JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection (PANDAS) Syndrome

Saranya P*[1], Jaya Shree S[1], Vivek A[1], Bharath S[1], Srikanth B[1], Ramachandran B[1], Rakshana V*[2], Srinivasan R[3]

[1]*UG Scholar, Bharath Institute of Higher Education & Research, Chennai, Tamil Nadu India*
[2]*Assistant Professor, Bharath Institute of Higher Education & Research, Chennai, Tamil Nadu India*
[3]*Dean and Professor, Bharath Institute of Higher Education & Research, Chennai, Tamil Nadu India*

Publication history: Received on 26th July; Revised on 3rd August; Accepted on 12th August 2024

Article DOI: 10.69613/h5p77g26

Abstract: Often preceded by a streptococcal infection, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections, or PANDAS, is an uncommon syndrome marked by the abrupt development of tic disorders or obsessive-compulsive disorder (OCD). It is thought that the infection generated an inflammatory reaction that resulted in brain inflammation and this disease. A multidisciplinary strategy combining medical practitioners, mental health specialists, and behavioural therapists is necessary for the effective management of PANDAS. Appropriate therapy and early diagnosis can assist enhance results and lessen the condition's long-term effects on children's lives. PANDAS and similar illnesses, such Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), which includes a wider spectrum of infections and immunological triggers, have been the subject of ongoing research in recent times. The goal of current research is to elucidate the connections between autoimmune reactions, infections, and neuropsychiatric disorders. PANDAS is still a subject of significant clinical and research interest. Although some medical and psychiatric organisations acknowledge it as a genuine diagnosis, there is ongoing discussion over its prevalence, etiology, and optimal methods for diagnosis and treatment. The conversation surrounding PANDAS is still being shaped by our growing understanding of the roles played by infections and autoimmune diseases in neuropsychiatric disorders. It is essential to comprehend the pathogenesis, diagnosis, treatment, signs, symptoms, and possible side effects of PANDAS in order to identify and manage the condition early.

Keywords: PANDAS; Autoimmune disease; Neuropsychiartic disorders; PANS; Streptococcal infection

1. Introduction

A team of scientists at the Johns Hopkins University School of Medicine in the United States initially put up the idea of PANDAS in the late 1990s. [1,2] They saw a group of kids who got streptococcal infections and went on to have OCD or tic disorders. They postulated that an autoimmune mechanism might be at play in the emergence of these symptoms in light of their findings. In the late 1990s, the idea of PANDAS—paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections—was born. [3, 4]

In 1998, Dr. Susan E. Swedo and associates coined the phrase. Their findings identified a subgroup of kids who had streptococcal infections and went on to develop tic disorders and obsessive-compulsive disorder (OCD). [1] The connection between PANDAS and Tourette Syndrome is still up for dispute. [5,6] While some doctors contend that PANDAS and Tourette Syndrome are two different illnesses, others think that PANDAS may be a subtype of the latter. PANDAS-P is a subtype of PANDAS defined by the co-occurrence of OCD and tic disorders with psychiatric symptoms including anxiety or mood disorders. The lack of clear diagnostic tools and the diversity of symptoms make diagnosing PANDAS difficult.[7-9]

To rule out other possible causes, a complete medical history, physical examination, and laboratory tests are frequently required. [1] Research is currently ongoing to determine how PANDAS affect kids' development and well-being over the long run. While a large number of PANDAS children may go through a remission of symptoms, some may still face persistent difficulties. For PANDAS to improve outcomes and reduce long-term consequences, early identification and treatment are essential. Early action can help minimise symptoms and avoid consequences. [10,11]

