Brief Report

Challenges in the Identification and Treatment of PANDAS: A Case Series

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Summary

Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS), is characterized by childhood-onset obsessive-compulsive disorder (OCD) and Tic disorder that has been found to have a post infectious autoimmune-mediated etiology, where the onset and subsequent exacerbations of symptoms is temporally related to group A beta-hemolytic streptococci (GABHS) infection. In addition to the use of anti-tic and antiobsessional agents, the use of Penicillin during the acute phase and for prophylaxis, tonsillectomy, immunomodulatory therapies such as plasma exchange and intravenous immunoglobulin, etc. have all been reported to improve the symptoms. We describe five cases of neuropsychiatric symptoms triggered by streptococcal infection in an Arab population and highlight the challenges faced by clinicians in the identification and management of PANDAS.

Key words: PANDAS, OCD, Tics, neuropsychiatric symptoms, streptococcal infection.

Introduction

A spectrum of neurobehavioral symptoms including Tics and Obsessive Compulsive Behaviors (OCB) occurring in association with streptococcal infection is termed Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS) [1]. In these patients, the symptoms of Tics, are exacerbated abruptly within days or weeks following Group A Beta Haemolytic Streptococcal (GABHS) infections as evidenced by high antibodies, throat culture and sensitivity.

The National Institute of Mental Health's (NIMH) criteria for PANDAS includes: (i) Tic disorder and/or OCD; (ii) Paediatric onset, from 3 years to puberty; (iii) Abrupt onset and a course characterized by dramatic exacerbations; (iv) The onset or exacerbation is temporally related to GABHS infection; (v) Neurological abnormalities; hyperactivity, fidgetiness, restlessness or abnormal movements such as choreiform movements.

While there is no single diagnostic laboratory test available, evidence of GABH streptococcal infection through throat culture, elevated antistreptolysin O (ASO) titer, etc. can support the diagnosis. ASO titer may be negative during the first attack or when symptomatic, but a rise in titer or if it became positive during exacerbations, that is good evidence for recent streptococcal infection. Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons have been described in chorea and acute rheumatic fever. In this regard, elevated antistreptococcal DNAase-B (AntiDNAse-B) titer and presence of anti-basal ganglia antibodies have been reported in PANDAS.

Zabriskie and colleagues [2] found a B-cell marker (later identified as D8/D17), a monoclonal antibody attached to the surface of B cells, as a susceptibility factor for Rheumatic Fever (RF). Parents and siblings of patients with RF were also found to have the same finding, thus suggesting a genetic susceptibility. A subsequent study found that this marker was positive in 85% of patients with PANDAS, 89% of Sydenham's Chorea patients but only in 17% of controls. Thus it was postulated that those with this particular B-cell marker are at greater risk of developing CNS sequelae and neuropsychiatric symptoms after a streptococcal infection. However, subsequent finding by Murphy and colleagues [3], that this marker was positive in a group of all 31 patients with Tourette's syndrome and OCD without any association with streptococcal infection,

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TABLE 1
Clinical characteristics of the patients

S.No:	Age (years)	Sex	Physical/Neurological symptom	Psychiatric features	Relevant investigation findings
1	11	F	URTI, Right hemi-chorea, severe hypotonia, severe difficulties in eating, drinking and writing legibly, abnormal speech	Emotionally labile, moody, anxious with excessive crying and irritability, obsessions	High ASO titer
2	11	M	URTI, Pharyngitis G1 apical systolic murmur	Facial tics, poor concentration and deterioration in scholastic performance, deterioration in memory, running away from home, secondary nocturnal enuresis	High ESR and ASO titer
3	11	M	URTI, Pharyngitis Choreiform movements, abnormal speech	Tics (eye blinking, tongue protrusion, shoulder shrug), nocturnal enuresis OCD (hand washing, cleaning rituals, checking behavior), hyperactivity	Positive throat culture for *Beta haemolytic streptococci*, high ASO titer during the attack
4	9	M	URTI	Motor tics, vocal tics, Hyperactivity, Impulsivity, compulsive licking, echolalia	High ASO titer
5	10	M	Two episodes of Tics exacerbating with URTI	Motor tics (facial grimacing, lip sucking, eye blinking, neck jerking), vocal tics (throat clearing and sniffing) hyperactivity, inattention, poor concentration and impulsivity, poor scholastic performance	Positive throat swab for *Beta haemolytic streptococci*, high ASO titer

and present in only one person in the control group weakened this argument.

Brain imaging studies have shown enlarged basal ganglia. Giedd and colleagues [4] compared the brains of 34 children with PANDAS to 82 'normal healthy' controls and found that the average sizes of the caudate, putamen and globus pallidus, but not of the thalamus or total cerebrum, were significantly greater in the PANDAS group.

