PERENC, Helena, PĘDRAS, Marek, PASIEKA, Karolina, MAJKA, Karolina, KRAWCZYK, Kornelia, KOSAR, Michał, KOSIOROWSKA, Paulina, KORZONEK, Urszula, and KUPNIEWSKI, Kuba. The pathogenesis of PANDAS syndrome – controversies and consequences – a literature review. Quality in Sport. 2024;25:54837. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.25.54837
https://apcz.umk.pl/QS/article/view/54837

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 02.09.2024. Revised: 24.09.2024. Accepted: 07.10.2024. Published: 14.10.2024.

The pathogenesis of PANDAS syndrome – controversies and consequences – a literature review

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Abstract:

Introduction

Pediatric autoimmune neuropsychiatric disorder associated with Streptococcal infections is a controversial topic. There are contradictory reports about some aspects of its etiology and pathogenesis. The aim of this study is to examine the nuance in the studies about the pathogenesis of PANDAS and to form conclusions about the consequences of these controversies regarding the possible treatment of this condition.

Material and methods

A PubMed and Google Scholar search was performed with specific keywords.

Current state of knowledge

The understanding of PANDAS became different over time. It was described both as a distinct disease and as a part of a broader spectrum – PANS. Many researchers have observed have shown no significant temporal relationship between Group A Streptococcal infection and the occurrence of PANDAS, while others have noted a clear link between GAS infections and increased risk of developing neuropsychiatric disorders. Elevated antistreptococcal antibodies were also observed in children with PANDAS diagnosis. There were also cases of tic disorders and OCD symptoms related to infections with pathogens different than GAS. Many researchers postulate that molecular mimicry is the mechanism by which the neuroinflammation develops. Anti-GAS antibodies produced during infections seem to target antigens of basal ganglia causing their malfunction, which would be consistent with the clinical presentation of the disease and which was proven by diagnostic imaging. Treatment options seem to target the pathogenesis of PANDAS well; however, their effectiveness is not consistently proven in different studies.

Conclusions

Although much is known about the pathophysiology of PANDAS, the targeted treatment is often not enough and there are no therapeutic protocols for the disease.

Key words: PANDAS; PANS; Streptococcus; pathogenesis

Introduction

PANDAS – Pediatric autoimmune neuropsychiatric disorder associated with Streptococcal infections – was first described in 1998 by Swedo et al. It is a condition characterized by sudden outbreak of symptoms of OCD – obsessive-compulsive disorder, and/or tic disorders, as a complication of GAS (Group A Beta-Haemolytic Streptococcus) infection in children of prepubertal age [1]. Swedo et al. proposed five criteria, all of which needed to be met to diagnose PANDAS: 1) Meeting the diagnostic criteria of OCD and/or tic disorder; 2) The onset of the symptoms between 3 years of age and the beginning of puberty; 3) Episodic course of symptoms, with acute onset and periods of exacerbation and decrease; 4) Relation to GAS

infection (the occurrence of symptoms was preceded with the infection, which was diagnosed with positive throat culture and/or elevated anti-GAS antibodies); 5) Abnormalities in neurological examination (with the exception of patients with primary OCD, who could have not presented with neurological symptoms during remission periods) [1].

A lot is still uncertain regarding the pathophysiology and, as a result, about optimal diagnostic and therapeutic approach to this condition; even the classification of PANDAS as a specific disease is considered controversial, although numerous cases have been reported [2]. The aim of this study is to examine the nuance in the current state of knowledge about pathogenesis of PANDAS and form conclusions about the consequences of that.

Material and methods

Extensive literature search was performed in the Pubmed and Google Scholar databases, using terms such as "PANDAS", "PANS", "CANS", "Pediatric autoimmune neuropsychiatric disorders assiociated with streptococcal infections" in combination with "pathogenesis", "diagnostic imaging", "neuroinflammation" and "treatment". Relevant studies, published in English language, between 1989 and 2023 were included.

