

REVIEW ARTICLE

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection (PANDAS)

Deborah Levy Miller¹ MD FRCPC

Ronald M Laxer², MD FRCPC

¹Fellow, Division of Pediatric Rheumatology, Children's Hospital of New York Presbyterian, Columbia University, New York, NY

²Professor of Pediatrics and Medicine, University of Toronto, Vice-President, Clinical and Academic Affairs, Hospital for Sick Children, Toronto, Ontario Canada

Corresponding Author:

Deborah Levy Miller, MD FRCPC

Pediatric Rheumatology

Children's Hospital of New York Presbyterian

CHN 106

3959 Broadway

New York, NY 10032

Phone: 212-305-2231

Fax: 212-305-4932

Email: deblevymiller@yahoo.com

Abstract

Several inflammatory disorders have been associated with preceding streptococcal infections, including acute rheumatic fever (ARF), post-streptococcal reactive arthritis, erythema nodosum, post-streptococcal glomerulonephritis and cutaneous polyarteritis. The spectrum of poststreptococcal disease has expanded with the addition of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS). PANDAS are a recently described subgroup of childhood disorders, and there has been a great deal of public and physician interest in their pathophysiology, diagnosis and management. The possibility that neuropsychiatric disorders such as Tourette's syndrome and obsessive-compulsive disorder (OCD) are related to a preceding streptococcal infection is certainly controversial. The pediatric rheumatologist may be asked to utilize his or her expertise of childhood autoimmune diseases to evaluate the use of immunomodulatory therapies in these children.

Clinical criteria proposed for the diagnosis of PANDAS include: the presence of OCD or a tic disorder; childhood onset; an abrupt onset of symptoms; exacerbations of symptoms temporally related to a preceding streptococcal infection; and the association of neurological abnormalities.

This review will discuss PANDAS in more detail, and present the literature as to the relationship between PANDAS and Sydenham's chorea. Additionally, the clinical features, evidence for treatment and prevention of PANDAS will be reviewed.

Introduction

Obsessive-Compulsive Disorder (OCD), tic disorders, Tourette's syndrome (TS) and Sydenham's chorea (SC) are neurobiologic disorders that are likely due to basal ganglia abnormalities. Both tics and OCD can result from damage to the basal ganglia, and obsessive-compulsive symptoms occur frequently in patients with SC. Group A beta-hemolytic streptococcus (GABHS), the etiologic agent responsible for acute rheumatic fever and SC, has recently been proposed to trigger tic disorders and OCD in genetically predisposed children.

OCD is observed in one to two percent of school-aged children. Obsessions and compulsions may change in both content and severity over time with no clear pattern of progression [1]. The disorder is chronic and disabling, but the course may wax and wane with exacerbations and remissions [2]. Comorbidities are very common, with tic disorders seen in 30% of children, major depression in 26%, attention deficit hyperactivity disorder (ADHD) in 10%, and other developmental disorders in approximately 20% [3]. Treatment of OCD includes behavioral and/or pharmacologic therapy, usually with selective serotonin reuptake inhibitors (SSRIs). Relapses often occur when treatment is discontinued, but fortunately complete remission may occur by late adolescence. Family studies and twin studies fit best with an autosomal dominant inheritance, however, since no gene has yet been identified, it is difficult to separate environmental and genetic factors.

TS has a lifetime prevalence of 1:1000, and is characterized by the childhood onset of chronic motor and vocal tics [4]. TS has a variable course, with symptoms often waxing and waning. Severity varies from a social nuisance to a severely debilitating condition [5]. Neuroleptics are the medications of choice for reducing tic severity, although symptoms are rarely entirely eliminated by therapy. TS is inherited in an autosomal dominant manner, although a mixed genetic and environmental model has been proposed. Monozygotic twin studies have shown that although both twins are generally affected, the severity of tics is discordant [6].

