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# Comparison of Clinical Characteristics of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections and Childhood Obsessive-Compulsive Disorder

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## Abstract

***Objective:*** The objectives of this study were to identify unique clinical characteristics of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) compared with a control group of children with non-PANDAS obsessive-compulsive disorder (OCD) with respect to ancillary symptoms, types of obsessions and compulsions, symptom severity, and co-morbid DSM-IV diagnoses.

***Method:*** Classification of PANDAS was based on review of pediatric and psychiatric records using the criteria developed by Swedo and colleagues. Children aged 6–14 with PANDAS ($n = 21$) and non-PANDAS OCD ($n = 18$) were assessed by blind independent evaluators using the PANDAS Questionnaire, Children's Yale-Brown Obsessive Compulsive Scale, Yale Global Tic Severity Scale, and Anxiety Disorders Interview Schedule for DSM-IV.

***Results:*** PANDAS children were significantly more likely to present with separation anxiety, urinary urgency, hyperactivity, impulsivity, deterioration in handwriting, and decline in school performance during their initial episode of neuropsychiatric illness compared with children with OCD. Total tics and vocal tics were more severe in PANDAS children. Separation anxiety disorder and social phobia were more prevalent in non-PANDAS OCD children. Children with non-PANDAS OCD were significantly more likely to include others in their rituals. There were no significant differences between groups on demographics or severity of OCD.

***Conclusions:*** Distinguishing clinical characteristics in PANDAS, which included urinary urgency, hyperactivity, impulsivity, and deterioration in handwriting, are linked to basal ganglia functions. These clinical characteristics will aid in the differentiation of PANDAS children for research and clinical purposes and ultimately advance our understanding and treatment of this disorder.

## Introduction

Obsessive-compulsive disorder (OCD) afflicts ~1%–3% of children (Douglass et al. 1995). OCD is a neurobiological disorder with several hypothesized etiologies, including inherited polymorphisms (Nicolini et al. 2009) and environmental triggers (Geller 2010). Poststreptococcal autoimmunity is hypothesized to be an additional etiologic pathway in a subset of children with OCD and tic disorders (Swedo et al. 1998). This subset of children experiences a sudden onset of OCD and/or motor tics in association with Group A streptococcal (GAS) infections (e.g., ''strep throat''), a disorder classified as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).

Although the clinical presentation of PANDAS was described over 10 years ago by Swedo et al. (1998), PANDAS remains controversial because a direct evidence of a pathogenic mechanism has yet to be found in human studies. Criticism of PANDAS research highlights the absence of clinical characteristics and biomarkers that differentiate PANDAS from childhood-onset OCD or tic disorders (Perrin et al. 2004). PANDAS is defined by five diagnostic criteria: (1) the presence of OCD and/or a tic disorder, (2) prepubertal symptom onset, (3) an abrupt onset of symptoms that are episodic in severity, (4) a temporal association between symptom exacerbations and GAS infections, and (5) the presence of neurological abnormalities (e.g., choreiform movements) during exacerbations (Swedo et al. 1998). Despite these defined criteria,

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establishing a diagnosis of PANDAS remains challenging, in part because of the difficulty in the documentation of temporal associations between GAS infection and exacerbations of PANDAS symptoms. Further, evidence from prospective and epidemiological studies exists, which both supports (Murphy and Pichichero 2002; Mell et al. 2005; Leslie et al. 2008; Lin et al. 2010) and contradicts (Kurlan et al. 2008; Singer et al. 2008; Schrag et al. 2009) a temporal association between streptococcal infection and symptom exacerbation in PANDAS patients.

The pathogenesis of PANDAS is hypothesized to begin during a GAS infection, leading to the production of antistreptococcal antibodies that cross-react with basal ganglia tissue. Studies have demonstrated a correlation between increased antistreptococcal antibody titers and basal ganglia volumes (Peterson et al. 2000) and elevated antineuronal antibodies in children with PANDAS (Singer et al. 2004; Dale et al. 2005). However, other reports have failed to find increased antineuronal antibodies in PANDAS patients or have found that titers of antineuronal antibodies fail to differentiate PANDAS subjects from Tourette or non-PANDAS OCD controls (Gause et al. 2009; Morris et al. 2009). Interestingly, a recent animal study demonstrated increased motor stereotypies, increased anxiety-related behaviors, and periventricular immunoglobulin deposition following passive transfer of antistreptococcal antibodies from one mouse to another (Yaddanapudi et al. 2010). Additional support for an autoimmune mechanism in PANDAS comes from studies demonstrating the therapeutic benefit of intravenous immunoglobulin and plasma exchange, two immunomodulatory therapies (Perlmutter et al. 1999; Elia et al. 2005).