Current state of knowledge

Definition and criteria

Throughout the years, understanding of PANDAS has changed and different definitions have been proposed. Before the establishment of PANDAS term and criteria, in 1995 Allen et al. described four cases of abrupt-onset OCD and/or tic disorders associated with infections, which were classified as PITANDS (pediatric infection-triggered autoimmune neuropsychiatric disorders); however, in these cases patients' history revealed not only infections with group A beta-haemolytic streptococci infections, but also other organisms [3]. Later, the researchers were focused on the comparison of Sydenham's chorea to rapid-onset OCD cases associated with GAS infections, therefore extensive longitudinal studies were performed to finally describe PANDAS [1,4,5,6]. However, the group of patients diagnosed with PANDAS was narrow and in clinical practice the connection between GAS infection and the symptoms was difficult to assess; cases of similar symptoms caused by infections with other pathogens were also observed, therefore in 2012 Swedo et al. introduced a term "PANS", which is pediatric acute-onset neuropsychiatric syndrome [7]. The definition of PANS is broader in terms of etiology and patients' ages, restriction of food intake is defined as a possible primary symptom along with OCD, and the criteria underline the necessity of proper differential diagnosis. What

is more, disorders with tics, without OCD, do not meet the criteria of PANS [7]. Another term – CANS – childhood-acute onset neuropsychiatric syndrome, was proposed by Singer et al. [8], however, in clinical practice cases of such disorders are not only diagnosed in children, but also patients up to 21 years of age, so the term "pediatric" in "PANDAS" seems to be more appropriate [1,9].

Epidemiology

Tics (as a symptom – which is different from Tourette's syndrome diagnosis) may be present at some time during the childhood of 1 in 5 children [10]. The prevalence of OCD in children is about 1-3% [11]. Group A streptococcal infections are present in every age group, but they are most common in children of 3 years of age and older, with the prevalence of *S. pyogenes* invasive infections of 2 to 4 per 100,000 population in developed countries [12]. Although it is known, that tics, OCD and GAS infections are present in the general population, there is a scarcity of data about the prevalence of PANDAS. The incidence of PANDAS seems to be rare; however, males are affected more often than females and the most common age of onset is between 3 and 12 years old, with the mean age of presenting tics being 6.3 and the mean age of presenting OCD being 7.4 [1,13,14].

Etiology and pathogenesis

The association between Streptococcal infections and PANDAS

The correlation between GAS infections and onset of PANDAS, as it was already mentioned, was first described by Swedo et al.[1] and it was later observed by other researchers in larger groups of patients. In 77% of cases examined by Swedo et al. streptococcal infection was documented [1].

Mell et al. examined a group of about 75.000 children of age between 3 and 14, who received their first diagnosis of tic disorders, Tourette's syndrome or obsessive-compulsive disorder. They concluded that, in comparison to healthy controls, patients with such diagnosis were more likely to have had previous streptococcal infection in the time period of 3 months prior to the onset of neuropsychiatric symptoms (OR: 2.22; 95% CI: 1.05, 4.69). Multiple streptococcal infections in the time period of one year prior to the diagnosis of OCD, TS or tic disorders were described as a risk factor of developing there neuropsychiatric diseases (OR: 13.6, 95% CI: 1.93, 51.0). More strict methodological approach did not influence these results in a significant way [15] .

Murphy et al. conducted a longitudinal study of 693 children (aged 3-12) and observed the causal and temporal relationship between GAS infections and sudden onset of changes in behaviour or choreiform movements. Strong relationship between neuropsychiatric symptoms and GAS infections in the time period of previous 3 months was described (RR=1.71; $p<0.0001$), with particular emphasis on non-tic grimacing as well as changes in balance/swaying (RR=2.92; $p<0.0001$). Changes in behaviour and the onset of choreiform movements were more prevalent in children who were diagnosed with repeated streptococcal infections [16].

Orlovska et al. conducted a cohort study on Danish population of over 1 milion patients under 18 years old throughout 17 years (1996-2013) and described the risk of psychiatric disorders after pharyngeal infections [17]. Participants received Strep tests and were followed up for diagnosis of mental disorders, especially OCD and tic disorders. Risk of developing any mental disorder was significantly higher in children with a positive streptococcal test (IRR=1.18; 95% CI 1.15-1.21; $p<0.001$). When taking into consideration just OCD and tic disorders, the risk was also elevated for both (IRR=1.51, 95% CI=1.28-1.77, $p<0.001$ and IRR 1.35, 95% CI=1.21-1.50, $p<0.001$, respectively) in comparison to participants with negative Strep test. The same relationship was observed in pediatric patients diagnosed with nonstreptococcal throat infections - increased risk of any mental disorder (IRR=1.08, 95% CI=1.06-1.11, $p<0.001$) OCD (IRR=1.28, 95% CI= 1.07-1.35, $p=0.006$) and tic disorders (IRR=1.25, 95% CI=1.12-1.41, $p<0.001$). However, the risk of any mental disorder and especially OCD was higher in pediatric patients after streptococcal infection than after a non-streptococcal infection [17].