SC is a variant of acute rheumatic fever (ARF). It occurs in childhood, with a peak age of onset between four and fourteen years of age. Pathophysiologically, the manifestations of ARF likely result from molecular mimicry, the immunologic process whereby antibodies to GABHS cross-react to self-proteins to induce an inflammatory autoimmune response. Specifically, antibodies against GABHS cross react with neuronal cells to produce inflammation in the CNS (particularly within the basal ganglia), resulting in the movement disturbances observed in SC [7]. SC follows a streptococcal infection by as much as nine months, but may occur as early as a few weeks after GABHS infection. Clinical manifestations include motor symptoms, emotional lability and behavioral changes (Table 1). Obsessive-compulsive symptoms are observed in greater than 70% of patients with SC, often preceding the chorea by days to weeks [8].

As similarities between SC and other neuropsychiatric disorders became more evident both clinically and pathophysiologically, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) was proposed as a distinct subgroup of childhood OCD and tic disorders.

PANDAS

To make a diagnosis of PANDAS, patients must fulfill proposed criteria [9] (Table 2) and have a clear association between GABHS infection and symptom exacerbation must be demonstrated. Evidence of GABHS infection includes a positive throat culture for GABHS, or elevated or increasing antibody titers (ASO, anti-DNase B) demonstrating a recent GABHS infection. However, not all PANDAS exacerbations follow GABHS infection exclusively, and non-GABHS related exacerbations have been documented [10]. Similarly, exacerbations of SC have been observed following non-GABHS infection [11]. GABHS is thought to be the initial autoimmune-inducing event, with subsequent exacerbations triggered by recurrent GABHS, or by other bacterial or viral infections.

PANDAS and SC have similar clinical features, including emotional lability, attention and impulsivity difficulties, motor hyperactivity and clumsiness, abnormal choreiform hand movements, and deterioration in fine motor skills, which are often observed at the onset of an exacerbation. True chorea must be differentiated from isolated choreiform movements, and although there is no strict definition, the presence of chorea excludes the diagnosis of PANDAS.

The first fifty PANDAS patients were reported in the literature in 1998 by Swedo et al) [9]. Two hundred and seventy patients referred to the National Institute of Mental Health (NIMH) were initially screened, of whom 50 ultimately met PANDAS criteria. The mean age of onset of tics was 6.3 years, and 7.4 years for OCD, almost 3 years younger than the average age of onset for childhood OCD and tic disorder. Among the 50 children, there were 144 separate episodes of symptom exacerbations, although only one third were associated with documented GABHS infection. A recent study prospectively identified 12 patients fulfilling PANDAS criteria, with onset of symptoms following GABHS pharyngitis. All children responded to antibiotic therapy with prompt improvements (in most cases, eradication) of their tic and OCD behaviors [12]. Since the writing of this paper, the authors have prospectively identified 13 additional children, observing that patients fall into three categories: sixteen of 25 presented acutely with explosive onset of symptoms, 4 of 25 presented after weeks of behavior change with significantly elevated streptococcal serology, and 5 of 25 patients were diagnosed after several episodes of worsening behaviors following GABHS [13]. In a recent case-control study, Cardona [14] studied 150 consecutive children presenting with tics demonstrating a significantly higher mean antistreptolysin O titers in the patients compared to controls. They noted a positive correlation between ASO titer and severity of tic disorder, but could not confirm that their patients fulfilled criteria for PANDAS as patients were not assessed longitudinally.

Is this an Immunologic Process?

The biologic evidence that PANDAS is an autoimmune-mediated process is compelling, but not conclusive. A potential B cell marker was identified, magnetic resonance imaging of the brain demonstrates basal ganglia changes consistent with inflammation, and immunomodulatory therapies have been studied with benefit in some patients. Antibiotic prophylaxis, although effective in ARF, remains questionable in PANDAS.

D8/17 Lymphocyte Marker

The B cell marker D8/17 was identified as a predictor of ARF and SC, diseases recognized to have genetic susceptibility. The cell surface marker was discovered on a subset of HLA-DR positive B cells in the peripheral circulation, and the alloantigen was recognized by a monoclonal antibody labelled D8/17[15], a mouse monoclonal IgM antibody[16]. Testing involves staining peripheral B cells with the antibody and counting positively stained cells. A positive result is defined as greater than 11.8% of B cells stained (one standard deviation above historical comparison values). The percent of antigenic expression is inherited, either in an autosomal recessive or autosomal dominant manner with variable penetrance [15].