Research suggests that obsessive-compulsive symptoms may involve abnormalities in cortical-striatal networks (Harrison et al. 2009; Olver et al. 2009). PANDAS, like Sydenham's chorea, is hypothesized to be an autoimmune attack against the basal ganglia and, as such, may have a unique profile of OCD symptoms, tic symptoms, or co-morbid psychiatric conditions. However, there has been limited research on the types of obsessions and compulsions experienced by children with PANDAS and patterns of co-morbid psychiatric conditions. The largest PANDAS cohort studied to date (50 cases) reported contamination as the most prominent obsessive symptom, and washing and cleaning as the most prevalent compulsion (Swedo et al. 1998). Additionally, there are case studies (Elia et al. 2005) and case series (Swedo et al. 1998; Murphy and Pichichero 2002; Mabrouk and Eapen 2009) that suggest a high rate of co-morbid psychiatric and behavioral symptoms in children with PANDAS.

One prospective study (Murphy and Pichichero 2002), a case report (Elia et al. 2005), and our clinical experience suggest that symptoms outside the canonical features of OCD or Tourette's disorder may be present in children with PANDAS. These symptoms include new-onset urinary urgency, impulsivity, acute deterioration in handwriting, and separation anxiety. These symptoms may be clinically relevant, as urinary urgency and handwriting are motoric processes at least partially governed by basal ganglia networks (Capone et al. 2009; Yamamoto et al. 2009). However, these hypothesized ''ancillary'' PANDAS symptoms have yet to be systematically studied in PANDAS patients and have not been examined in children with OCD.

In the present study, clinical differences between children with PANDAS and children with non-PANDAS OCD and/or tic disorders are explored. Based on previous PANDAS research, we hypothesized that PANDAS children would display a unique constellation of ancillary PANDAS symptoms when compared with a control group of children with non-PANDAS OCD. In addition, exploratory investigations were undertaken to compare the severity of OCD and tic symptoms, types of obsessions and compulsions, and prevalence of co-morbid *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) disorders between children with PANDAS and children with non-PANDAS OCD and/or tic disorders.

## Methods

### *Participants*

Participants included 39 children (24 boys and 15 girls) who were evaluated over a 3-year period between February 2007 and January 2010. All participants met DSM-IV criteria for OCD. Twenty-one participants were classified as having PANDAS and 18 were classified as non-PANDAS OCD. Participants were included in the PANDAS group if they met the five criteria as defined by Swedo et al. (1998) based on review of the Medical History Questionnaire, pediatric records, and psychiatric records by the first two authors. In making a diagnosis of PANDAS, we required two ''spikes'' in clinical OCD and/or tics, each associated with pharyngitis and laboratory documentation of streptococcal infection (e.g., positive rapid strep test, positive strep culture, and/or elevation in antistreptolysin O [ASO] and/or anti-DNAse B titers). The documentation was usually obtained retrospectively by review of records. This requirement was not met by five PANDAS participants who were evaluated during their initial neuropsychiatric episode. To meet PANDAS criterion 5 (presence of neurological symptoms), we included children with choreiform movements, hyperactivity, and/or tics, based on chart reviews and Medical History Questionnaire. Categorization into PANDAS and non-PANDAS groups was completed prior to data analyses.

### *Procedure*

This study was approved by the University of Minnesota Institutional Review Board. Subjects were recruited by mailings and e-mails to child and adolescent psychiatrists, pediatricians, and child psychologists. In addition, flyers were posted in the Psychiatry Outpatient Clinic at the University. The study was listed on the local website for the Obsessive Compulsive Foundation. Many of the participants were referred from the Child and Adolescent Anxiety and Mood Disorders Clinic at the university where we specialize in OCD. For this reason, our comparison sample of children was more likely to include children with OCD compared with children with tic disorders. Inclusion criteria were children aged 6–14 years, who were English speaking, and who met criteria for OCD and/or tics. Exclusion criteria included diagnoses of pervasive developmental disorder, psychosis, bipolar disorder, and mental retardation (IQ $<$ 80 on the Wechsler Abbreviated Scales of Intelligence) (Wechsler 1999). Parents provided written consent and children provided written assent prior to participation.

