



PANDAS: a new disease?

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Abstract

Objective: To establish the diagnostic criteria for PANDAS and to analyze the existing evidence regarding its etiopathogenesis, treatment and prophylaxis.

Sources: Review of the scientific literature through a MEDLINE search carried out between 1989 and 2006.

Summary of the findings: The diagnostic criteria for PANDAS were established nearly 10 years ago, but a lot of controversy still exists over the actual existence of this new pediatric disease. The name of this new disease, supposedly of poststreptococcal etiology, derives from an acronym that stands for pediatric autoimmune neuropsychiatric disease associated with streptococcal infection. Tics and obsessive-compulsive symptoms are the major clinical signs of the disease, which develop after streptococcal infections, probably through autoimmune mechanisms. Even though these neuropsychiatric symptoms are common in rheumatic chorea, whose etiology is also poststreptococcal, the classic choreiform movements and other symptoms of rheumatic fevers are absent in PANDAS. The use of antimicrobial and immunologic therapy has been investigated and considered feasible in some cases.

Conclusions: Further research is still necessary in order to answer the question posed in the title of this article. In the meantime, the identification of tic disorders and obsessive-compulsive disorders in children should include the possibility of PANDAS, seeking to provide evidence of previous streptococcal infection.

J Pediatr (Rio J). 2007;83(3):201-208: PANDAS, streptococci, chorea, rheumatic fever, tics, obsessive-compulsive disorder.

Introduction

The recognition of a new disease is a slow process that demands repeated observations and data analyses. This was true for rheumatic fever (RF), and so it is for PANDAS, a poststreptococcal disease whose actual existence has been questioned.¹⁻⁴

The term PANDAS is an acronym that stands for pediatric autoimmune neuropsychiatric disease associated with streptococcal infection.^{5,6} The major clinical manifestations include tics and obsessive-compulsive symptoms. This type of neuropsychiatric symptoms are also observed in Sydenham's chorea,⁷ sometimes before the onset of

uncoordinated and involuntary movements. Since Sydenham's chorea is a poststreptococcal disease, it has been suggested that this kind of symptoms could occur in the absence of chorea. Research into this hypothesis has shown that this might actually happen, leading researchers to propose the existence of a new entity termed PANDAS. These patients did not present with classic choreiform movements or other symptoms of RF, but only with tics and/or obsessive-compulsive symptoms.⁵

This idea of a new disease described in the late 20th century was certainly viewed with suspicion and, despite numerous published and also ongoing studies, there has been a lot of debate over its real existence. Some pathogenic

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mechanisms suggested for RF have been considered for PANDAS, as an attempt to show that they have the same etiology, but different clinical manifestations.

Methods

Review of the scientific literature using MEDLINE database, searched between 1989 and 2006, with the aim of determining the basis for the diagnosis of PANDAS and also the evidence surrounding its etiopathogenesis, treatment and prophylaxis.

Etiopathogenesis

The etiology of tics and obsessive-compulsive disorders (OCD) is unknown, although both might result from genetic and environmental factors.

Streptococci

Among environmental factors, infection is an etiologic possibility. The oldest correlation between tics and infection dates back to 1929, being later reiterated in 1957 among patients with sinusitis.^{8,9} Only in 1989, when the criteria for OCD had been established, Swedo et al. identified OCD and tics in two thirds of patients with Sydenham's chorea, a disease recognizably associated with streptococci.⁷ In Brazil, in a study of 30 patients with chorea, OCD and/or tics were observed in 70% of cases.¹⁰ Studies comparing children with OCD and/or tics and a healthy control group revealed that the former were more closely associated with streptococcal infections, suggesting that the symptoms might result from infectious autoimmune phenomena.^{11,12}

We examined two siblings with tics associated with previous streptococcal infection, one diagnosed with PANDAS and the other with rheumatic chorea. This association may demonstrate genetic predisposition to movement disorders caused by streptococci or may act in favor of certain types of strains associated with neuropsychiatric symptoms.

The selection of 50 patients that helped establish the diagnostic criteria for PANDAS was based on the past history of oropharyngeal infection, positive throat swab culture and increase in antistreptococcal antibody levels. No association between PANDAS and streptococcal infections at other sites, such as the skin, has been investigated, and no investigation has been made into whether some subtype of streptococcus could be causing the symptoms. The diagnosis based on elevated antistreptolysin O (ASO) levels is also inaccurate, since it may occur after group A, C and G beta-hemolytic streptococcal infection.