Clinical symptoms can vary and the expanded criteria for PANDAS includes streptococcus triggered abrupt onset of separation anxiety disorder; late onset hyperactivity disorder not meeting typical Attention Deficit Hyperactivity Disorder (ADHD) criterion (e.g. onset >7 years); mood changes including emotional lability and irritability; fidgeting; and school difficulties such as deterioration in math skills, memorizing and handwriting. Other symptoms that are reported in PANDAS variants include sleep disturbance, night time bed wetting or day time urinary frequency and joint pain. We describe five cases with varying clinical presentations of PANDAS.

Case Reports

The clinical features of the five children who presented with abrupt onset of symptoms following oropharyngeal infection by streptococci and who had an episodic course with dramatic exacerbations and spontaneous remissions are detailed in Table 1. There were four boys and one girl and the mean age at onset was 10.4 years. Cases 1, 2 and 4 had 'Probable PANDAS' as characterized by the criteria that include at least one documented episode triggered by streptococcal infection, and another one with an Upper Respiratory Tract Infection (URTI) or evidence of a missed streptococcal infection. Case 3 had 'Possible PANDAS' as characterized by sudden exacerbation of symptoms; Positive throat culture and antibody titers; and high or rising throat titers 6 weeks after the exacerbation. Case 5 had 'Definite PANDAS' as characterized by at least two exacerbations that are documented to be triggered by streptococcal throat infection; the child is free of streptococcal infection during remissions; and high titers and culture positive when ill and low titers and culture negative when well.

Only one of our patients had cardiac involvement and this is consistent with another study that observed that only one in 60 children with PANDAS had a positive Echocardiographic finding [5]. The evidence of a clear lack of rheumatic carditis in these children supports the hypothesis that PANDAS is a distinct neuropsychiatric diagnosis separate from Sydenham's chorea.

Discussion

While streptococcal infections are common in childhood, neuropsychiatric symptoms are not. Similarly, not all streptococcal infections cause RF, or SC or PANDAS. However, GABHS-associated toxin may *trigger an autoimmune reaction in genetically susceptible children* leading to any of the above conditions with different sero-types causing clinically different conditions. GABHS Related Spectrum of neuropsychiatric symptoms include Tics, OCD, ADHD, PANDAS, Anxiety, mood swings (emotional lability, sad mood, irritability), sleep disorders, learning and writing problems [6]. Although some other conditions including Anorexia Nervosa, Autism, etc. have been suggested to be associated with PANDAS, the evidence is limited. Current guidelines for treatment include the use of Penicillin during the acute phase for those confirmed to have streptococcal infection by throat swab, and conventional therapy for Tics and OCD. The usefulness of Penicillin prophylaxis is not certain [7]. Immunomodulatory therapy is not without risk and hence this should be reserved for severely ill patients. Both plasma exchange and intravenous immunoglobulin (IVIG) have been found to be effective in lessening the symptom severity in children with infection triggered OCD and Tic disorders [8], while this mode of treatment has been found to have no benefit for children who do not have GABHS infection [9].

Pediatricians, General Practitioners and other health professionals involved in the care of children should be aware of the possibility of neuropsychiatric symptoms triggered by streptococcal infection [10]. In any child presenting with abrupt onset or exacerbation of Tics, OCD or late onset of ADHD (after 7 years), clinicians need to look for history of throat infection and evidence for GABHS infection.

References

1. 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.
2. Zabriskie JB, Lavenchy D, Williams RC, *et al.* Rheumatic fever associated B cell alloantigens as identified by monoclonal antibodies. Arthritis Rheum 1985;28:1047–51.
3. Murphy TK, Goodman WK, Fudge MW, *et al.* B lymphocyte antigen D8/17: a peripheral marker for childhood-onset obsessive-compulsive disorder and Tourettes syndrome. Am J Psychiatry 1997;154:402–7.
4. Giedd JN, Rapport JL, Leonard HL, *et al.* Case study: acute basal ganglia enlargement and obsessive-compulsive symptoms in an adolescent boy. J Am Acad Child Adolesc Psychiatry 1996;35:913–5.
5. Snider LA, Sachdev V, Mackaronis JE, *et al.* Echocardiographic findings in the PANDAS subgroup. Pediatrics 2004;114:748–51.
6. Betancourt YM, Jimenez-Leon JC, Jimenez-Betancourt CS, *et al.* Trastornos neuropsiquiatricos autoinmunes asociados a la infeccion estreptococia en la edad pediatrica: PANDAS. Rev Neurol 2003;36(suppl 1): S95–107.
7. Garvey MA, Perlmutter S, Allen AJ, *et al.* A pilot of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. Society of Biol Psychiatry 1999;45:1564–71.
8. Nicolson R, Swedo SE, Lenane M, *et al.* An open trial of plasma exchange in childhood-onset obsessive-compulsive disorder without poststreptococcal exacerbations. J Am Acad Child Adolescent Psychiatry 2000;39:1313–5.
9. Perlmutter SJ, Leitman SF, Swedo SE, *et al.* Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and Tic disorder in childhood. Lancet 1999;354:1153–58.
10. Swedo SE, Garvey MA, Snider LA, *et al.* The PANDAS subgroup: recognition and treatment. CNS Spectrums 2001;6:419–26.