The Anxiety Disorders Interview Schedule (ADIS) for DSM-IV, Child Version (Silverman and Albano 1996), Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill et al. 1997), CY-BOCS Checklist, Yale Global Tic Severity Scale (YGTSS) (Leckman et al. 1989), and PANDAS Questionnaire were administered by trained independent evaluators who were blind to the classification of PANDAS versus non-PANDAS. The ADIS, YGTSS, and PANDAS Questionnaire were administered to the parent about the child and the CY-BOCS was given to the parent and child together. The information from the parent and child was

integrated by the independent evaluator when arriving at scores on the CY-BOCS. The ADIS was administered to parents and not to children because of time constraints. While the parents were completing the ADIS, the children were completing neuropsychological testing, which will be the basis of another manuscript. Physical and neurological examinations were not performed on participants.

Of the 39 participants, 31 were considered in exacerbation at the time of the assessment and 8 were in remission. Of the 31 in exacerbation, 16 were in the PANDAS group and 15 were in the non-PANDAS group. Of the 8 in remission, 5 were in the PANDAS group and 3 were in the non-PANDAS group. Our definition of exacerbation was CY-BOCS $> 15$ and/or YGTSS $> 19$ and remission was CY-BOCS $< 16$ and YGTSS $< 20$.

### *Instruments*

Anxiety Disorders Interview for DSM-IV, Child Version. The DSM-IV is a semistructured interview for the evaluation of anxiety and other disorders. Test–retest reliability of the ADIS is good to excellent (Silverman et al. 2001), interrater reliability is good (Lyneham et al. 2007), and there is strong support for concurrent validity of the instrument (Wood et al. 2002).

Children's Yale-Brown Obsessive Compulsive Scale. The CY-BOCS is a 10-item clinician-rated semistructured instrument to assess the severity of obsessions and compulsions. Scores are generated for the Obsessions and Compulsions Subscales, as well as a Total Score (Scahill et al. 1997). A Likert scale, ranging from 0 to 4, is used to rate the same five items (time occupied by obsessions or compulsions, resistance against obsessions or compulsions, interference, distress, and control) for the Obsessions and Compulsions Subscales. The Total Score ranges from 0 to 40. The CY-BOCS Checklist of 72 obsessions and compulsions was also administered. Psychometric properties of the CY-BOCS have been satisfactory (Storch et al. 2006; Yucelen et al. 2006).

Yale Global Tic Severity Scale. The YGTSS is a semistructured instrument that evaluates motor and vocal tics (Leckman et al. 1989; Storch et al. 2005). The presence of tics is based on parent report and clinician's behavioral observations. Once tics are documented, the parent rates the severity of motor and vocal tics on five independent dimensions (i.e., number, frequency, intensity, complexity, and interference). Index scores are generated including Total Motor Score (range: 0–25), Total Phonic Score (range: 0–25), and Total Tic Score (range: 0–50). The instrument has good construct, convergent, and discriminant validity (Leckman et al. 1989). The instrument was completed by parents about their children.

PANDAS Questionnaire. This 51-item instrument was developed for this study. The answers to the items were yes/no without an associated ordinal scale. Nineteen of the 51 items on the PANDAS Questionnaire were selected as key symptoms of interest for data analysis because they described characteristics that had been reported in the literature as associated with PANDAS or were characteristics observed in our clinic patients with PANDAS. These 19 items were distributed in the following categories of the questionnaire: Separation anxiety (1 item), night-time fears (2 items), enuresis (3 items), sensory defensiveness (1 item), food intake (1 item), emotional lability (3 items), inattention/hyperactivity/impulsivity (3 items), choreiform movements (2 items), handwriting deterioration (1 item), and school performance (2 items). This instrument was administered by independent evaluators in an interview format with parents of PANDAS and non-PANDAS participants based on the children's initial episode of symptoms.

Medical History Questionnaire. This questionnaire was developed for this study. Parents completed the questionnaire to obtain detailed information on the child's medical history, especially related to streptococcal infections, OCD symptoms, and tics. A review of pediatric and psychiatric records was also completed to corroborate and add to the information provided on the questionnaire. In all cases but one, mothers completed this form.

Wechsler Abbreviated Scales of Intelligence. It provides an abbreviated measure of cognitive functioning. This was used to ensure that the participants had an IQ $> 79$.