* Corresponding author: Rakshana V

2. Etiology

The precise etiology of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) remains unclear, but the prevailing hypothesis suggests an autoimmune mechanism triggered by streptococcal infections [12]. The proposed pathogenesis involves a sequence of events: initially, a child contracts a Group A Streptococcus (GAS) infection, commonly manifesting as strep throat or scarlet fever. In response, the immune system produces antibodies to combat the bacteria. These antibodies may cross-react with brain-derived proteins, potentially due to molecular mimicry between streptococcal and neuronal antigens [12-14]. This cross-reactivity can lead to inflammation in brain regions associated with motor control and cognitive function, resulting in the characteristic PANDAS symptoms [15]. While streptococcal infections are the primary focus, other infectious agents such as Borrelia burgdorferi (Lyme disease) and Mycoplasma pneumoniae have been implicated in some cases [16]. It's important to note that while the autoimmune hypothesis is widely accepted, other factors may contribute to PANDAS development, including genetic susceptibility, environmental influences, and psychological stressors. [17]

3. Pathophysiology

The pathophysiology of PANDAS remains a subject of ongoing debate. Some researchers view PANDAS as part of the broader Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) spectrum, acknowledging that Group A Streptococcus (GAS) may not be the sole trigger for neuropsychiatric symptoms in children [18]. This perspective is further complicated by varying classification criteria proposed for PANS patients.

Current evidence supports an autoimmune pathogenesis similar to Sydenham's chorea (SC), where antibodies generated against GAS epitopes cross-react with self-antigens, particularly proteins expressed in basal ganglia neurons, through molecular mimicry [2]. Numerous functional studies have focused on specific neural targets to elucidate the immunological pathophysiology, including tubulin, lysoganglioside, and dopamine receptors (D1R, D2R) [19].

The pathophysiology of PANDAS syndrome involves several interacting factors (Illustrated in Figure 1):