The D8/17 marker has high sensitivity for ARF, in that 90 to 100% of individuals with ARF are positive regardless of the disease activity. In initial studies, the marker's specificity was high, as only 5-15% of healthy controls had positive expression. Therefore, it appeared to function as a trait marker for ARF. Additional support was provided when patients with poststreptococcal

glomerulonephritis were found to express low numbers of positive cells. Siblings and parents of patients with ARF and SC also demonstrate higher numbers of positive D8/17 B cells than control subjects [17], which lends further support to a genetic susceptibility to ARF.

Based on the similarities of SC to other neuropsychiatric disorders, it was further hypothesized that the D8/17 marker might also be able to identify patients with OCD and TS. A group of 31 children with TS and/or OCD and 21 healthy controls were studied [18]. All patients positively expressed the D8/17 marker versus only one positive among the control patients. A subsequent study examined 27 children with PANDAS, 9 children with SC, and 24 healthy controls [19]. Eighty-five percent of the PANDAS children were positive, 89% in the SC group were positive, and only 17% of controls were positive ($p < 0.0001$ for both comparisons). These results support the hypothesis that there may be a group of children who are susceptible to developing PANDAS instead of SC or other manifestations after streptococcal infections. Testing for the presence of the D8/17 marker cannot alone differentiate children with TS and OCD from those with PANDAS since in the first study 100% of OCD and TS patients were positive for the marker, regardless of levels of antistreptococcal antibodies. Additionally, as this test is not commercially available, its utility in the diagnosis of PANDAS remains unclear.

MRI Studies

Abnormalities in the basal ganglia region are seen on MRI in patients with SC, predominantly increased volumes of the caudate nucleus, putamen and/or globus pallidus [20,21]. In a MRI study of 34 children with PANDAS compared to 82 age and sex-matched controls, significantly larger basal ganglia volumes were demonstrated in the PANDAS group [22]. There was no significant difference in total brain volume, which suggests the specificity of basal ganglia involvement. The increased volumes are presumably due to acute inflammation within the basal ganglia.

The clinical application of MRI studies is limited, as the increased volumes observed on MRI do not correlate with symptom severity in children with PANDAS. If a control group of children with OCD or TS not associated with GABHS infections had demonstrated normal sized basal ganglia, this information would have been clinically more important.

Therapeutic Options

SC is generally a self-limited disorder, with symptoms resolving in weeks to months. As antibodies are thought to be instrumental in its pathogenesis, immunosuppressive therapy might be a reasonable treatment option for patients with persistent symptoms. Corticosteroids have been used, although not well studied in the treatment of SC exclusive of other signs of ARF such as carditis. Alternatively, immunomodulatory treatment with either intravenous immunoglobulin (IVIG) or plasma exchange may hasten recovery. In one non-randomized study (published in abstract form) of 9 patients, 5 patients underwent plasma exchange and improved without recurrences for

10 months, and 4 patients received IVIG, with 3 demonstrating recurrent chorea several weeks later[23].

Prior to establishing the large cohort of PANDAS patients, case reports of patients benefiting from immunosuppressive therapy were published. The first report of successful treatment of patients with a post infectious PANDAS-like illness with IVIG, plasma exchange and prednisone studied only four patients[10]. A larger treatment trial has recently demonstrated that plasma exchange or IVIG may be effective therapies for children with severe recalcitrant PANDAS[24]. Thirty children with PANDAS were randomized to IVIG, plasma exchange, or “placebo” (saline infusion resembling IVIG infusion); a placebo for plasma exchange was not used. All patients had “severe” symptoms at time of entry, based on several rating scores. At one month, the children in both the IVIG and plasma exchange groups had symptom improvement, but those in the placebo group were unchanged. At one year, 80% of patients who had received plasma exchange had sustained improvement. However, 50% of children were on the same or higher doses of their baseline medications, thus it is not entirely clear that immunomodulatory therapy was beneficial. Additionally, it is possible that some of these children’s symptoms, especially tics, spontaneously improved after one year. IVIG and plasma exchange are invasive and costly therapies. In addition, significant side effects were observed in 7/10 patients who received plasma exchange, 6/10 patients who received IVIG, and 2/10 patients who received placebo. These adverse events included nausea, abdominal pain, headache and fever.