Genetic predisposition

Streptococcal infections are common among children, but neuropsychiatric symptoms are not. This suggests that

only some patients are predisposed to PANDAS after streptococcal infection. A study on the presence of tics and OCD in 157 first-degree relatives (100 parents and 57 siblings) of 54 children diagnosed with PANDAS showed that the frequency of these symptoms was much higher than in the healthy population, but similar between those previously reported for tics and OCD.¹³

Two decades ago, some studies attempted to encounter some evidence of genetic predisposition for RF, and found a B-cell marker, later identified by a monoclonal antibody known as D8/17. The test consists in determining the percentage of B cells positively stained with the monoclonal antibody, and a positive result is characterized by the recognition of a certain amount of B cells stained with this antibody (around 12%). The first results showed a 90% positivity among rheumatic patients and only 15% in the healthy population.¹⁴ Parents and siblings of patients with RF also had a large number of stained cells, suggesting genetic susceptibility to RF.¹⁵ These findings obtained with D8/17 in RF were not reproduced in a similar fashion in all study populations.¹⁶

Based upon the similarities between chorea (symptom of RF) and PANDAS, some studies sought to define whether this marker was also more frequent in patients with tics, OCD and PANDAS.^{17,18} The presence of this marker was investigated in 27 boys with PANDAS, nine with chorea and 24 healthy controls: 85% of PANDAS, 89% of chorea and 17% of controls were positive.⁵ These data support the idea that there must be a group of susceptible children, in which D8/17 acts as a marker for the development of PANDAS or RF.

With regard to tics, whether or not they are associated with streptococcal infections, the presence of D8/17 was also investigated. A group of 31 children with Tourette's syndrome and OCD without any association with streptococcal infection and a group of 21 healthy children revealed positivity in all patients with tics and OCD and in only one patient (5%) in the control group.¹⁷

Also with the aim of assessing the importance of D8/17 in identifying genetic susceptibility to PANDAS, the presence of tics and OCD was investigated in unselected children, who had been classified as positive and negative for D8/17. Of 2,681 Mexican children who had been typed, 240 were still being followed up and could be investigated. Of these, 108 were positive and 132 were negative for D8/17, but no significant association was observed between positive D8/17 and the presence of tics and OCD.¹⁹

More recent studies have not confirmed the usefulness in determining the presence of D8/17 in RF or Tourette's syndrome.^{19,20} In conclusion, the functional importance of

this marker remains unknown, the test is not commercially available and D8/17 positivity is not enough to flag abnormal immune susceptibility to streptococci. Therefore, D8/17 is not currently regarded as useful for the diagnosis of PANDAS.

Autoimmunity

Clinical similarities

Clinical manifestations of tics and OCD are observed in both chorea and PANDAS, and both diseases may be associated with other symptoms, such as attention deficit hyperactivity disorder. This suggests that an autoimmune process affecting the basal ganglia can be triggered by streptococci in genetically susceptible patients.

Antineuronal antibodies

Comparisons between rheumatic chorea and PANDAS have persisted throughout the last 10 years. In addition to clinical symptoms, autoimmune disorders were also investigated. The suggested hypothesis was based on molecular mimicry, in which streptococcal infection in susceptible individuals evokes antibodies that are capable of cross-reacting with the cellular components of the basal ganglia.²¹

The hypothesis that both PANDAS and rheumatic chorea are autoimmune diseases caused by streptococci was suggested by the detection of antineuronal antibodies with the same reactivity in both diseases.^{11,22} In 1993, Kissiling published a study showing the relationship between the presence of antineuronal antibodies in patients with tics without chorea, as had been shown for chorea (44 *versus* 46%).²³

There has been a paucity of evidence confirming the autoimmune mechanism proposed for PANDAS. The presence of anti-basal ganglia antibodies was observed in 64% of a group of 22 patients with PANDAS and in only 9% of 22 patients in the control group, made up of children with streptococcal infection not associated with neuropsychiatric symptoms, suggesting that the presence of these antibodies cannot be explained only by the history of group A beta-hemolytic streptococcal infection.²⁴ Another study of 48 patients with PANDAS, 46 with Tourette's syndrome and 43 healthy patients of similar ages assessed the presence of antineuronal antibodies using ELISA and Western immunoblotting against a wide variety of epitopes on the nerve tissue, but it did not reveal any difference between the groups, nor did it show immunoreaction against supposedly pathological antigens. The repetition of tests after preabsorption of sera with streptococcal epitopes also did not

demonstrate loss of reactivity, thus not supporting the hypothesis that PANDAS and Tourette's syndrome are secondary to antibodies.²⁵

