ORIGINAL ARTICLE

Journal of Pre-Clinical and Clinical Research
www.jpccr.eu

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Current knowledge of PANDAS and PANS syndromes in paediatric patients – etiology, diagnosis and therapies

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Zych K, Burdan O, Ziomek WN, Białek AB, Wróbel J, Cieślik-Porębska M, Urbańska S, Chrościńska-Krawczyk M. Current knowledge of PANDAS and PANS syndromes in paediatric patients: etiology, diagnosis and therapies. J Pre-Clin Clin Res. doi: 10.26444/jpccr/193989

Abstract

Introduction and Objective. PANDAS (Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) and PANS (Paediatric Acute-onset Neuropsychiatric Syndrome) are rare diseases and there is scant information about diagnostic and treatment options. The aim of this study is to summarise the current state of knowledge about the diseases.

Review Methods. Articles from the PubMed database were sought and articles found dealing with the diseases were summarised and the knowledge assessed.

Brief description of the state of knowledge. The etiology of PANDAS and PANS syndromes has not yet been defined. There are hypotheses assuming that streptococcal infection can trigger an immune response that results in prominent neuropsychiatric symptoms. Diagnostic criteria focus on a clinical picture that includes the sudden onset of tics, obsessive-compulsive behaviour, anxiety and mood disorders following infection. Therapy for PANDAS and PANS syndromes is based at present on a number of therapeutic avenues for selecting the best plan. Immunomodulatory therapies, such as plasmapheresis and immunoglobulin administration, are being explored as methods to reduce the severity of the intractable symptoms in children. In addition, behavioural and pharmacological therapies, such as antipsychotics or anticonvulsants, are being used to manage symptoms.

Summary. Despite the clear interest in understanding these syndromes, there is a need for further research, especially in the area of identifying pathomechanisms and optimal treatment strategies. Improving diagnostic and therapeutic processes will ensure faster recovery and prevention of these conditions in paediatric patients in the interest of their well-being and comfort.

Key words

PANDAS, PANS, neuropsychiatric disorder, Streptococcal infections, obsessive-compulsive disorder, tics

INTRODUCTION

PANDAS (Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) and PANS (Paediatric Acute-onset Neuropsychiatric Syndrome) syndromes are neuropsychiatric disorders associated with infections caused by streptococci or other pathogens that occur in paediatric patients. The fact that the pathomechanisms of the aforementioned syndromes are not yet fully known is the subject of many clinical studies aimed at expanding knowledge about these conditions.

The autoimmune neuropsychiatric disorder associated with streptococcal infection, stemming from group A streptococcal (GAS) infection, was first described in 1998. Since its initial description, the acknowledgment of PANDAS as a distinct clinical entity separate from Sydenham's chorea, childhood-onset obsessive-compulsive disorder (OCD), or childhood tics has sparked controversy. These concerns primarily revolved around the inclusion of tics as a defining symptom, and the association of this syndrome with GAS as the initiating event and cause of exacerbations in neuropsychiatric symptoms. A decade later, the term Paediatric Acute-Onset Neuropsychiatric Syndrome (PANS) was introduced to broaden the scope of the disorder, and encompass provocative events beyond GAS [1].

Given the unresolved questions regarding the role of streptococcal infection in children with obsessive-compulsive disorder with explosive onset (OCD) and tics with new onset, the undetermined natural history of this condition, and the efficacy of symptomatic and disease-modifying therapies, including antibiotics, immunotherapy and psychoactive drugs, the concept of PANDAS is challenging for clinicians, patients and their families. In addition, inconsistent application of the PANDAS diagnostic criteria can lead to overuse of this diagnosis in children who are unlikely to have immune-mediated symptoms. Families with children exhibiting this phenotype often endure anxiety, frustration, and a feeling of being unheard. Their narratives are frequently

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Received: 12.08.2024; accepted: 01.10.2024; first published: 16.10.2024

showcased in the media and conveyed through reports. Support groups like the PANDAS Network in the USA and PANDASHELP in Canada have emerged to advocate for policy changes at governmental level [2].

Researchers initially identified a cohort of 50 patients exhibiting a constellation of symptoms termed PANDAS. These individuals presented with an abrupt onset of obsessive-compulsive disorder (OCD) and/or tics, often concurrent with attention deficit/hyperactivity disorder, separation anxiety, oppositional behaviour, and emotional variability. These manifestations followed previous documented streptococcal infections. The proposed diagnostic criteria for PANDAS encompass meeting the criteria for OCD and/or tics, symptom onset spanning from early childhood to adolescence, episodic symptomatology with a sudden and severe onset, temporal correlation between symptom onset, or exacerbation and Group A beta-hemolytic streptococcal infections (GABHS), and an association with neurological manifestations such as motor hyperactivity, tics, or choreiform movements [2, 3].

Subsequently, a modification in diagnostic criteria was suggested, introducing the term 'Paediatric Acute-Onset Neuropsychiatric Syndrome (PANS)'. PANS delineates a sudden onset of obsessive-compulsive disorder and/or severe eating restrictions, concomitant with other cognitive, motor, behavioural, or affective symptoms [3].