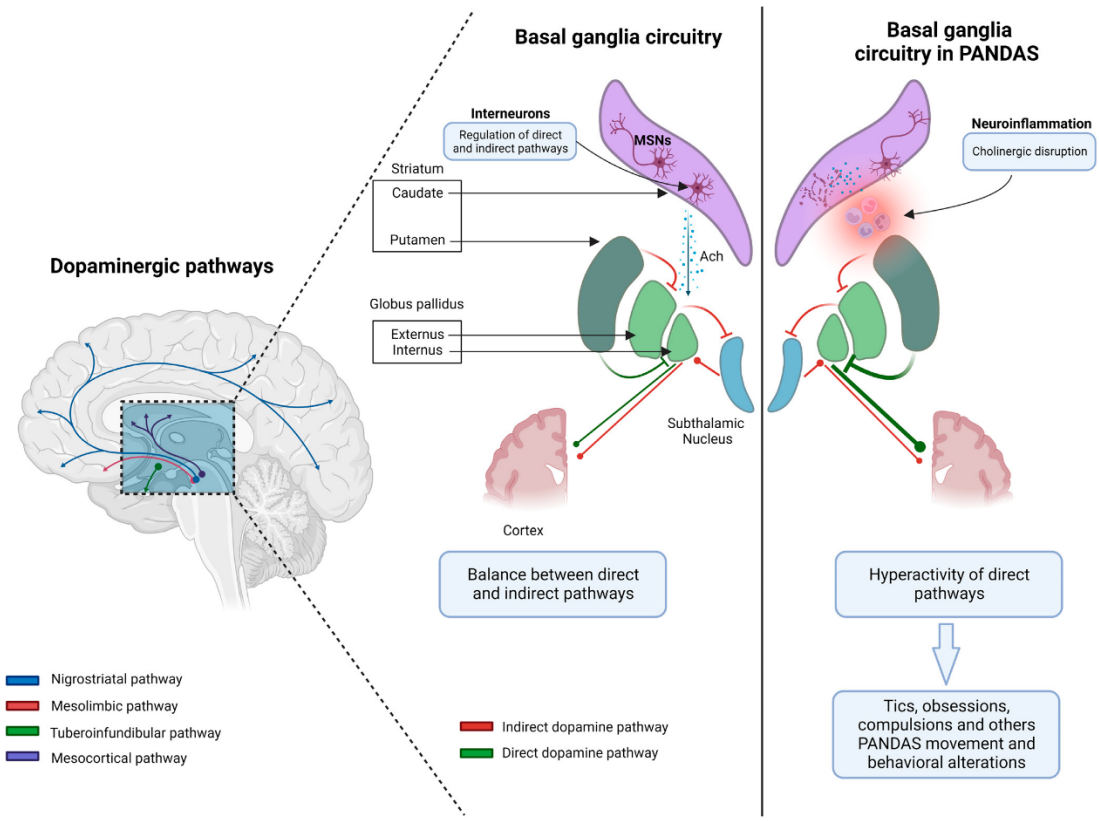

Figure 1. Pathophysiology of PANDAS Syndrome

3.1. Autoimmune Response

- Cross-reactivity between antibodies produced against streptococcal infections and brain proteins.

- Resulting inflammation in brain regions responsible for motor control and cognitive function.

3.2. Neurological Alterations

- Basal ganglia involvement, affecting movement and cognition.
- Neurotransmitter imbalances, particularly in dopamine and serotonin, influencing mood, behavior, and motor function.
- Development or exacerbation of OCD and tic disorders due to these imbalances.

3.3. Neuroinflammation

- Infiltration of immune cells into brain tissue.
- Impairment of normal brain cell function, contributing to symptom onset.

3.4. Genetic Factors

- Potential genetic susceptibility to PANDAS.
- Gene-environment interactions may increase the risk of developing the disorder.
- Epigenetic mechanisms, such as DNA methylation and histone modifications, may influence gene expression. [20]

4. PANS vs PANDAS Syndrome:

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) and PANDAS are related disorders affecting children, characterized by sudden onset or exacerbation of psychiatric symptoms, often following an infection [21]. While similar, they have some key differences:

4.1. Similarities

- Abrupt onset or worsening of symptoms.
- Common neuropsychiatric symptoms including OCD, tic disorders, mood changes, and sensory sensitivities.
- Association with preceding infections.

4.2. Differences

- Etiology: PANDAS is specifically linked to streptococcal infections, while PANS can be triggered by various infections or environmental factors.
- Symptom Range: PANDAS primarily focuses on OCD and tic disorders, whereas PANS may present a broader spectrum of symptoms, including separation anxiety and mood disorders.
- Diagnostic Criteria: PANDAS requires evidence of a streptococcal infection, while PANS uses broader diagnostic criteria [22].

5. Signs and Symptoms

PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) is essentially a subset of PANS (Pediatric Acute-onset Neuropsychiatric Syndrome), focusing specifically on the role of streptococcal infections in triggering neuropsychiatric disorders [23]. It's important to note that distinguishing between PANS and PANDAS can be challenging, and some medical professionals consider them potentially different manifestations of the same underlying condition.

PANDAS is characterized by the sudden onset or exacerbation of neuropsychiatric symptoms following a streptococcal infection [24]. Common signs and symptoms include:

5.1. Behavioral and Emotional Changes

- Sudden onset or worsening of OCD symptoms
- Development or exacerbation of tic disorders
- Significant mood changes (irritability, anxiety, depression)
- Separation anxiety and social withdrawal
- School refusal or academic difficulties
- Personality changes or regression

5.2. Motor Symptoms

- Motor tics (e.g., eye blinking, throat clearing, shoulder shrugging)
- Dystonia (muscle contractions causing abnormal postures)
- Coordination issues or clumsiness
- Sensory sensitivities (hypersensitivity to touch, sound, or light)

5.3. Other Symptoms

- Headaches or abdominal pain
- Sleep disturbances (insomnia, nightmares)
- Reduced appetite or weight loss
- Fever or other signs of infection

6. Diagnosis and Treatment

6.1. Diagnosis

Diagnosing PANDAS involves ruling out other potential causes of neuropsychiatric symptoms (Table 1). A comprehensive evaluation typically includes:

