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# Anti-brain Antibodies in PANDAS Versus Uncomplicated Streptococcal Infection

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**The objective of this study was to assess brain involvement through the presence of antineuronal antibodies in Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS) and in uncomplicated active Group A streptococcal infection. We compared serum antibrain antibody to human basal ganglia sections assessed by indirect tissue immunofluorescence in two groups: a PANDAS group, comprised of 22 patients (mean age 10.1 years; 20 male, 2 female) who met strict National Institutes of Mental Health diagnostic criteria for PANDAS and had clinically active tics or obsessive-compulsive disorder, or both; and a GABHS control group consisting of 22 patients (mean age 9.1 years; 15 mol/L, 7 female) with clinical evidence of active Group A β-hemolytic streptococcal (GABHS) infection confirmed by throat culture and elevated antistreptolysin O titers but without history or clinical evidence of tics or obsessive-compulsive disorder. We observed positive anti–basal ganglia staining (defined as detectable staining at 1:10 serum dilution) in 14/22 patients in the PANDAS group (64%) but only 2/22 (9%) in the GABHS control group ($P < 0.001$, Fisher's exact test). These results suggest that antibrain antibodies are present in children with PANDAS that cannot be explained merely by a history of GABHS infection.** 

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## Introduction

The presence of features of tics, Tourette syndrome, or obsessive-compulsive disorder in the context of an immediately precedent streptococcal infection has led Swedo et al. [1,2] at the National Institutes of Mental Health to propose the general concept of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (abbreviated by the acronym PANDAS). The PANDAS concept emphasizes the range of clinical neuropsychiatric symptoms [2] that may be observed in a given patient.

The diagnosis of PANDAS requires a prospectively determined association between Group A beta-hemolytic streptococcal (GABHS) infection and obsessive-compulsive disorder or tic disorder.

As has been reported for Sydenham's chorea, also for PANDAS, antibrain (and more specifically antibasal ganglial) antibodies have been demonstrated in the serum [2,3]. It is possible that these antibrain antibodies represent antibodies that are formed as a direct result of a normal response to GABHS infection, i.e., representing spurious cross-reactivity with streptococcal antigens. If this were the case, then patients with GABHS pharyngitis, but without PANDAS, might be expected to display such antibrain antibodies in the blood. Furthermore, if this were the case, it would make such antibodies unlikely to be involved in the pathophysiology of PANDAS.

The objective of the present study was to examine the frequency of antibrain antibody in patients with PANDAS as a consequence of direct brain involvement, compared with those with documented GABHS infection, but without neuropsychiatric symptoms.

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**Table 1A. Patients with tic or obsessive-compulsive disorder**

| Patient No. | Sex | Age | Anti-streptolysin O titers (Normal value: < 250 U/I) | Antideoxyribonuclease B (Normal value: < 250 U/I) | Antineuronal Antibodies (Normal value: < 1/10) | Interval Between the Onset of Disease and the Assay of Antibody (Mean duration: 51 days) |
|---|---|---|---|---|---|---|
| 1 | M | 12 | 54 | 207 | neg | 45 |
| 2 | M | 9 | 400 | 650 | 1/40 | 67 |
| 3 | M | 10 | 374 | 306 | neg | 73 |
| 4 | M | 11 | 306 | 124 | 1/10 | 21 |
| 5 | M | 14 | 532 | 664 | 1/40 | 90 |
| 6 | M | 7 | 150 | 263.6 | 1/20 | 32 |
| 7 | M | 15 | 280 | 376.1 | neg | 12 |
| 8 | M | 14 | 106 | 203 | 1/40 | 79 |
| 9 | M | 12 | 358 | 287 | 1/100 | 82 |
| 10 | M | 8 | 600 | 983 | 1/80 | 3 |
| 11 | M | 10 | 864 | 1499 | 1/100 | 57 |
| 12 | M | 9 | 168 | 1027 | 1/100 | 66 |
| 13 | M | 11 | 215 | 450 | 1/20 | 39 |
| 14 | M | 9 | 370 | 54 | neg | 25 |
| 15 | M | 9 | 62 | 37 | 1/10 | 63 |
| 16 | M | 14 | 120 | 196 | neg | 77 |
| 17 | M | 8 | 612 | 993 | 1/20 | 56 |
| 18 | M | 10 | 375 | 37.8 | neg | 37 |
| 19 | F | 9 | 294 | 74.4 | neg | 29 |
| 20 | M | 6 | 54 | 199 | neg | 84 |
| 21 | M | 7 | 291 | 600 | 1/40 | 65 |
| 22 | F | 9 | 194 | 297 | 1/20 | 20 |