To identify plasma exchange as a superior treatment would have also required a control group for the plasma exchange group, although sham plasma exchange was not an ethically viable option. Interestingly, the children in the placebo group (IVIG control group) subsequently received plasma exchange in an open trial, and had only minor improvements. A larger randomized controlled trial of immunomodulatory therapy is required before recommending this treatment, and the NIMH (National Institute of Mental Health) recommends this therapy only as part of a research protocol.

Prophylaxis – is it useful?

Penicillin prophylaxis is efficacious for the prevention of recurrent rheumatic fever. The original trials evaluating prophylaxis and recurrence of rheumatic fever included more than 400 patients who were followed over five years[25,26]. A pilot study of prophylaxis for PANDAS examined 37 children over eight months in a double-blind cross-over study with oral penicillin vs. placebo[27]. An equal number of infections were observed in the active and placebo phases, and no significant changes were observed in OCD or tic severity. The duration of the study was limited, and since the study failed to demonstrate effective streptococcal prophylaxis with penicillin, at this time there is no recommendation for antibiotic prophylaxis for PANDAS.

Widening the PANDAS spectrum

Over the last few years, in addition to OCD and TS, anorexia nervosa, attention deficit hyperactivity disorder (ADHD), and autism have also been considered, though not yet accepted, to fit under the PANDAS umbrella.

An infection-triggered, autoimmune subtype of anorexia nervosa (AN) has been proposed. A recent report described four children with possible PANDAS AN who were treated with antibiotics in an open trial[28]. The patients were followed at a large eating disorders clinic, and also received conventional therapy including nutrition, behavioral therapy and pharmacologic treatments. All four children fulfilled DSM-IV criteria for AN, in addition to at least four of five criteria for PANDAS. Two of the four patients had a comorbid diagnosis of OCD, and all four had evidence of a prior GABHS infection with positive antistreptococcal antibody titers. Sinusitis was documented in relation to AN symptom exacerbations and treatment with amoxicillin resulted in significant weight gain and improvement in restricting behaviors in all children. Despite inconsistencies in the evidence of GABHS infection, and in the antibiotic dosage and duration, this study may provide preliminary evidence of a subtype of AN that fits into the PANDAS spectrum. A further study examining the D8/17 antigen expression in 16 PANDAS AN patients demonstrated that 81% of patients had positive levels, compared to 12% D8/17 positive in a group of comparison subjects (17 psychiatric patients without eating disorders)[29]. The validity of this study is questioned because the authors did not examine eating disordered patients without PANDAS symptoms.

ADHD is a frequent comorbid feature of TS and OCD, but recent literature postulates ADHD without tics or OCD as part of the PANDAS spectrum[30]. Peterson suggests that evidence of recurrent streptococcal infections in a patient with ADHD predicts increased basal ganglia volumes as seen in patients with SC and PANDAS[31].

The evidence for autism as part of the PANDAS spectrum remains circumstantial. A study of 18 children with autism demonstrated a higher frequency of D8/17 positive B cells than a control group. The D8/17 positive children had more severe repetitive behaviors and significantly higher compulsion scores[32], suggesting that autism may have an autoimmune basis in a subset of patients, which in itself remains controversial.

Conclusions

Certainly many controversies arise when a new diagnostic construct is proposed. The prevalence of acute or recent streptococcal infection in school-aged children is high, and tics, TS and OCD are prevalent in this age group. OCD and tic disorders typically wax and wane, and may be exacerbated by stress, anxiety, fatigue and illness (such as streptococcal infection).