Imaging

Both chorea and PANDAS show abnormal magnetic resonance imaging findings. In a study of 24 cases of chorea and 48 controls and in another one of 34 cases of PANDAS and 82 controls, the caudate nucleus, *globus pallidus* and putamen were enlarged, which could be compatible with inflammation of the basal ganglia, since these findings were not observed in the thalamus or total cerebrum or in the thalamus. The presence of inflammation is consistent with the hypothesis of autoimmune response to streptococci.^{26,27}

Therapeutic response

Two types of immunomodulatory therapy – plasmapheresis (PMP) and intravenous immunoglobulin (IVIG) – shortened the course of symptoms and helped with the recovery of patients with PANDAS, suggesting that an autoimmune process is implicated in its pathogenesis.²⁸

Diagnostic criteria for PANDAS

The diagnostic criteria for PANDAS were established in 1998, based on the information obtained from the analysis of 50 cases with 144 episodes isolated from symptom exacerbations.⁶

Criterion 1: age at onset

PANDAS is a pediatric disease that affects both sexes, but it is predominant among males (2.6:1). Age at onset ranges from 3 years to the beginning of puberty: tics (6.3 years) and OCD (7.4 years), which corresponds to nearly 3 years before the mean age for these nonstreptococcal symptoms. Adolescents and adults are likely to have infection-mediated tics and OCD, but this has not been investigated yet, and should then not be termed PANDAS.

Criterion 2: tics and OCD

The diagnosis of tics and OCD is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) published by the American Academy of Psychiatry. The same percentage of patients with tics and OCD (48 and 52%, respectively) was observed among the analyzed patients; however, 80% presented with both types of symptoms.

The prevalence of PANDAS among children with tics and OCD is not known, but it has been reported that 11% of a group of patients with tics showed symptom exacerbation within 6 weeks of an episode of streptococcal infection.²⁹

Criterion 3: onset and course of the disease

The dramatic onset of symptoms is of major importance. Usually, patients remember how and when the symptoms developed, and sometimes they even remember the day and time when they appeared. Resolution is slow and gradual, taking weeks, months, or even longer. Patients have an uneventful recovery for weeks or months until a new streptococcal infection causes a new outbreak of tics and OCD, characterizing a clinical course with remissions and relapses.

Criterion 4: streptococcal infection

When streptococci were suggested as etiologic factor of RF, fierce controversy broke out over this issue. Likewise, several debates have taken place about the concept of tics and OCD caused by streptococcal infections. It is recommended to ascertain whether streptococci are still colonizing the oropharynx or whether antistreptococcal antibody titers have increased. The antistreptococcal antibodies used include ASO, whose titer is at its peak 3 to 6 weeks after streptococcal infection, and anti-DNase after 6 to 8 weeks. The rate of increase is irrelevant, since elevated titers do not translate into increased severity. However, looking only at the elevated titers of these antibodies is not sufficient for the diagnosis of infection, since these titers may remain elevated for months after the infection. Therefore, initial antibody levels should be measured, and then measured again after some weeks to check whether antibody titers are rising, which then means recent infection.

It should be underscored that if PANDAS is somewhat similar to RF as autoimmune response to streptococci, not every outbreak of streptococcal infection will be followed by exacerbation, and exposure will vary from one year to the next. As pharyngitis and tics are common among children, the best way to confirm whether they share some association is to follow up children, trying to observe at least two episodes that include streptococcal infection.

Streptococci are the causative agent of initial autoimmunity, and subsequent exacerbations may be caused by new streptococcal infections. Nevertheless, one should not rule out the hypothesis that other stimuli may cause an outbreak, as occurs in chorea.

Criterion 5: associated neuropsychiatric symptoms

During an outbreak of PANDAS, neuropsychiatric symptoms other than tics and OCD may appear. The most common symptoms include learning difficulty, attention deficit hyperactivity disorder, depression, anxiety, mood swings (irritability, sadness, emotional lability), sleep disorders, and fine or gross motor impairment (writing).³⁰

Treatment**Immunosuppressants**

If PANDAS is an autoimmune disease, immunosuppressive therapy is a reasonable option to treat persistent symptoms. We, as rheumatologists, think of steroids, immunosuppressive drugs, PMP, and IVIG when treating autoimmune diseases.