MATERIALS AND METHOD

A narrative review was undertaken of articles that address etiology, epidemiology, symptoms, diagnosis and treatment options of PANDAS and PANS. The Pubmed, Google Scholar and Embase databases were searched from January 2014 – July 2024, 4 of which were older than this time period (2003, 2004, 2005, 2012). This wide timeframe was chosen for the selection of information that was sufficiently comprehensive on the topic researched. A point was made to ensure that all articles older than 2019 only concern comparisons with the current results of newer studies in order to make this review as up-to-date as possible. This decision was made due to the fact that the PANDAS and PANS teams have been reported in the scientific literature only for a relatively short time. The key words used in the search were; 'PANDAS', 'PANS', 'PANDAS diagnosis', 'PANS diagnosis', 'PANDAS treatment', 'PANS treatment', 'PANDAS etiology', and 'PANS etiology', in order to find a sufficient range of articles covering the topic. Articles were accepted in English which related to the paediatric population diagnosed with PANDAS or PANS. Repeated articles were removed manually. Finally, 56 articles were taken into account. Case studies, conference abstracts and preprint articles were excluded.

DEFINITIONS – PANDAS/PANS/CANDS/PITANDS

PANDAS was defined for the first time in 1998 by Swedo et al., based on a study of 50 patients with acute, sudden onset obsessive-compulsive disorder (OCD), with or without tic disorder, who had previously developed group A beta-haemolytic streptococcal infection (GAS). The concept showed clear similarities to Sydenham's chorea (SC), which also often co-occurs with OCD. However, PANDAS have been considered controversial due to inconsistencies in immunologic and epidemiologic findings, as well as a lack of clinical features and specific biomarkers, unlike SC. Therefore, it was hypothesised that the immune mechanism responsible for PANDAS involves molecular mimicry [2, 3].

In 2010, Swedo et al. found the definition of PANDAS syndrome to be too limited and raised the issue of patients meeting all diagnostic criteria, except for streptococcal infection. This resulted in the label PANS, which covered a broader spectrum. A major difference became the move away from recognizing tic disorders as a primary criterion, while focusing on OCD and eating disorders. The broader definition against PANDAS, however, raised a new question: are the diagnostic criteria for PANS narrow enough to distinguish a new clinical entity? The argument for doing so became the inclusion of sudden onset of psychiatric symptoms in the list of criteria. This made it possible to distinguish a smaller subgroup from among children who met all other criteria. In addition, it was noted that PANS and PANDAS cannot occur simultaneously [1–3]. Two years later (2012), Singer et al. decided to redefine the concept of neuropsychiatric syndromes in children, describing Childhood Acute Neuropsychiatric Syndrome (CANS). CANS was intended to select more appropriate criteria, and to marginalise the role of GAS – Group A streptococcus infection. Ultimately, that diagnosis was found to be accurate for both patients included in the PANDAS and PANS criteria. Although the new proposed approach has taken a more comprehensive form, the authors are still reluctant to use the term [3–5].

Another concept describing neuropsychiatric syndromes diagnosed in children was 'Paediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders (PITANDs), described in 1995 by Allen et al. They included a subgroup of children diagnosed with OCD whose psychiatric symptoms appeared suddenly, usually after various infections, but the term is no longer used today [3,4].

Etiology. The pathophysiology of PANDAS involves an autoimmune response triggered by GAS infection. Antibodies produced against GAS epitopes may cross-react with self-tissue, particularly proteins expressed in basal ganglia neurons, through molecular mimicry, a mechanism similar to that observed in Sydenham chorea (SC). Functional studies have pinpointed specific neuronal targets involved in PANDAS, including lysoganglioside, tubulin, and dopamine 1 and 2 receptors (D1R, D2R). Animal models have shown that antibodies from GAS infections can cause neurological disorders by attacking cerebellar tissue and disrupting the blood-brain barrier, leading to neuropsychiatric symptoms [6, 7].

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 behaviours similar to Tourette syndrome [8]. Notably, PANDAS IgG does not bind to GABAergic interneurons or medium spiny neurons expressing D1R-D2R [6]. Advanced imaging techniques, such as PET scans and MRI, have revealed increased neuroinflammation in basal ganglia and the thalamus regions in PANDAS patients. MRI studies also show larger sizes of specific basal ganglia structures in PANDAS patients compared to controls, and neuroinflammation tends to decrease following treatment with intravenous

Table 1. Comparison of PANDAS, PANS, CANS and PITANDs [2,3]