### *Training of independent evaluators*

Independent evaluators included two graduate students in psychology, a medical student, a psychiatry resident, an individual with a bachelor's degree, and two undergraduate students. Three to 6 weeks of training were provided to evaluators, depending on their level of experience. Training was provided by the second author and included readings and discussion of DSM-IV, observation of the administration of interviews and rating scales, and administration of interviews by independent evaluators with observation by the second author. The second author reviewed all ADIS results with the independent evaluators to ensure correct administration and scoring.

### *Data analysis*

Chi-square analyses and independent samples *t*-tests were calculated to assess demographic, medical, and psychiatric differences between the two groups of participants (PANDAS and non-PANDAS children). Chi-square analyses were used with categorical data and *t*-tests were used with continuous data. The tests were two tailed. Significance threshold was considered to be $p = 0.05$, except for the analyses of the PANDAS Questionnaire for which the family-wise Bonferroni correction for multiple comparisons was used. On the PANDAS Questionnaire, 19 of the 51 items were analyzed. The number of items analyzed in each category of the PANDAS Questionnaire using the family-wise Bonferroni correction is noted in the Instruments section. No corrections for multiple comparisons were used for exploratory analyses of severity of OCD and tic symptoms, types of obsessions and compulsions, and rates of co-morbid disorders.

## Results

### *Sample characteristics*

The mean age at the first episode of neuropsychiatric symptoms for the total sample was 7.94 years and did not differ significantly between children with and without PANDAS. There were no significant differences between the two diagnostic groups on demographics (Table 1). The average socioeconomic status was 50.9 based on Hollingshead Four-Factor Index corresponding to upper-middle class (Hollingshead 1975). There was no significant difference between groups on the measure of socioeconomic status. The mean IQ score from the Wechsler Abbreviated Scales of Intelligence was a standard score of 110.44, with no difference between groups (Table 1). This places the participants within a high average range of cognitive functioning.

Table 1. Demographics and Severity Scores

| | *PANDAS* (n = *21*) | *Non-PANDAS* (n = *18*) | *Total sample* (n = *39*) |
|---|---|---|---|
| Age at onset, mean (SD) | 7.27 (2.61) | 8.65 (3.35) | 7.94 (3.03) |
| Age at assessment, mean (SD) | 9.79 (2.40) | 11.63 (2.38) | 10.66 (2.53) |
| Gender, *n* (%) | | | |
| Male | 14 (66.67) | 10 (55.60) | 24 (61.50) |
| Female | 7 (33.33) | 8 (44.40) | 15 (38.50) |
| Ethnicity, *n* (%) | | | |
| White | 21 (100.00) | 17 (94.40) | 38 (97.44) |
| Hispanic | 0 (0.00) | 1 (5.60) | 1 (2.56) |
| Native American | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| Family constellation, *n* (%) | | | |
| Two parent | 20 (95.20) | 17 (94.40) | 37 (94.87) |
| Single parent | 1 (4.80) | 1 (5.60) | 2 (5.13) |
| SES[a] mean (SD) | 52.70 (9.72) | 49.10 (8.20) | 50.90 (9.02) |
| WASI IQ, mean (SD) | 110.81 (11.25) | 110.00 (16.39) | 110.44 (13.67) |
| CY-BOCS Total, mean (SD) | 18.48 (7.29) | 21.39 (7.86) | 19.82 (7.60) |
| YGTSS Total Tic Score, mean (SD) | 10.95[b] (12.75) | 2.50 (5.32) | 6.84 (10.63) |
| YGTSS Motor Tic Score, mean (SD) | 5.37 (6.74) | 2.28 (4.68) | 3.86 (5.96) |
| YGTSS Phonic Tic Score, mean (SD) | 5.68[c] (6.94) | 0.22 (0.94) | 3.03 (5.67) |

[a]Based on Hollingshead Four-Factor Index of Social Status.
[b]PANDAS significantly different from non-PANDAS, $p < 0.05$.
[c]PANDAS significantly different from non-PANDAS, $p < 0.01$.
*Abbreviations:* CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale; PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; SES = socioeconomic status; WASI = Wechsler Abbreviated Scales of Intelligence; YGTSS = Yale Global Tic Severity Scale.