Murphy et al. examined 109 children with tics, obsessive-compulsive disorder, or both, with personal and family history, physical examination, analysis of their health records and assessment of streptococcal antibodies levels [18]. The results of the study showed that in comparison to children without the diagnosis of PANDAS, patients with PANDAS were more likely to have had a history of streptococcal infections or tonsillectomy/adenoidectomy [18].

Leslie et al. analyzed data from Thompson's Healthcare MarketScan database. In the time period of 1998-2004 they found 742 cases of newly diagnosed mental disorders such as tic disorders, Tourette syndrome or OCD [19]. In comparison to healthy controls, participants with such disorders were significantly more likely to have suffered from streptococcal infections in the 12 months prior to the new diagnosis (OR 1.54, 95% CI 1.29-2.15) [19].

Specific antibodies

A factor which is considered to support the hypothesis of linkage between GAS and PANDAS is the presence of specific antibodies in patients with rapid onset of Tourette syndrome, tic disorders or OCD. These are anti-streptolysin-O (ASO) or anti-DNase B (ADB) titers [20,21]. It is important to interpret the results of such measurements correctly. The rise of ASO begins after 1 week of GAS infection, the peak level is achieved 3 to 5 weeks later, which is followed by decrease, but it can stay elevated for even more than 6 months, whereas ADB rise is noted usually after 2 weeks of GAS infection, the peak level is observed 6-8 weeks later and it starts to decline 3 months after the GAS infection [22]. Another streptococcal antibody is carbohydrate A. A study by Murphy et al showed the correlation between the tic disorders, Tourette's syndrome or OCD of rapid onset and the presence of mentioned antibodies [23]. Kiessling et al. also examined the presence of antineuronal antibodies in children with rapid onset of movement disorders. In this study, published in 1993 – before the first description of PANDAS as a distinct disease, the researchers deducted that children with movement disorders were more likely to test positive for at least one antistreptococcal titer than the children without movement disorders [24].

Controversies about the association between GAS infection and PANDAS

Some studies had shown that the temporal relationship between GAS infection and PANDAS symptom exacerbation was not present in most participants and therefore it was not classified as significant [25,26,27,28]. These findings make it questionable if PANDAS should be considered a separate diagnosis from tic disorders which exacerbate for different reasons. On the other hand, studies examining disorders of new onset, and studies describing exacerbation of symptoms in patients previously diagnosed with PANDAS may not be comparable.

Pathogens other than GAS

Studies have shown that the onset or exacerbation of neuropsychiatric disorders may be triggered by pathogens other than beta-haemolytic *Streptococci*, such as *Mycoplasma pneumoniae*, influenza virus, Epstein Barr virus or *Borellia burgdorferi* [3,29-35]. Such findings may support the hypothesis according to which PANDAS is a subtype of PANS. On the other hand, it makes the pathogenesis more difficult to understand. There is a lack of studies to determine the mechanism of pathogens other than Group A *S. pyogenes* leading to rapid onset movement disorders.

Molecular mimicry and its consequences

The postulated mechanism of PANDAS pathogenesis is molecular mimicry. This mechanism involves the activity of anti-GAS antibodies, which are produced during GAS infections, and may target human antigens of basal ganglia as an abnormal immune response, similarly to Sydenham chorea [36,37]. Dopamine receptors – D1R and D2R, as well as tubulin and lysoganglioside were demonstrated to be the specific targets of anti-GAS antibodies in Sydenham chorea, and, therefore, probably in PANDAS [38,39,40,41]. The GAS antibodies might interfere directly with the receptors of basal ganglia or they may cause neuroinflammation of such areas [42,43].

Kirvin et al characterized the signal transduction in PANDAS. The autoimmune antibodies affected the neuronal cell surfaces and caudate-putamen by inducing the activity of CaM (calcium-calmodulin dependent protein) kinase II in these cells, which resulted in dopamine dysregulation [44]. It was more prevalent in children with PANDAS than in children with OCD, ADHD and Tourette Syndrome, as well as healthy controls [41,44].