PANDAS	PANS	CANS	PITANDs
– Tic syndrome and/or OCD. – Symptoms between the age of 3 and onset of adolescence. – Episodic course. – Association with GAS infection. – Association with neurological abnormalities.	– Sudden onset of obsessive-compulsive symptoms meeting the hallmarks of OCD or eating disorders. – Simultaneous presence of at least 2 of the following: a. Anxiety and/or restlessness. b. Emotional vacillation and/or depression; c. Aggression, irritability and/or severe oppositional behaviour; d. Behavioural regression; e. Deterioration in academic performance; f. Somatic symptoms. – Exclusion of other disorders (SC, Tourette's syndrome, etc.)	– Sudden onset of symptoms. – Primary Criterion: OCD. – Secondary criteria: tics, dysgraphia, hyperactivity, anxiety, clumsiness, psychosis, emotional vacillation, developmental regression, sensitivity to sensory stimuli. – Mono- or polyphasic course	– Symptoms in childhood – Sudden onset or sudden recurrent, clinically significant exacerbations and remissions. – Exacerbations not solely related to disease or stress. – When untreated for exacerbations, duration of at least 4 weeks. – During exacerbations of OCD and/or tics, there are mostly abnormalities on neurological examination, often with random movements. – Previous or concurrent infection. – Possibility of clinically significant symptoms between episodes of OCD and/or tic disorders.

immunoglobulin (IVIg), supporting the autoimmune nature of PANDAS [9].

The basal ganglia, crucial for motor control and emotional regulation, have been a focus of PANDAS research. Medium-sized spiny neurons (MSNs) and cholinergic interneurons within the basal ganglia are key components. PANDAS IgG binds to dopamine 2 receptors (D2R) on MSNs, disrupting circuitry and causing neuropsychiatric symptoms [6]. The molecular mimicry hypothesis proposes that antibodies against streptococcal proteins cross-react with central nervous system (CNS) antigens in the basal ganglia, leading to the autoimmune response seen in PANDAS [10]. Antibodies targeting dopamine (D1/D2) receptors, beta-tubulin receptors, and Lysoganglioside (lyso-GM1) receptors, collectively known as the 'Cunningham Panel', have been identified in PANDAS patients, although their exact role remains debated [11].

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 behavioural changes in PANDAS [12, 13]. Genetic susceptibility is also suggested, with a greater prevalence of autoimmune disorders among the mothers of PANDAS children, although further investigation is needed [5]. Various theories involving regulatory T-cells, cytokines, immune-associated genes and immunoglobulins have been proposed to explain the immune dysregulation in PANDAS [10]. These theories also require further validation to identify specific immune biomarkers associated with this complex clinical entity.

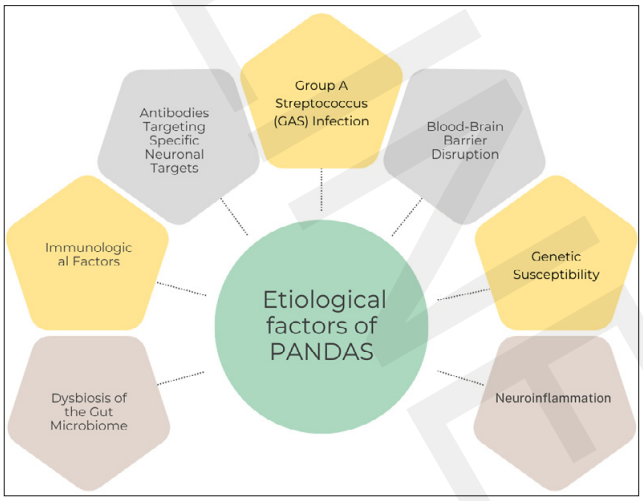

Figure 1. Etiology of PANDAS summarised. [6–13]

Symptoms. The onset of the symptoms is four to six weeks after a streptococcal infection. In children, PANDAS syndrome is characterised by severe, dramatic onset or acute symptom exacerbations. Behavioural abnormalities, neuropsychiatric symptoms, including compulsive-obsessive disorders and tics, become more severe and usually reach a maximum within two or three days, unlike other childhood psychiatric diseases that develop gradually [14].

PANDAS is chronic disease that occurs with periods of exacerbations and remissions, with an average remission period of 3.3 years. It was observed that the majority of children (approximately 72%) showed at least one exacerbation of PANDAS symptoms throughout the period of gradual remission [6,13]. 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 [6]. Untreated or unrecognised manifestations of PANDAS can also increase the risk of obsessive-compulsive manifestations and tics during adulthood.

A common manifestation of the disease is obsessive-compulsive disorder (OCD), and elevated levels of anti-streptococcal antibodies are usually associated with greater severity of the disorder [15]. OCD is characterised by the presence of obsession – recurrent and persistent thoughts, urges, or images that are experienced as intrusive and unwanted, and compulsions – repetitive behaviours or acts that the patient feels driven to perform in response to an obsession. The abrupt overnight onset of initial OCD is characteristic of these disorders in opposition to typical OCD. These behaviours are experienced as useless and patients try hard to fight against it. In most cases, anxiety is present. If compulsions are suppressed, anxiety increases significantly [16].

Disorders often consisted of an obsessive fear of germs and compulsive washing of hands, perfectionism. In youths with PANDAS, food restriction occurs in the context of obsessional fears about contamination, as well as in the context of fears of swallowing and choking that are often

associated with sensory phenomena (texture or appearance. These fears lead to the refusal to ingest anything orally, including any liquids. This may cause loss of body weight and dehydration [17]. Restricted eating has also been reported to occur secondary to a new onset of body image distortions – of being 'too fat' or not having a 'six-pack'.