### *OCD and tic symptoms*

OCD and tic severity scores are included in Table 1. The CY-BOCS Total Score showed no significant difference between the PANDAS and non-PANDAS groups, with both groups scoring in the moderate range of severity ($t\,(37) = 1.20, p = 0.238$). Similarly, there were no significant differences between the PANDAS and non-PANDAS groups on the Obsessions and Compulsions Subscale scores of the CY-BOCS.

Of the 31 participants who were considered in exacerbation at the time of assessment, 7 scored greater than 19 on the YGTSS. All seven were in the PANDAS group. The mean YGTSS Total Tic Score was significantly higher in the PANDAS group compared with the non-PANDAS group ($t\ (35) = -2.60,\ p = 0.013$). This difference was due to the significant difference in the YGTSS Phonic Tic Score between the two groups ($t\ (35) = -3.31,\ p = 0.002$). There was no significant difference between groups on the YGTSS Motor Tic Score ($t\,(35) = -1.61, p = 0.116$).

### *Antistreptococcal antibody titers*

ASO and anti-DNAse B titers were obtained. During exacerbation, ASO titers were higher in the PANDAS group compared with the non-PANDAS group, with mean titers of 175.07 (SD = 209.54) and 99.93 (SD = 124.23), respectively, but the difference was not significant ($t\ (26) = -1.15,\ p = 0.261$). The anti-DNAse B titers were also higher in the PANDAS group (446.79 [SD = 511.94]) compared with the non-PANDAS group (285.77 [SD = 365.75]), but the finding was not significant ($t\,(25) = -0.93, p = 0.359$).

### *Obsessions and compulsions*

The children's obsessions and compulsions by categories from the CY-BOCS are shown in Table 2. The only obsessive-compulsive symptom that was significantly different between groups was involving other people in their rituals; children without PANDAS endorsed this symptom more frequently than children with PANDAS ($\chi^2 = 5.57, p = 0.018$).

### *Co-morbid diagnoses*

Based on the ADIS interview, children with non-PANDAS OCD were more likely to have a co-morbid diagnosis of separation

Table 2. Obsessions and Compulsions Endorsed on the Children's Yale-Brown Obsessive Compulsive Scale Checklist

| | *PANDAS* (n = *21*) | | *Non-PANDAS* (n = *18*) | | |
|---|---|---|---|---|---|
| *Symptom domain* | n | % | n | % | p |
| Obsessions | | | | | |
| Aggressive | 13 | 61.9 | 12 | 66.7 | 0.757 |
| Contamination | 11 | 52.4 | 14 | 77.8 | 0.099 |
| Hoarding | 5 | 23.8 | 6 | 33.3 | 0.510 |
| Religious | 6 | 28.6 | 5 | 27.8 | 0.956 |
| Sexual | 1 | 4.8 | 3 | 16.7 | 0.222 |
| Magical | 6 | 28.6 | 3 | 16.7 | 0.379 |
| Somatic | 5 | 23.8 | 6 | 33.3 | 0.510 |
| Compulsions | | | | | |
| Washing/cleaning | 9 | 42.9 | 12 | 66.7 | 0.137 |
| Checking | 9 | 42.9 | 10 | 55.6 | 0.552 |
| Counting | 4 | 19.0 | 4 | 22.2 | 0.807 |
| Hoarding | 6 | 28.6 | 6 | 33.3 | 0.748 |
| Repeating | 10 | 47.6 | 5 | 27.8 | 0.204 |
| Ordering | 4 | 19.0 | 6 | 33.3 | 0.308 |
| Magical games | 3 | 14.3 | 3 | 16.7 | 0.837 |
| Rituals involving others | 5 | 23.8 | 11 | 61.1 | 0.018 |

anxiety disorder ($\chi^2 = 5.37$, $p = 0.020$) and social phobia ($\chi^2 = 3.94$, $p = 0.047$) compared with children with PANDAS. There were no significant differences in the rates of other co-morbid disorders between the two groups (Table 3). No children met criteria for panic disorder, agoraphobia, posttraumatic stress disorder, conduct disorder, sleep terror disorder, bipolar disorder, autism, pervasive developmental disorder, schizophrenia, and substance abuse or substance dependence.