**Table 1B. Group A β-hemolytic streptococcal infection tonsillopharyngitis (GABHS)**

| Patient No. | Sex | Age | Anti-streptolysin O titers (Normal value: < 250 U/I) | Antideoxyribonuclease B (Normal value: < 250 U/I) | Antineuronal Antibodies (Normal value: < 250 U/I) | Interval Between the Onset of Disease and the Assay of Antibody (Mean duration: 19 days) |
|---|---|---|---|---|---|---|
| 1 | M | 9 | 1309 | 537 | neg | 12 |
| 2 | M | 8 | 680 | 243 | neg | 14 |
| 3 | F | 9 | 591 | 528 | 1/40 | 22 |
| 4 | F | 10 | 270 | 186 | neg | 30 |
| 5 | M | 13 | 120 | 196 | neg | 11 |
| 6 | M | 6 | 299 | 1965 | neg | 16 |
| 7 | M | 14 | 265 | 386 | neg | 10 |
| 8 | F | 10 | 63 | 52.5 | neg | 21 |
| 9 | F | 11 | 322 | 140.1 | neg | 25 |
| 10 | M | 7 | 437 | 167 | neg | 26 |
| 11 | M | 10 | 365 | 221 | neg | 18 |
| 12 | M | 10 | 183 | 37.8 | 1/20 | 17 |
| 13 | M | 11 | 245 | 548.7 | neg | 19 |
| 14 | M | 9 | 129 | 429.4 | neg | 13 |
| 15 | M | 8 | 65 | 565.7 | neg | 29 |
| 16 | M | 10 | 213 | 438 | neg | 20 |
| 17 | M | 9 | 413 | 641 | neg | 13 |
| 18 | F | 8 | 255 | 1965 | neg | 11 |
| 19 | M | 8 | 261 | 389 | neg | 21 |
| 20 | F | 6 | 69 | 72.5 | neg | 27 |
| 21 | F | 7 | 322 | 140.1 | neg | 25 |
| 22 | M | 7 | 289 | 53 | neg | 18 |

Abbreviation:
GABHS = Group A β-hemolytic streptococcal infection

## Materials and Methods

Our study involved two groups of patients. The first group ("PANDAS group") included 22 patients with an age between 6 and 15 years and mean age of 10.09 (±2.505), referred to the Day Hospital of Neuropediatrics, Division of Pediatrics of the University of Catania in the period from January 1999 to April 2002. All but two in the PANDAS group were male (Table 1A). Diagnosis was established based on National Institutes of Mental Health diagnostic criteria for PANDAS. Additionally, all the patients were studied by electroencephalogram and

**Table 2. Antineuronal antibodies detected in PANDAS and GABHS patients**

| | Antineuronal Antibodies Positivity | Total |
|---|---|---|
| Patients with OCD and/or tics (PANDAS) | 14 (63.6%) | 22 (100%) |
| Patients with a recent streptococcal infection (GABHS) | 2 (9%) | 22 (100%) |
| | | 44 |

Abbreviations:
GABHS = Group A β-hemolytic streptococcal infection
OCD = Obsessive-compulsive disorder
PANDAS = Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus

neuroimaging (either head computed tomography or magnetic resonance imaging) which were normal. The second group ("GABHS tonsillopharyngitis"; Table 1B) consisted of 22 patients, with clinical signs of tonsillopharyngitis such as sore throat, fever, and headache. The clinical manifestations had a duration of 2 and 5 days (mean 3 days); seven were female and 15 were male, with ages ranging from 6 to 14 years and mean age of 9.091 (±2.18). All the patients had evidence of a recent GABHS infection confirmed by throat culture or antistreptolysin O titers higher than 250 U/I.

All the patients were screened using guidelines set forth in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, to exclude other neuropsychiatric disorders, other than attention deficit hyperactivity disorder which is frequently observed as a co-morbid condition in Tourette syndrome. We examined antistreptolysin O titers, antideoxyribonuclease B, and antineuronal antibodies in all patients in both groups, at an interval of 3 days to several months (mean duration: 51 days) from the onset of neuropsychiatric symptoms in the PANDAS group and 10-30 days (mean duration: 19 days) after the onset of tonsillopharyngitis in the GABHS group without neuropsychiatric symptoms.

All the patients with GABHS tonsillopharyngitis were treated with either oral penicillin or other specific antistreptococcal oral antibiotics; no steroids were used. No treatment was initially used in the PANDAS group patients. No new infections were recorded during the study period in either group.