Different kinds of anxiety are often observed in children: separation anxiety (most often), generalised anxiety, worry, phobias, panic attacks with physical symptoms, night fears and irrational fears. Patients report emotional lability – sudden and unexpected changes in mood, inner sense of restlessness, agitation, and dissociation; 35% may indulge in self-harm behaviours and suicidal tendencies. Parents notice irritability in their children, aggression, severe oppositional behaviour, impulsivity, motoric hyperactivity, tantrums, concentration and memorisation difficulties, deficit in maths skill and handwriting. In as many as 81% of children with PANDAS, all this translates into worsening results at school, [18].

Children often experience sensory abnormalities, e. g. sensitivity to sound, noises, textures, temperature, light, tastes, visual or auditory hallucinations; many experience behavioural regression, constant screeching and screaming, loss of age-appropriate language. With the onset of the disease may occur speech disfluency – higher rate of speech and superfluous verbal behaviour. Selective mutism may also occur [19]. Psychiatric comorbidities observed within PANDAS cohorts encompass attention-deficit/hyperactivity disorder (ADHD) at a prevalence rate of 40%, oppositional defiant disorder (ODD), also at a prevalence rate of 40%, and depression at a prevalence rate of 36% [6].

The described disorders are accompanied by somatic symptoms and motor abnormalities. Common abnormalities include sleep disturbance – waking up from sleep, difficulty falling asleep, night terrors, and urinary system symptoms without signs of infection – urinary urgency, urinary frequency, nocturnal enuresis [20]. The most common motor abnormalities, however, are tics. These are rapid, non-rhythmic, recurring movements or vocalisations which can be simple or complex. The most common symptoms include motor tics of the head and neck and ocular tics, followed by symptoms affecting the oral cavity and lower limbs. Elevated levels of anti-streptococcal antibodies correlate with greater severity of tics [21]. Children diagnosed with PANDAS demonstrated a higher frequency and intensity of tic symptoms, compared with other individuals [6].

Other motor disorders include chorea (in most children) and dysgraphia, dysarthria, dyskinesia. Disorders may occur, such as constant nail biting, skin pinching and hair pulling. Characteristics of PANDAS are slight movements of the fingers and toes that resemble playing the piano. Among patients with PANDAS, 67,7% had otolaryngological symptoms, i.e. sinusitis, ear inflammation, enlarged tonsils and pharyngitis. There is also a higher risk of rheumatic fever [3].

Other possible symptoms include joint pain, skin lesions, a systolic heart murmur, and abnormalities in echocardiography [11]. In the case of PANDAS syndrome, the changes are serious, occur suddenly and are dramatic, and significantly impair the functioning of the affected children.

Distinguishing PANDAS from Sydenham's chorea and Tourette syndrome. Sydenham's chorea typically appears later than PANDAS, mostly in girls, and is associated with several different M-strains of Streptococcus bacteria which are rheumatogenic strains. In contrast, PANDAS occurs from the age of three years to adolescence, with a significantly higher prevalence in boys than girls [22, 23]. Motor symptoms of Sydenham's chorea include hypotonia, pronator sign, darting tongue, choreic hand, and dysarthria, whereas PANDAS presents with motor hyperactivity and adventitious movements, such as choreiform movements. Psychiatric symptoms in Sydenham's chorea consist of emotional lability, anxiety, tics, ADHD, and obsessive-compulsive symptoms in 70% of patients, while PANDAS exhibits emotional lability, separation anxiety, night-time fears, ADHD, and oppositional behaviours. Additionally, the duration of Sydenham's chorea is relatively short, usually ending within six months, whereas PANDAS episodes can end and than recur, which can be distressing for the affected children [24]. These differences highlight the distinct clinical features and characteristics of Sydenham's chorea and PANDAS.

PANDAS and Tourette's syndrome are two distinct neuropsychiatric disorders with different etiologies, symptoms, diagnostic criteria, and treatment approaches. The

Table 2. Summarise of PANDAS symptoms [13–19]

Symptom Category	Symptoms	Description
Behavioural	Sudden and dramatic exacerbation	Symptoms appear rapidly within 2–3 days
Neuropsychiatric	OCD, tics	Obsessions (intrusive thoughts), compulsions (repetitive behaviours), tics (quick, uncontrollable movements)
Eating Disorders	Restricted eating, fear of swallowing	Obsessive fears of contamination, fear of choking, can lead to weight loss and dehydration
Anxiety Disorders	Separation anxiety, generalised anxiety, panic attacks	Fear of separation, constant worrying, panic attacks with physical symptoms
Emotional	Emotional liability, aggression, impulsivity	Sudden mood changes, irritability, aggressive behaviours, difficulty concentrating and remembering
Sensory	Sensitivity to sounds, light, temperature	Increased sensitivity to sensory stimuli, visual or auditory hallucinations
Speech and Language	Behavioural regression, speech disfluency	Screaming, loss of age-appropriate language, selective mutism
Psychiatric Comorbidities	ADHD, ODD, depression	ADHD (40%), ODD (40%), depression (36%)
Somatic	Sleep disturbances, urinary symptoms	Difficulty falling asleep, bedwetting, frequent urination
Motor Disorders	Tics, dyskinesia, dysgraphia	Quick, non-rhythmic movements, writing and speech disorders, chorea
Otolaryngological Symptoms	Sinusitis, ear inflammation, enlarged tonsils	Sinus infections, ear infections, enlarged tonsils
Other Symptoms	Joint pain, skin lesions, heart murmurs	Joint pain, skin lesions, heart murmurs, echocardiography abnormalities