Steroid therapy was not the first option to be tested, since a publication in 1993 reported on the worsening of OCD in a child submitted to treatment with this type of drug.³¹ Nonetheless, there are some reports on the improvement of movements in Tourette's syndrome and in one case of PANDAS after steroid therapy.³²⁻³⁴

IVIG and PMP were initially chosen, as they proved safe and efficacious in some autoimmune diseases. Patients with PANDAS were randomized into three groups: IVIG (1 g/kg/day/2 days), PMP, and placebo (10 PMP, nine IVIG and 10 placebo). All of them had severe symptoms at the beginning of the study, according to a symptom scoring system. After 1 month, the assessment of children with IVIG and with PMP showed improvement of tics and OCD, of anxiety and of the general function, differently from the control group, which remained unchanged. After 1 year, 20% of the patients from the PMP group had recurrent episodes, and half of them required medications in equal or larger doses, so it is not clear whether immunomodulatory therapy brought any benefits. Another hypothesis that should be considered is that some children might have improved spontaneously after 1 year, especially with regard to tics.²⁸

Another study assessed the efficacy of PMP for 2 weeks in five patients with chronic OCD not associated with streptococci. None of the patients benefited from the therapy, suggesting that it was not appropriate for OCD of nonstreptococcal etiology.³⁵

Currently, due to the lack of randomized controlled trials, these treatment modalities are not recommended, as it is necessary to assess the real value of these expensive therapies, which are not risk-free and have not yielded reliable results.

Tonsillectomy

Despite the report of a case of two siblings, one with OCD and the other one with tics, who improved after tonsillectomy,³⁶ there was a case in which tonsillectomy preceded OCD symptoms.³⁷

Antibiotics

Given that PANDAS is a new disease related to an infection, it has been argued whether antibiotic therapy

should be used. Antibiotics eradicate bacteria, but PANDAS is not an infectious disease, but rather a postinfectious one, in which an autoimmune mechanism is implicated.

In the acute phase of RF, we use antibiotics in case there are still some viable bacteria in the oropharynx that have to be eliminated. The latency period of rheumatic chorea may be long, lasting some months, and it is often difficult to confirm the presence of streptococcal infection in a throat swab culture or serological tests. In PANDAS, the latency period seems to be much shorter (few days to 1 week) and the oropharynx is likely to be still colonized.

The first prospective study showing that PANDAS was associated with streptococcal infection was published in 2002. Antibiotics were administered to 12 patients who met the criteria for PANDAS and whose symptoms followed beta-hemolytic streptococcal infection in the oropharynx after a short latency period, ranging from days to 1 week (sentinel episode). All children recovered quickly (in nearly all of them the symptoms of tics OCD were eliminated). During the follow-up period, reinfection and a new episode of PANDAS (no case of PANDAS occurred without infection) occurred in six patients. Response to antibiotic therapy occurred on average after 14 days of treatment (being faster with cephalosporin than with penicillin and amoxicillin), supporting the assumption that these patients were not mere carriers of the disease.³⁸

Prophylaxis

Since benzathine penicillin is efficacious in the prevention of RF, a study was carried out to verify whether antibiotics may prevent outbreaks of PANDAS. The first study on PANDAS was quite small, compared to other studies on the efficacy of RF prevention using penicillin and that included hundreds of patients during several years.

This double-blind, cross-sectional pilot study on the prophylaxis of PANDAS followed 37 children for 8 months, comparing the use of oral penicillin *versus* placebo. Patients received either placebo or oral penicillin (Pen-Ve 250 mg x 2) for 4 months. Patients swapped treatments after the fourth month. Throughout the study, patients were clinically monitored and submitted to monthly throat swab cultures and to antistreptococcal antibody tests. An identical number of infections was observed in the active and placebo phases, and symptoms did not worsen. The duration of the study was too short and the study failed to prove the efficacy of this type of prophylaxis with oral penicillin. Prophylactic failure does not allow for favorable conclusions, and further studies with a larger patient population, longer observation period or use of more efficacious drugs are needed.³⁹

Another study, published in 2005, compared the efficacy of oral penicillin prophylaxis (250 mg twice a day) with two doses of 250 mg of azithromycin once a week. Both drugs showed favorable responses to the number of streptococcal infections and to the number of recurrent neurological symptoms when compared to data from the previous year, without prophylaxis. However, the study has some shortcomings, since the data from the previous year were retrospective and history-based, the patient population was small, and besides, there was no control group.⁴⁰

To date, antibiotic prophylaxis, which is efficient against RF, is arguable and is still being investigated in patients with PANDAS.