Many questions remain. PANDAS (like SC) are purported to be post-streptococcal disorders, yet exacerbations often present long after the acute symptoms of infection, when antibody titers may have already normalized and throat cultures are negative. Immunomodulatory therapies such as IVIG and plasma exchange have significant risks, and cannot be universally prescribed before larger randomized controlled trials are conducted. Although only small studies

have been completed, prophylaxis remains ineffective in preventing exacerbations, and the utility of treating positive surveillance cultures (as has been done in prophylaxis studies) needs to be objectively evaluated. Most importantly, the recent prospective study by Murphy[12] lends credence to the PANDAS entity, demonstrating that an antecedent GABHS infection is specifically associated with the onset and exacerbation of tic disorders or OCD. Additionally, in this cohort of patients OCD and tic symptoms were relieved in all children with antibiotic therapy of the acute streptococcal infection, with none requiring “immunomodulatory” therapy.

PANDAS are a group of disorders recently recognized as a clinical entity. Recent GABHS infection should be considered in a child who presents with a sudden explosive onset of tics or OCD symptoms. However, in considering the prevalence of childhood onset TS and OCD, the diagnosis of PANDAS is rare. This spectrum of disorders may broaden to include anorexia nervosa, ADHD, and autism in the future as more conclusive research emerges. For now, the diagnosis of PANDAS must be made by strict criteria, and although the D8/17 marker may be useful in identifying patients at risk, until it is a universally accepted, replicable and commercially available test, its utility remains limited. At present, there is no clearly effective immunomodulatory treatment, nor has prophylaxis been effective in the prevention for PANDAS, and large, well-designed randomized controlled trials examining these problems are eagerly awaited. Ongoing NIMH studies accepting new patients are detailed on the PANDAS website[33] and interested patients and families should be referred for further information.

TABLES

Table I: Motor Manifestations of Sydenham's
Chorea

Ballismus
Facial grimacing
Tongue fasciculations
Loss of fine motor control
Hypotonia
Motor impersistence ("milkmaid's grip")
Gait Disturbance
Speech Abnormalities (dysarthria, explosive
speech)

Table 2: Criteria for PANDAS diagnosis

1. Presence of OCD and/or tic disorder (by DSM-IV criteria)
 2. Onset in childhood, between 3 years and onset of puberty
 3. Abrupt onset of symptoms, or course characterized by dramatic exacerbations
 4. Onset of exacerbations of symptoms temporally related to GABHS infection (preferably on two or more occasions)

 5. Abnormal neurologic examination (hyperactivity, choreiform movements, tics) during an exacerbation
-

References

1. Rettew DC, Swedo SE, Leonard HL, Lenane MC, Rapoport JL. Obsessions and compulsions across time in 79 children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry* 1992; 31:1050-6.
2. Hanna GL. Demographic and clinical features of obsessive-compulsive disorder in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1995; 34:19-27.
3. Snider LA, Swedo SE. Pediatric obsessive-compulsive disorder. *JAMA* 2000; 284:3104-6.
4. Singer HS, Walkup JT. Tourette syndrome and other tic disorders. Diagnosis, pathophysiology, and treatment. *Medicine (Baltimore)* 1991; 70:15-32.
5. Trifiletti RR, Packard AM. Immune mechanisms in pediatric neuropsychiatric disorders. Tourette's syndrome, OCD, and PANDAS. *Child Adolesc Psychiatr Clin N Am* 1999; 8:767-75.
6. Personal communication, Dr. Paul Sandor
7. Swedo SE. Sydenham's chorea. A model for childhood autoimmune neuropsychiatric disorders [clinical conference] [see comments]. *JAMA* 1994; 272:1788-91.
8. Swedo SE, Rapoport JL, Cheslow DL, et al. High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. *Am J Psychiatry* 1989; 146:246-9.
9. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases *Am J Psychiatry* 1998; 155:264-71.
10. Allen AJ, Leonard HL, Swedo SE. Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry* 1995; 34:307-11.
11. Berrios X, Quesney F, Morales A, Blazquez J, Bisno AL. Are all recurrences of "pure" Sydenham chorea true recurrences of acute rheumatic fever? *J Pediatr* 1985; 107:867-72.

12. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Arch Pediatr Adolesc Med* 2002; 156:356-61.
13. Personal communication, Dr. Michael Pichichero
14. Cardona F, Orefici G. Group A streptococcal infections and tic disorders in an Italian pediatric population. *J Pediatr* 2001; 138:71-5.
15. Khanna AK, Buskirk DR, Williams RC, Jr., et al. Presence of a non-HLA B cell antigen in rheumatic fever patients and their families as defined by a monoclonal antibody. *J Clin Invest* 1989; 83:1710-6.
16. Zabriskie JB, Lavenchy D, Williams RC, Jr., et al. Rheumatic fever-associated B cell alloantigens as identified by monoclonal antibodies. *Arthritis Rheum* 1985; 28:1047-51.
17. Feldman BM, Zabriskie JB, Silverman ED, Laxer RM. Diagnostic use of B-cell alloantigen D8/17 in rheumatic chorea. *J Pediatr* 1993; 123:84-6.
18. Murphy TK, Goodman WK, Fudge MW, et al. B lymphocyte antigen D8/17: a peripheral marker for childhood-onset obsessive-compulsive disorder and Tourette's syndrome? *Am J Psychiatry* 1997; 154:402-7.
19. Swedo SE, Leonard HL, Mittleman BB, et al. Identification of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections by a marker associated with rheumatic fever [see comments]. *Am J Psychiatry* 1997; 154:110-2.
20. Giedd JN, Rapoport JL, Kruesi MJ, et al. Sydenham's chorea: magnetic resonance imaging of the basal ganglia. *Neurology* 1995; 45:2199-202.
21. Castillo M, Kwock L, Arbelaez A. Sydenham's chorea: MRI and proton spectroscopy. *Neuroradiology* 1999; 41:943-5.
22. Giedd JN, Rapoport JL, Garvey MA, Perlmutter S, Swedo SE. MRI assessment of children with obsessive-compulsive disorder or tics associated with streptococcal infection. *Am J Psychiatry* 2000; 157:281-3.
23. Garvey MA, Swedo SW, Shapiro MB, et al. Intravenous immunoglobulin and plasmapheresis as effective treatments of Sydenham's chorea. *Neurology*, 1996; 46:A147.

24. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet* 1999; 354:1153-8.
25. Wood HF, Feinstein AR, Taranta A, Simpson R. Rheumatic fever in children and adolescents. III. Comparative effectiveness of three prophylaxis regimens in preventing streptococcal infections and rheumatic fever. *Ann Int Med*, 1964; 60(suppl 5):31-46.
26. Maliner MM, Amsterdam SD: Oral penicillin in the prophylaxis of recurrent rheumatic fever. *J Pediatr*, 1947; 31:658-61.
27. Garvey MA, Perlmutter SJ, Allen AJ, et al. A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. *Biol Psychiatry* 1999; 45:1564-71.
28. Sokol MS. Infection-triggered anorexia nervosa in children: clinical description of four cases. *J Child Adolesc Psychopharmacol* 2000; 10:133-45.
29. Sokol MS, Ward PE, Tamiya H, Kondo DG, Houston D, Zabriskie JB. D8/17 expression on B lymphocytes in anorexia nervosa. *Am J Psychiatry* 2002; 159:1430-2.
30. Waldrep DA. Two cases of ADHD following GABHS infection: a PANDAS subgroup? *J Am Acad Child Adolesc Psychiatry* 2002; 41:1273-4.
31. Peterson BS, Leckman JF, Tucker D, et al. Preliminary findings of antistreptococcal antibody titers and basal ganglia volumes in tic, obsessive-compulsive, and attention deficit/hyperactivity disorders. *Arch Gen Psychiatry* 2000; 57:364-72.
32. Hollander E, DelGiudice-Asch G, Simon L, et al. B lymphocyte antigen D8/17 and repetitive behaviors in autism. *Am J Psychiatry* 1999; 156:317-20.
33. <http://intramural.nimh.nih.gov/research/pdn/web.htm>