccessible areas, especially in the low- and middle-income parts of the world. The rapid onset of acute symptoms and the spontaneity of the syndrome necessitates rapid action to avert severity among children. Thus, future studies and policymakers should establish a rational approach to suppress potential severity among patients in underserved areas. This recommendation comes in handy when expanding supportive care and patient education to expand their knowledge of home care. Lastly, further investigations should seek effective treatment modalities for autoimmune-associated and streptococcal-induced PANS/PANDAS. A two-fold study would unveil standard treatment guidelines and modalities for patients, including specific approaches for patients with HIV, COVID-19, and OCD.

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