A recent Brazilian study on rheumatic chorea revealed that relapses occurred even among those patients receiving regular secondary prophylaxis. Out of 85 cases of chorea, Terrieri detected one or more relapses in 25 (29%); of these, 17 were followed for later analysis, and 14 relapses of chorea occurred, but in 71% of patients there was no failure in the secondary prophylaxis.⁴¹ In PANDAS, as also occurred in chorea, patients receiving prophylactic treatment may have new outbreaks caused by different stimuli from streptococcal infection.⁴²

Current management

No studies have been carried out showing what the treatment of PANDAS should be like. Current guidelines underscore the confirmation of streptococcal infection by means of throat swab culture, and treatment of positive cases with oral penicillin for 10 days or any other appropriate antibiotic. If the culture is negative and if OCD symptoms and/or tics appeared less than 4 to 6 weeks ago, antistreptococcal antibody levels should be measured as an attempt to detect the recency of streptococcal infection and to perform the longitudinal assessment.

The prospective analysis of streptococcal infections by throat swab culture must be performed in every child with tics or OCD in order to confirm the actual association with these symptoms.

The usefulness of antibiotic prophylaxis is still unclear, but it should be determined by the physician on a case-by-case basis, who should weigh both risks and benefits.

Immunomodulatory therapy is not risk-free and is only recommended in study protocols. Based on the available findings, first-line treatment should consist of the conventional therapy used for tics and OCD: serotonin reuptake inhibitors (SRI) (response of 50 to 75%) and cognitive behavioral therapy (67 to 100%).^{43,44}

PANDAS spectrum

In the last few years, in addition to tics and OCD, other neuropsychiatric symptoms, such as anorexia nervosa (AN), attention deficit hyperactivity disorder (ADHD), acute disseminated encephalomyelitis (ADEM), autism and separation anxiety disorder, have been suggested as variants of PANDAS, but there is only flimsy evidence, based mainly on the presence of streptococci, on the increase in antistreptococcal antibody titers and on D8/17 positivity.

Anorexia nervosa

The first four patients (11 to 15 years) with probable AN related to PANDAS met at least four of the five criteria for PANDAS, all of them with positive throat swab culture or positive serological tests (ASO/anti-DNase) showing previous streptococcal infection. Two of them had the diagnosis of OCD as comorbidity. All of them were positive for D8/17 (> 12% of positive B cells). Conventional treatment and antibiotic therapy resulted in weight gain.⁴⁵ Two years later, the same authors analyzed 16 patients with AN, aged 7 to 21 years, and termed the disease PANDAS anorexia nervosa, since 81% of 16 patients had > 12% of B lymphocytes positively stained with D8/17, differently from the control group, without any eating disorder, in which positive results were found in only 12%. In these cases, the diagnosis of previous streptococcal infection was inconsistent because it was solely based upon serological test results and on the history of sinusitis. The validity of this study is questionable, since the authors did not consider the percentage of patients with anorexia nervosa without PANDAS.⁴⁶

Attention deficit hyperactivity disorder

It may be a comorbidity with Tourette's syndrome and OCD, but recent literature postulates that "pure" ADHD, without association of tics or OCD, may also belong to the PANDAS spectrum, since children can have elevated ASO and anti-DNase titers.^{47,48}

Acute disseminated encephalomyelitis

This is an immune inflammatory disease that mainly affects the gray matter. Viruses, bacteria and vaccines have been implicated as etiologic factors. Recently, 10 cases with dystonic movements and behavioral disorders associated with group A beta-hemolytic streptococci showed an increase in anti-basal ganglia antibody titers comparatively to cases not associated with streptococci.⁴⁹

Autism

Evidence of autism as part of PANDAS remains circumstantial based solely on the presence of D8/17. The frequency of D8/17 was higher in 18 autistic patients than in

the control group. D8/17-positive children had more repetitive behaviors and higher compulsion score, suggesting that there may be an autoimmune basis in a subgroup of patients in autism, even though this is still quite controversial.⁵⁰

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