quality of neuropsychiatric symptoms in PANDAS is linked to prior streptococcal infections and subsequent autoimmune reactions, with a strong association with streptococcal infections [3, 25]. Antibodies circulating in the patient's body attack brain structures, particularly the basal ganglia.

Tourette's syndrome is a neurological disorder characterised by sudden, rapid, often loud vocal and motor tics. Its etiology is more complex and not fully understood, but it is believed to have genetic, immunological and environmental components [26]. Symptoms of PANDAS include obsessions, tic-like movements, learning difficulties, and other neuropsychiatric disorders. These symptoms often appear suddenly after a streptococcal infection and may be cyclical. The primary symptom of Tourette's syndrome is tic-like movements which can be simple or complex, as well as vocal tics. Patients may also experience obsessions, impulse control difficulties, and emotional and social problems. Diagnosis of PANDAS is based on assessing the patient's medical history, particularly regarding streptococcal infections, and the presence of neuropsychiatric symptoms. Laboratory tests, such as measuring levels of anti-streptococcal antibodies, can also be useful. Diagnosis of Tourette's syndrome is based on observing tics for at least one year during which the doctor evaluates the type, frequency, severity, and location of the patient's tics [27, 28].

The treatment for Tourette's syndrome depends on the severity and type of tics. It may include pharmacotherapy, behavioural therapy, cognitive-behavioural therapy, as well as psychological and social support [29, 30].

Treatment for PANDAS includes the use of antibiotics (to eliminate streptococcal infection), intravenous immunoglobulin (IVIG) therapy to reduce the autoimmune reaction, and behavioural therapy

Diagnostics. The diagnosis of PANDAS or PANS syndrome continues to be a challenge due to the wide variety of symptoms, which can be similar to other disease entities such as obsessive-compulsive disorder, tics or motor hyperactivity [2, 13]. An additional problem is the lack of specific biological markers and clinical features that would allow an unequivocal diagnosis [6]. The exact etiology and role of streptococcal infection in the development of these diseases is also unconfirmed [31, 32].

The currently diagnostic criteria required for diagnosing PANDAS are shown in Table 3.

- the presence of obsessive-compulsive disorder and/or tics;
- the criterion for age (onset of symptoms between the age of three and the onset of puberty);
- an acute onset and episodic course of symptoms;
- association with group A streptococcal infection, and the presence of coexisting neurological disorders [2, 3, 13].

One of the basic requirements for a diagnosis of PANDAS syndrome is confirmation of Group A Streptococcus (GAS) infection with a positive throat swab and/or an increased titer of antistreptolysin-O (ASO) or anti-DNase B. However, due to much controversy over the above criteria, particularly the need to confirm GAS infection and the difficulties associated with it, scientists have proposed new criteria and a new disease entity – PANS [3, 13].

Diagnostic criteria for PANS are shown in Table 4. include the sudden onset of obsessive-compulsive disorder or significant reduction in food intake; concurrent occurrence of additional neuropsychiatric disorders of severe and acute onset like anxiety, emotional instability and/or depression, behavioural regression, deterioration in school performance, mood disorders, sensory or motor difficulties and somatic symptoms; and current symptoms that cannot be explained by a known neurological or medical disorder, such as Sydenham's chorea [2, 3, 13].

Table 3. Criteria required to diagnose PANDAS [2, 3, 13]

Diagnostic criteria for PANDAS
1. Presence of obsessive-compulsive disorder and/or tics.
2. Age (onset of symptoms between the age of 3 and the onset of puberty).
3. Acute onset and episodic course of symptoms.
4. Association with group A streptococcal infection.
5. Coexisting neurological disorders.

Research does not exclude that the etiology of PANS syndrome is also caused by autoimmune reactions. When making the diagnosis, it is worth considering infectious agents such as Mycoplasma pneumoniae, Influenza Virus, EBV and Borrelia burgdorferi, as it is suggested that they may act to trigger the disease. However, unlike PANDAS syndrome, it is not necessary to confirm group A streptococcal infection [3, 26, 33].

Currently, there is no single biomarker or test to diagnose PANDAS or PANS [3]. The diagnosis is clinical and requires the fulfilment of the above criteria and a comprehensive diagnostic assessment, including:

A thorough and comprehensive medical history, including assessment of the patient's current symptoms and medical history. Particular attention should be paid to recent infections, especially those that may indicate Group A Streptococcal etiology [14, 34].