- Detailed medical history, including recent streptococcal infections
- Physical examination
- Laboratory tests (e.g., blood tests for streptococcal infection markers)
- Neurological evaluation
- Psychiatric evaluation [25]

Table 1. Diagnostic Criteria for PANDAS

Criterion	Description
Age of onset	Symptoms begin between 3 years of age and puberty
Sudden onset	Abrupt, dramatic onset of OCD or severely restricted food intake
Temporal relation	Symptoms worsen following streptococcal infections
Neuropsychiatric symptoms	Presence of OCD and/or tic disorders
Associated features	Presence of at least two additional neuropsychiatric symptoms*
Streptococcal infection	Evidence of recent or current streptococcal infection

*Additional neuropsychiatric symptoms may include: anxiety, emotional lability, depression, irritability, aggression, behavioral regression, deterioration in school performance, sensory or motor abnormalities, and somatic signs (e.g., sleep disturbances, enuresis, urinary frequency).

6.2. Treatment

PANDAS treatment often involves a multifaceted approach:

- Antibiotics to treat the underlying streptococcal infection
- Psychiatric medications to address neuropsychiatric symptoms
- Psychotherapy to help manage emotional and behavioral challenges

Specific treatment approaches (Table 2) may include:

- Antibiotics (e.g., penicillin, cephalosporins)
- Selective Serotonin Reuptake Inhibitors (SSRIs) or alpha-adrenergic agonists for OCD or tic disorders
- Cognitive-Behavioral Therapy (CBT)

Treatment plans are individualized based on each child's specific symptoms and needs. Early diagnosis and appropriate treatment can improve outcomes and reduce the long-term impact of the disorder [26].

Table 2. Treatment Options for PANDAS

Treatment Category	Specific Treatments	Purpose
Antibiotics	Penicillin, Amoxicillin, Cephalosporins	Treat streptococcal infection
Psychiatric Medications	SSRIs (e.g., Fluoxetine, Sertraline)	Manage OCD symptoms
	Alpha-2 agonists (e.g., Clonidine, Guanfacine)	Control tics
Immunomodulatory Therapies	Intravenous Immunoglobulin (IVIG)	Modulate immune response
	Plasmapheresis	Remove harmful antibodies
	Corticosteroids	Reduce inflammation
Cognitive Behavioral Therapy (CBT)	Exposure and Response Prevention (ERP)	Manage OCD symptoms
	Habit Reversal Training	Control tics
Supportive Care	Nutritional support	Address restricted eating
	Educational accommodations	Support academic performance
	Family therapy	Provide family support

Note: Treatment should be tailored to each individual patient based on their specific symptoms and needs. Some treatments, particularly immunomodulatory therapies, are typically reserved for severe cases that don't respond to standard treatments

6.3. Adverse Drug Reactions

Medications used in PANDAS treatment, particularly those addressing neuropsychiatric symptoms, may cause side effects [27]. Common adverse reactions include:

6.3.1. Selective Serotonin Reuptake Inhibitors (SSRIs)

1. Gastrointestinal disturbances
2. Weight changes
3. Sleep disturbances
4. Increased anxiety or agitation
5. Sexual dysfunction
6. Headaches
7. Serotonin syndrome (rare but potentially serious)

6.3.2. Alpha-Adrenergic Agonists

1. Sedation
2. Dry mouth
3. Constipation
4. Headaches
5. Hypotension
6. Bradycardia

7. Conclusion

PANDAS, or Paediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections, is a complicated disorder that affects children and is distinguished by the sudden start or development of neuropsychiatric symptoms following a streptococcal infection. While the precise mechanisms underlying PANDAS are still being investigated, it is thought to be caused by an autoimmune response provoked by infection.PANDAS diagnosis and treatment can be difficult, and the specific strategy may differ depending on the individual child's symptoms and requirements. Early diagnosis and treatment are critical for enhancing outcomes and minimising the condition's long-term consequences.Ongoing research aims to better understand the pathophysiology of PANDAS, develop more accurate diagnostic methods, and investigate new treatment options.As our understanding of PANDAS grows, we expect to develop more effective and focused interventions to help children with this disorder

References

[1] Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry. 1998;155(2):264-271.