Antineuronal antibodies were determined using human basal ganglia section, according to the method of Husby et al. [3], and scored using criteria described therein.

## Results

Antineuronal antibodies were detected in 63.6% of the patients of the PANDAS group (14 of 22; Table 2). We detected a high titer of antistreptolysin O and antideoxyribonuclease B in 13/22 patients in the PANDAS group, but there was no significant correlation between the presence of antistreptolysin O, antideoxyribonuclease B, and antineuronal antibodies. In the "GABHS pharyngitis" group, i.e., in the patients with a streptococcus infection of recent data, antineuronal antibody staining was detected in 2/22 patients. Statistical analysis using Fisher's exact test indicated a significance ($P < 0.001$) demonstrating that PANDAS and GABHS tonsillopharyngitis differ significantly with respect to the presence of antineuronal antibodies.

In children with tics (PANDAS), a positive correlation between antineuronal antibodies and severity of tic disorder (measured by the Yale Global Tic Severity Scale) was demonstrated.

## Discussion

As reported in Table 2, antineuronal staining was detected in 63.6% of the PANDAS group, whereas in the GABHS group only 9% displayed antineuronal antibodies.

Kondo and Kabasawa [4] reported an 11-year-old Japanese male who developed acute onset of vocal and motor tics indistinguishable from those observed in idiopathic Tourette syndrome. These symptoms had an explosive onset approximately 10 days after a recent streptococcal infection. This male failed to respond to conventional tic-suppressing drugs, including haloperidol; he had a rapid and dramatic response to corticosteroid therapy. Matarazzo [5] reported two children who developed acute onset of Tourette syndrome after streptococcal infection, and who likewise failed to respond to neuroleptics but responded to adrenocorticotrophic hormone and prednisone therapy. These case reports suggest a subgroup of patients with Tourette syndrome who may have symptoms triggered by streptococcal infection, and this group might respond to corticosteroid therapy. Many more patients with similar clinical profiles have been subsequently characterized, and many have been demonstrated, by prospective study, to have PANDAS. Additionally, detailed characterization of patients with Sydenham's chorea led to the discovery that many of these patients manifested symptoms of obsessive-compulsive disorder. These findings suggest a potential clinical overlap between Sydenham's chorea, tic disorders, and obsessive-compulsive disorder.

An antineuronal antibody was first identified in the circulation of patients with Sydenham's chorea by Zabriskie and coworkers over 30 years ago [6]. These Sydenham-associated antineuronal antibodies or their targets still have not been characterized apart from qualitative properties. When compared with patients with rheumatic fever who did not have chorea, patients with chorea more commonly had antibodies in their serum which both recognized cells within the subthalamic and caudate nuclei and were adsorbed by streptococcal cellular components. This observation is consistent with the notion of "molecular mimicry," i.e., spurious cross-reactivity between antigens in disease associated streptococci and brain proteins. Patients with chorea associated with other illnesses, such as hereditary chorea (i.e., Huntington's disease) and lupus chorea, had antibodies which also recognized cells in the caudate nuclei, but did not bind to streptococcal cellular components [3].

Recent evidence also suggests the presence of antineuronal antibodies in children with PANDAS, Tourette

syndrome, or obsessive-compulsive disorder. Using a method similar to that used by Zabriskie to detect antineuronal antibodies in Sydenham's chorea (staining of brain sections with crude serum), Kiessling et al. demonstrated that patients with a variety of pediatric movement disorders (including Tourette syndrome, motor or vocal tics, chorea, and choreiform movements) manifested a level of staining comparable to that observed in Sydenham's chorea [7–9]. Of note, studies have detected no correlation of these antibodies with either clinical status or the presence or absence of antistreptococcal antibodies [10,11], similar to our findings here. The biochemical nature of putative target brain antigens in either Sydenham's chorea, Tourette syndrome, or obsessive-compulsive disorder has also been a focus of recent investigations. Using overlay Western immunoblotting, two groups [11], including our own [12,13], have reported the association of antibodies to an 83-kilodalton protein (which we have termed ts83) and Tourette syndrome–obsessive-compulsive disorder. These results suggest that the antineuronal antibodies detected in these patients may be directed primarily to a small number of antigens. More work needs to be performed to determine the precise nature of these immune abnormalities, their specificity for Tourette syndrome and obsessive-compulsive disorder [14], and their possible role in the pathophysiology of these disorders. Our current results strongly suggest that, whatever the nature of these antibodies, they cannot be explained as a consequence of acute GABHS infection alone.

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