Family history of both recent possible infections and neurological diseases and immunodeficiency syndromes. Questions about psychiatric and autoimmune disorders should also be included, as first-degree relatives of children with PANDAS have been found to be up to 10 times more likely to have OCD and tics [3, 34, 35].

Psychiatric interview, including full assessment of psychiatric and behavioural symptoms. All symptoms, both psychiatric and behavioural, should be noticed, including

Table 4. Criteria required to diagnose PANS [2, 3, 13]

Diagnostic criteria for PANS
1. Sudden onset of obsessive-compulsive disorder or significant reduction in food intake
2. Concurrent occurrence of additional neuropsychiatric disorders of severe and acute onset (at least 2 of the following):
• Anxiety
• Emotional instability and/or depression
• Behavioural regression
• Deterioration in school performance
• Mood disorders (irritability, aggression and/or severe oppositional behaviour)
• Sensory or motor difficulties
• Somatic symptoms (including sleep disturbances, increased frequency of urination or enuresis)
3. Current symptoms that cannot be explained by a known neurological or medical disorder, such as Sydenham's chorea

those that threaten the patient and family because of the possibility of self-harming thoughts and behaviours. Therefore, an assessment by an experienced child psychiatrist or psychologist would be most optimal [31, 33, 36].

A physical examination that not only searches for symptoms consistent with PANDAS or PANS, but also includes a comprehensive assessment of the patient to rule out other conditions that may be causing the presenting symptoms [33].

Additional tests – although there are currently no conclusive results to make a diagnosis of PANDAS or PANS. Patients should have a range of laboratory tests performed, including complete blood cell count with manual differential, inflammatory markers, urinalysis, and a comprehensive metabolic panel. The results should also be interpreted in relation to other diseases [14, 31, 37].

The diagnosis of PANDAS or PANS syndrome requires the exclusion of other conditions that may cause similar complaints. Therefore, it is important to consider other disease entities, such as obsessive-compulsive disorder, mental anorexia, transient tic disorder, Tourette's syndrome, systemic autoimmune disease, autoimmune encephalitis, Sydenham's chorea, Wilson's disease, and bipolar affective disorder [14, 33, 34].

Researchers are constantly searching for markers that would allow a definitive diagnosis. One such promising set of tests is the Cunningham Panel which detects: autoantibodies to dopamine receptors D1 and D2, tubulin, and lysoganglioside-GM1 (lyso-GM1), and calcium/calmodulin-dependent protein kinase II. However, it has been observed that the reliability of the test may be insufficient due to low specificity, and its prophylactic use is not recommended [14, 39]. Other neuroimaging or biochemical studies have also not yielded satisfactory results [3, 13].

Treatment. Various studies propose different therapeutic options for PANDAS/PANS. The main treatment options being discussed include: cognitive-behavioural therapy (CBT), affecting OCD and tics, and antibiotic therapy or tonsillectomy to prevent GABHS infections. Corticosteroids are mentioned as therapeutic options that address the theory of an autoimmune etiology of the disease. Therapeutic plasma exchange (TPE) and intravenous immunoglobulin (IVIG) were also investigated among possible treatments [4].

Cognitive behavioural therapy with response prevention and with selective serotonin reuptake inhibitors (SSRI) is used to treat obsessive compulsive disorder. PANS and PANDAS are two subtypes of OCD. Hesselmark et al. (2019) report that among 29 people with confirmed or suspected PANS/PANDAS who received CBT treatment only seven participants (24%) had satisfactory effect and only 46% who received SSRI. Also two of 24 (8%) reported SSRI treatment to be deteriorating [39]. Some studies suggest that CBT can be used in patients with OCD symptoms resistant to antibiotic treatment with satisfactory effect, while others state that CBT should be launched at the beginning of therapeutic process to maximise effects of managing OCD, anxiety and life stressors [36, 39, 40].

Antibiotics are used in PANDAS as a secondary antimicrobial prophylaxis of streptococcal infections. The decisive factor for the introduction of this form of therapy for PANDAS was the positive effects of the treatment of patients with rheumatic fever and Sydenham's chorea [41]. Penicillin and azithromycin groups have proven to be effective in terms of preventing GAS infections, and in the reduction of GAS-triggered neuropsychiatric exacerbations in patients with PANDAS. Due to public health concerns about the development of macrolide-resistant streptococci, the routine use of azithromycin for the prevention of GAS infections is being discouraged, recommending instead the use of penicillin as the first-line treatment [5, 6, 40]. Another therapeutic option dealing with GAS infection is tonsillectomy, which Demesh et al. have proved to be effective in some patients, and may present an alternative therapy for children whose response to antibiotics was unsatisfactory. However, due to the small sample size, this therapy should be subjected to further research [42, 43].

Corticosteroids are considered therapeutic options to deal with the possible neuroimmune background of PANDAS of mild-to-moderate intensity. Risk-to-benefit ratio supports the use of corticosteroids as they provide patients with a faster return of their basic functioning. They should be used carefully in patients with mood instabilities due to possible exacerbation of the symptoms, but short courses of corticosteroids at low doses are usually not associated with long-term side effects [44, 45].