[2] Chang K, Frankovich J, Cooperstock M, Cunningham MW, Latimer ME, Murphy TK, et al. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS Consensus Conference. J Child Adolesc Psychopharmacol. 2015;25(1):3-13.

[3] Cunningham MW. Streptococcus and rheumatic fever. Curr Opin Rheumatol. 2012;24(4):408-416.

[4] Murphy TK, Patel PD, McGuire JF, Kennel A, Mutch PJ, Parker-Athill EC, et al. Characterization of the pediatric acute-onset neuropsychiatric syndrome phenotype. J Child Adolesc Psychopharmacol. 2015;25(1):14-25.

[5] Calaprice D, Tona J, Parker-Athill EC, Murphy TK. A survey of pediatric acute-onset neuropsychiatric syndrome characteristics and course. J Child Adolesc Psychopharmacol. 2017;27(7):607-618.

[6] Sigra S, Hesselmark E, Bejerot S. Treatment of PANDAS and PANS: a systematic review. Neurosci Biobehav Rev. 2018;86:51-65.

[7] Sarella PN, Mangam VT. AI-Driven Natural Language Processing in Healthcare: Transforming Patient-Provider Communication. Indian Journal of Pharmacy Practice. 2024;17(1).

[8] Lakshmi SS, Sarella PN, Adarsh K, Padmini PL, Kumar MV. Concurrent Diagnosis of Renal Calculi, Uterine Fibroids and Ovarian Cysts: A Complex Case Study. Journal of Clinical and Pharmaceutical Research. 2023 Oct 24:22-7

[9] Frankovich J, Swedo S, Murphy T, Dale RC, Agalliu D, Williams K, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part II—use of immunomodulatory therapies. J Child Adolesc Psychopharmacol. 2017;27(7):574-593.

[10] Thienemann M, Murphy T, Leckman J, Shaw R, Williams K, Kapphahn C, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part I—psychiatric and behavioral interventions. J Child Adolesc Psychopharmacol. 2017;27(7):566-573.

[11] Frick LR, Rapanelli M, Jindachomthong K, Grant P, Leckman JF, Swedo S, et al. Differential binding of antibodies in PANDAS patients to cholinergic interneurons in the striatum. Brain Behav Immun. 2018;69:304-311.

[12] Gromark C, Harris RA, Wickström R, Horne A, Silverberg-Morse M, Serlachius E, et al. Establishing a pediatric acute-onset neuropsychiatric syndrome clinic: baseline clinical features of the pediatric acute-onset neuropsychiatric syndrome cohort at Karolinska Institutet. J Child Adolesc Psychopharmacol. 2019;29(8):625-633.

[13] Asogwa PO, Sarella PN. Observational Studies of Prescription Pattern and Use of Antibiotics in Selected Rural Areas. Int J Pharm Sci and Medicine. 2023;8:21-30.

[14] Murphy TK, Storch EA, Lewin AB, Edge PJ, Goodman WK. Clinical factors associated with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. J Pediatr. 2012;160(2):314-319.

[15] Cooperstock MS, Swedo SE, Pasternack MS, Murphy TK. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part III—treatment and prevention of infections. J Child Adolesc Psychopharmacol. 2017;27(7):594-606.

[16] Garvey MA, Giedd J, Swedo SE. PANDAS: the search for environmental triggers of pediatric neuropsychiatric disorders. Lessons from rheumatic fever. J Child Neurol. 1998;13(9):413-423.

[17] Swedo SE, Leckman JF, Rose NR. From research subgroup to clinical syndrome: modifying the PANDAS criteria to describe PANS (pediatric acute-onset neuropsychiatric syndrome). Pediatr Therapeut. 2012;2(2):113.