The consequence of such signal transduction would be forming specific autoantibodies targeting the structures of human brain. This logic is consistent with the findings of Church et al. who described higher mean levels of anti-basal ganglia antibodies in children with PANDAS compared to controls with neurological diseases, uncomplicated streptococcal infections and autoimmune diseases [45]. Pavone et al compared the presence of antineuronal antibodies between children with PANDAS and children with uncomplicated GAS infection, and they also observed that the levels of antibodies were higher in children with PANDAS than in controls [46]. However, Singer et al found no significant difference in the measurements of anti-basal ganglia antibodies levels between children with PANDAS and controls, even with the application of the same methodology of data analysis as Church et al, except for one fraction of antibodies, present in higher level in patients with PANDAS primarily presenting with tics [47]. Signer et al, as well as Morris et al, also conducted studies in which they concluded that there was no significant difference between the serum autoantibodies in patients with PANDAS and Tourette syndrome [48,49]. Morris-Berry et al also described a lack of correlation between antibody levels and the exacerbation of PANDAS or Tourette syndrome symptoms [50]. Pavone et al suggested that the presence of the antibodies may be a result of multiple factors, not only GAS infection, which would partially explain the discrepancies [46]. Methodological differences and other issues may also play a role [51].

Although humans are the only hosts for *S. pyogenes*, numerous studies involving animal models support the claim that molecular mimicry and the activity of antineuronal antibodies are

underlying causes of rapid onset movement disorders [52-56]. In contrast to these findings, Loiselle et al described no significant changes of behaviour and movement in rodents injected with sera of PANDAS and Tourette syndrome patients [57].

Involvement of microglia

Microglial abnormalities may also contribute to the development of rapid onset movement disorders. In general, microglia serves a neuroprotective function in the brain, e.g. by performing synaptic pruning or acting as a main form of central nervous system immune defense. The dysregulation of microglia may cause the brain to be more prone to inflammation [58]. Such process can be a result of contact with GAS. Dileepan et al described intranasal infections with GAS in mice as a factor causing increased number of CD68+/Iba1+ activated microglia in olfactory bulb and abnormal synaptic pruning. Also, the close proximity of CD4+ T cells to the activated microglia was suggestive for previous antigen presentation to Th17 cells in these areas [58,59].

Striatal cholinergic interneurons

Apart from the pathology of dopamine receptors, other structures in the brain which seem to be affected by PANDAS are CINs – striatal cholinergic interneurons. Xu et al conducted a study to determine if IgG antibodies of children with PANDAS and controls would bind to CINs. In three independent study groups, the bonding of antibodies to CINs was more prevalent in PANDAS patients compared to controls and the function of CINs was altered [60]. Changes in these neurons were previously described in patients with Tourette syndrome [61,62]. However, during the observed bonding of IgGs with CINs, IgGs did not bind to any other neurons, except for CINs, which expressed D2R receptor. These findings suggest that D2R is responsible for high avidity of bond between IgGs and CINs. The role of CINs is also supported by the fact that immunotherapy with IVIG resulted in clinical improvement and decrease in the bond between antibodies and CINs [63].

Diagnostic imaging as evidence for neuroinflammation

The neuroinflammation in certain parts of the brain may be visible in diagnostic images. Giedd et al conducted studies in which they performed diagnostic imaging in patients with acute symptoms of PANDAS. These children were compared to age- and sex-matched healthy controls. In children with PANDAS, the sizes of the caudate, globus pallidus and putamen were increased in comparison to the healthy controls, whereas the thalamus and total cerebrum sizes

were not significantly different [42,43]. Kumar et al conducted a study involving children with PANDAS, children with Tourette syndrome and healthy controls and performed examination using PET scanning. Researchers examined imaging and binding potential and calculated the binding between the ^{11}C-[R]-PK11195 radiotracer, ("PK" for short) and TSPO receptors expressed by activated microglia in basal ganglia and thalamus. It was found that in children with PANDAS the biggest binding potential was present in the bilateral caudate and bilateral lentiform nuclei, which are both part of the striatum, whereas in children with Tourette syndrome the binding was mostly present in bilateral caudate nuclei only. What is more, the binding potential decreased in almost every patient after intravenous immunoglobulin treatment. The binding potential in the thalamus was not significantly different in any group in comparison to the rest. This study supports the claims that the pathogenesis of PANDAS includes neuroinflammation of basal ganglia and that there are differences in presentation of patients with PANDAS and Tourette syndrome [64].