Since PANDAS symptoms are considered to correlate with the presence of anti-neuronal antibodies, therapeutic plasma exchange has been inserted in order to remove them for the alleviation of symptoms. Latimer et al. report that all patients in their study obtained some benefits from therapeutic plasma apheresis (TPA) – the decrease in symptoms was measured in a six-month period with satisfying results [44, 46]. TPE has been used also among adult patients with autoimmune neuropsychiatric disorders associated with streptococcal infections, but with lower effect [47, 48].

Intravenous immunoglobulin (IVIG) is proven to present satisfying effects in terms of reducing the intensity of OCD symptoms [40]. However, Williams K. A. et al. report that the use of intravenous immunoglobulin (IVIG) in treatment of patients with PANDAS did not make any significant difference when compared to participants receiving placebo. One of the distinguishing features of IVIG therapy is the considered high patient satisfaction which may indirectly indicate the effectiveness of the therapy [49]. There are indications that one of the possible drugs for the treatment of PANDAS could be rituximab; however, there is still little information available on its applicability and effectiveness [21, 44].

Strategies for the treatment of PANDAS depend on the trajectory of the disease. A newly-diagnosed or acute flare is treated in sequence with: 1) anti-infective; **(?)** 2) CBT or other supportive therapies; 3) corticosteroids; 4) IVIG or other immunomodulatory therapies.

In the case of relapses, the likelihood of recurrent infections/exposures causing exacerbations should be additionally checked and appropriate interventions introduced [44].

DISCUSSION

Despite the increasing recognition of PANDAS/PANS syndromes, the underlying pathomechanisms remain incompletely understood, posing significant challenges for both diagnosis and treatment. The ambiguity surrounding the PANDAS and PANS pathomechanisms calls for a multidisciplinary approach in research which should be

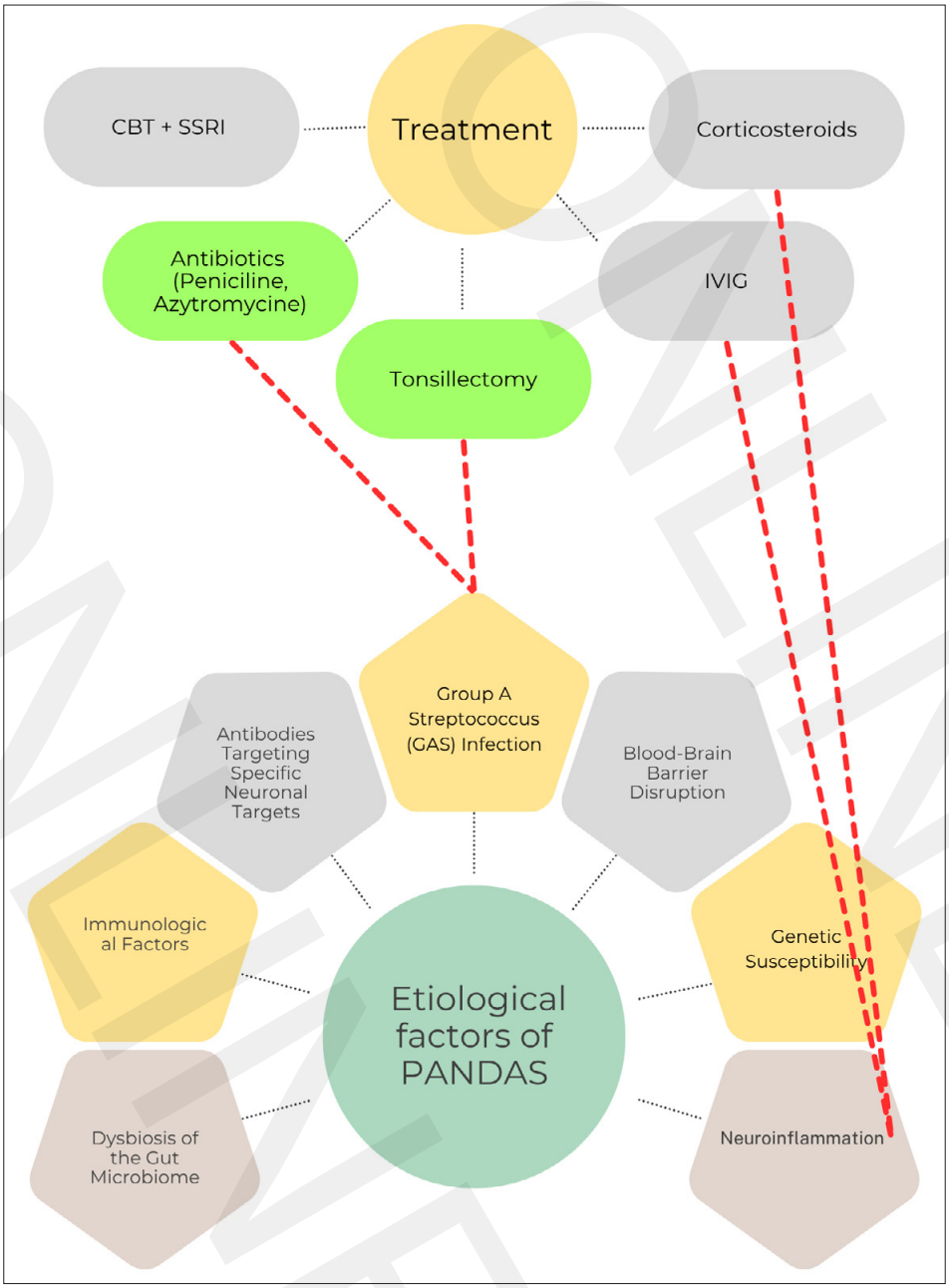

Figure 2. Treatment of PANDAS/PANS and etiology affected [40–49]