[18] Murphy TK, Gerardi DM, Leckman JF. Pediatric acute-onset neuropsychiatric syndrome. Psychiatr Clin North Am. 2014;37(3):353-374.

[19] Sarella PN, Maddali SS, Asogwa PO, Kakarparthy R. Persistent Infection in a Patient with Tibial Non-union. Journal of Clinical and Pharmaceutical Research. 2023 Jul 17:1-3.

[20] Swedo SE, Seidlitz J, Kovacevic M, Latimer ME, Hommer R, Lougee L, et al. Clinical presentation of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections in research and community settings. J Child Adolesc Psychopharmacol. 2015;25(1):26-30.

[21] Cox CJ, Sharma M, Leckman JF, Zuccolo J, Zuccolo A, Kovoor A, et al. Brain human monoclonal autoantibody from sydenham chorea targets dopaminergic neurons in transgenic mice and signals dopamine D2 receptor: implications in human disease. J Immunol. 2013;191(11):5524-5541.

[22] Brimberg L, Benhar I, Mascaro-Blanco A, Alvarez K, Lotan D, Winter C, et al. Behavioral, pharmacological, and immunological abnormalities after streptococcal exposure: a novel rat model of Sydenham chorea and related neuropsychiatric disorders. Neuropsychopharmacology. 2012;37(9):2076-2087.

[23] Kirvan CA, Swedo SE, Snider LA, Cunningham MW. Antibody-mediated neuronal cell signaling in behavior and movement disorders. J Neuroimmunol. 2006;179(1-2):173-179.

[24] Dale RC, Merheb V, Pillai S, Wang D, Cantrill L, Murphy TK, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain. 2012;135(11):3453-3468.

[25] Perlmutter SJ, Leitman SF, Garvey MA, Hamburger S, Feldman E, Leonard HL, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet. 1999;354(9185):1153-1158.

[26] Allen AJ, Leonard HL, Swedo SE. Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. J Am Acad Child Adolesc Psychiatry. 1995;34(3):307-311.

[27] Williams KA, Swedo SE. Post-infectious autoimmune disorders: Sydenham's chorea, PANDAS and beyond. Brain Res. 2015;1617:144-154.

Author's short biography

Dr Rakshana V:

Assistant Professor, Departments of Pharmacy Practice, Doctor of Pharmacy, my research project /experience is mainly in the field of Pharmacy Practice.

Miss Saranya P

UG Scholar with a keen interest in pharmaceutical research. Currently focusing on various aspects within the field of pharmacy and aiming to contribute more to the scientific community through future research endeavors.

Miss Jayashree S

UG Scholar passionate about advancing pharmaceutical knowledge. Actively engaged in research within the pharmacy department, with aspirations to expand her contributions to the field through continued studies and investigations.

Mr Vivek A

UG Scholar dedicated to exploring innovative areas in pharmaceutical sciences. His research interests lie within the pharmacy department, and he is committed to pursuing further research opportunities to enhance the field.

Mr. Bharath S

UG Scholar with a strong inclination towards pharmaceutical research. Currently involved in projects within the pharmacy department and eager to undertake more research initiatives to contribute to advancements in the field.

Mr. Srikanth B

UG Scholar actively involved in pharmacy-related research. He is enthusiastic about expanding his research portfolio and making meaningful contributions to pharmaceutical sciences.

Mr Ramachandran B

UG Scholar with a focus on research within the pharmacy department. He is motivated to engage in more research work, aiming to contribute to the growth and development of pharmaceutical knowledge.

Dr. Srinivasan R

Dean and Professor with extensive experience in pharmaceutical research. His primary focus areas include the development, synthesis, characterization, and application of novel polymers. Dr. Srinivasan has led multiple projects in pharmaceutical analysis and quality assurance, contributing significantly to the field through his expertise and guidance