Association with clinical presentation

The areas which were noted to be affected by PANDAS are part of a system in the brain called basal ganglia. This group of subcortical nuclei includes the striatum (which consists of caudate nucleus, putamen, nucleus accumbens and olfactory tubercle), the globus pallidus, the ventral pallidum, the substantia nigra and the subthalamic nucleus. They are connected to other motor-related parts of the brain and receive input from motor and premotor cortical areas. The biggest component - the striatum – receives input from numerous areas of the brain, but it sends output only to the other components of basal ganglia. The role of this system is to select the proper behaviors to execute and enable smooth voluntary movements, e.g by suppressing the movements which are not selected at the particular moment [65]. Moreover, the basal ganglia are involved in the regulation of executive functions, cognitive functions, learning, habit formation and emotional regulation [66,67,68]. According to the model proposed by Redgrave et al, the basal ganglia enable the selection of the most efficient and suitable behavior under conditions of limited resources [66]. The malfunction of the basal ganglia results in disorders of selective functions. According to this model, tic disorders result from the failure of mechanisms which suppress activity of non-selected movement impulses and/or the lower adjustment of thresholds which allows motor interruptions [66,69]. Furthermore, obsessive-compulsive disorder is a consequence of disruption of mechanisms which terminate a behavior by proving its already achieved effectiveness [66,70].

This is consistent with the clinical presentation of PANDAS – typical symptoms, of rapid and pronounced occurrence, are tics and/or OCD, but also attention deficits and hyperactivity (ADHD), impulsiveness, eating disorders, urinary urgency, worsened academic performance, emotional labiality and separation anxiety [63]. However, no significant differences were described between the clinical presentation of PANDAS and OCD or tics not associated with GAS. The only significant difference seems to be the presence of other psychiatric symptoms in children with PANDAS [18,25,71].

Possible treatment options

The aim of possible treatment options is to target etiology and pathogenesis of PANDAS, as well as the symptoms. Such treatments are: antibiotics, tonsillectomy/adenoidectomy, immunomodulatory therapy, corticosteroids, rituximab, mycophenolate mofetil, psychological and behavioral therapy and psychopharmacology [63]. Antibiotics are the primary therapeutic option used in patients diagnosed with PANDAS, but the results of the studies examining their effectiveness are not consistent. Garvey et al noted that in their study sample the effectiveness of antibiotics was not significantly different in comparison to placebo [72]. However, many researchers report significant reduction in PANDAS symptoms after antibiotic administration [18,73,74]. Treating the GAS infection seems to lower the risk of developing PANDAS to the level of the risk in a child who was healthy or had suffered from viral infection [27]. Other forms of treatment seem promising [63]. However, according to the meta-analysis by Cocuzza et al, although in many cases the PANDAS OCD symptoms were alleviated by medical treatment or surgery, the reported effects were not statistically significant which may be due to the variability of patient response to different types of treatment administered in at different times. The authors also noted that existing studies regarding therapeutic approach to PANDAS do not follow a unified protocol, which negatively influences the quality of enrolled samples and makes them difficult to analyze [75].

Conclusions

A lot is known about the pathogenesis of PANDAS. The symptoms seem to be the result of neuroinflammatory processes involving basal ganglia. However, the link between S. pyogenes infections and neuroinflammation is not clear, and it is difficult to differentiate if PANDAS is a distinct diagnosis or a part of a PANS spectrum. There is a scarcity of research to describe the mechanisms in which pathogens other than S. pyogenes may cause neuroinflammation and rapid-onset neuropsychiatric symptoms.

Uncertainty in terms of pathogenesis of PANDAS, along with the lack of awareness in health providers and its rare occurrence lead to difficulties in clinical approach. Existing treatment methods seem to target the pathogenesis of the disease well, however, the outcome is not satisfactory and therefore there are no clear therapeutic guidelines for medical providers. Standardized cohort studies on larger study groups are needed to develop such guidelines.

Author's contribution

Conceptualization, HP, MP, KP, KM, KMK, MK, PK, UK and KK; methodology, HP, MP, KP, KM, KMK, MK, PK, UK and KK; software, HP, MP, KP, KM, KMK, MK, PK, UK and KK; check, HP, MP, KP, KM, KMK, MK, PK, UK and KK; formal analysis, HP, MP, KP, KM, KMK, MK, PK, UK and KK; investigation, HP, MP, KP, KM, KMK, MK, PK, UK and KK; resources, HP, MP, KP, KM, KMK, MK, PK, UK and KK; data curation, HP, MP, KP, KM, KMK, MK, PK, UK and KK; writing - rough preparation, HP, MP, KP, KM, KMK, MK, PK, UK and KK; writing - review and editing, HP, MP, KP, KM, KMK, MK, PK, UK and KK; visualization, HP, MP, KP, KM, KMK, MK, PK, UK and KK; supervision, HP, MP, KP, KM, KMK, MK, PK, UK and KK; project administration, HP, MP, KP, KM, KMK, MK, PK, UK and KK; receiving funding – not applicable. All authors have read and agreed with the published version of the manuscript.

Funding Statement

No external funding was received to perform this review.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflict of Interest Statement

The authors declare no conflict of interest.

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