focused not only on immunological aspects, but also on genetic predisposition, environmental factors and the understanding of the role of pathogens other than streptococcus. This would broaden the range of potential triggers and consequently improve diagnostic criteria. It is already known that not only streptococcus can potentially cause the symptoms of OCD symptoms in patients, but also SARS-CoV2, EBV or Mycoplasma [50–52]. One major challenge is the inconsistent application of PANDAS diagnostic criteria. This inconsistency can lead to the overuse of the diagnosis in children who may not actually have immune-mediated symptoms. Such overdiagnosis can result in unnecessary treatments, contributing to further confusion and potential harm. [14].

The ongoing controversy and evolving definitions of syndromes combining psychiatric and neurological symptoms caused by infectious agents highlight the complexities associated with the diagnosis and treatment of infection-related neuropsychiatric disorders. Continued research is critical for unravelling these complexities, refining diagnostic criteria, and developing effective treatment protocols that address the multifaceted nature of these conditions. The dynamic nature of this field underscores the importance of maintaining a flexible and open approach as our understanding continues to increase [34, 54].

Given the unresolved questions regarding the role of streptococcal infection in children with obsessive-compulsive disorder (OCD) with explosive onset and new onset tics, the concept of PANDAS (Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) remains challenging for clinicians, patients, and their families. The natural history of this condition is still not well understood, and the efficacy of various therapies – including antibiotics, immunotherapy, and psychoactive drugs – remains uncertain [4, 36, 41].

The severe, dramatic onset or acute exacerbations of symptoms, including behavioural abnormalities, OCD and tics, differentiates PANDAS from other childhood psychiatric disorders that develop gradually. Identifying the most characteristic symptoms and understanding the variability in clinical presentation among patients is crucial. Common manifestations, such as compulsive hand washing, perfectionism, and various forms of anxiety including separation anxiety and panic attacks, pose significant challenges for diagnosis and management [3, 6, 54]. The impact of PANDAS on the daily functioning and overall quality of life of a child is profound. Symptoms such as irritability, aggression, hyperactivity, and academic difficulties, significantly affect both the patient and the family. Emotional lability, sensory abnormalities, and psychiatric comorbidities further complicate the clinical picture. Comprehensive support systems, including psychological and educational interventions, are necessary to address these challenges [2, 36, 55].

Preventive measures against PANDAS include timely treatment of streptococcal infections and monitoring for early signs of neuropsychiatric symptoms. Identifying children at high risk and implementing preventive interventions can potentially reduce the incidence and severity of PANDAS. Public health initiatives aimed at raising awareness and promoting early diagnosis are therefore essential [36, 56].

Although current research is focused on elucidating the pathophysiology of PANDAS, improving diagnostic criteria, and evaluating treatment efficacy, and despite advancements, significant gaps in knowledge remain. Further studies are required to validate the autoimmune hypothesis, refine diagnostic tools, and develop new therapeutic strategies.

Strengths and weaknesses of the article. The methodology used allowed research in multiple databases which provided a wide and comprehensive range of articles, thus increasing the likelihood of retrieving relevant research on PANDAS and PANS. The inclusion of studies dating from January 2015 – July 2024 allowed a comprehensive review of recent literature, ensuring that the review included the latest developments as well as the historical context. Weaknesses of the applied methodology may include potential bias in language limitation, the evolving nature of the subject, and possibility of the review being quickly outdated. Narrative reviews, such as the current one, while useful for summarising broad topics, are more susceptible to subjective interpretation and may lack the systematic rigour and reproducibility of systematic reviews or meta-analyses. By recognizing these strengths and weaknesses, the review can be more transparent and critically assessed for its contributions to the understanding of PANDAS and PANS.

CONCLUSIONS

The understanding of PANDAS and PANS remains complex and is still evolving. The underlying pathomechanisms are still not fully understood, making accurate diagnosis and effective treatment challenging. Multidisciplinary research that includes immunologic, genetic and environmental factors is essential to improve knowledge of potential triggers and correct diagnostic criteria. Inconsistent use of diagnostic criteria and over-diagnosis must be addressed to prevent unnecessary treatment. Continued research is crucial to improve diagnostic tools. Raising awareness and implementing preventive interventions against streptococcal infections can potentially reduce the prevalence and severity of these syndromes, eventually improving patient outcomes and quality of life.

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