### *Medical Questionnaire*

There was a trend showing that a higher percentage of children with PANDAS had a history of tonsillectomy/adenoidectomy compared with children without PANDAS (38.9% and 12.5%, respectively, $\chi^2 = 3.031$, $p = 0.082$). Children in the non-PANDAS group were significantly more likely to be currently prescribed a selective serotonin reuptake inhibitor (SSRI) compared with children in the PANDAS group (71.4% and 25.0%, respectively, $\chi^2 = 6.467$, $p = 0.011$). There was one child in the non-PANDAS group who was prescribed risperidone in addition to an SSRI and another child in the non-PANDAS group who was taking clomipramine and quetiapine. Two children in the PANDAS group were currently on prophylactic antibiotics to prevent streptococcal infections.

### *Ancillary symptoms during initial episode*

Thirty-seven parents completed the PANDAS Questionnaire to assess their children's symptoms during the sentinel episode of OCD and/or tic disorder. Children with PANDAS were significantly more likely than children without PANDAS to demonstrate separation anxiety, urinary urgency, oppositional defiant behavior, mood swings, inattention, hyperactivity, impulsivity, abnormal hand or finger movements, and decline in their handwriting and school performance (Table 4).

## Discussion

The aim of this study was to clarify the unique clinical characteristics of children with PANDAS with respect to severity of symptoms, obsessive-compulsive symptom dimensions, co-morbid psychiatric diagnoses, and ancillary PANDAS symptoms. This article compares clinical correlates between children with PANDAS and children with non-PANDAS OCD.

Children with and without PANDAS were indistinguishable on demographic characteristics, severity of OCD, and types of obsessions and compulsions. Separation anxiety disorder and social phobia were the only co-morbid diagnoses that differentiated the two groups, with the non-PANDAS children showing higher rates of each of these disorders. The severity of total tics and severity of vocal tics were higher in the PANDAS compared with the non-PANDAS participants, although this may be due to having an overrepresentation of children with OCD in the psychiatric control group, as opposed to children with tic disorders because many referrals were from the Child and Adolescent Anxiety and Mood Disorders Clinic. A greater number of children in the OCD group were receiving SSRIs compared with those in the PANDAS group, perhaps because the non-PANDAS OCD children were almost 2 years older at assessment than PANDAS children.

The most common obsessions (aggressive and contamination) and compulsions (washing/cleaning and checking) in the present study are consistent with findings from previous studies of children with non-PANDAS OCD (Swedo et al. 1989; Geller et al. 1998) and PANDAS (Swedo et al. 1998). Interestingly, only rituals involving others were significantly more common in the non-PANDAS group. Sixty-one percent of children with non-PANDAS OCD involved family members in rituals compared with only 24% of children

Table 3. Co-morbid Diagnoses Based on the Anxiety Disorders Interview Schedule

| | *PANDAS (n = 21)* | | *Non-PANDAS (n = 18)* | | |
|---|---|---|---|---|---|
| *Co-morbid diagnosis* | n | % | n | % | p |
| Separation anxiety disorder | 1 | 4.8 | 6 | 33.3 | 0.020 |
| Generalized anxiety disorder | 6 | 28.6 | 8 | 44.4 | 0.303 |
| Social phobia | 1 | 4.8 | 5 | 27.8 | 0.047 |
| Major depressive disorder | 2 | 9.5 | 2 | 11.1 | 0.871 |
| Dysthymic disorder | 1 | 4.8 | 2 | 11.1 | 0.458 |
| ADHD | 5 | 23.8 | 2 | 11.1 | 0.303 |
| Oppositional defiant disorder | 4 | 19.0 | 3 | 16.7 | 0.847 |
| Enuresis | 2 | 9.5 | 1 | 5.6 | 0.643 |

*Abbreviations:* ADHD = attention-deficit/hyperactivity disorder.

Table 4. Items Endorsed During Initial Episode on the Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections Questionnaire

| | *PANDAS (n = 19)*[a] | | *Non-PANDAS (n = 18)* | | |
|---|---|---|---|---|---|
| *Item* | n | % | n | % | p |
| Separation anxiety | 14 | 73.7 | 7 | 38.9 | 0.033[b] |
| Bedtime fears | 9 | 47.4 | 3 | 16.7 | 0.046 |
| Nightmares | 6 | 31.6 | 1 | 5.6 | 0.043 |
| Increase in frequency of urination | 5 | 26.3 | 0[c] | 0.0 | 0.023 |
| Urinary urgency | 6[c] | 33.3 | 0[c] | 0.0 | 0.009[b] |
| Enuresis | 8 | 42.1 | 4 | 22.2 | 0.197 |
| Sensory defensiveness | 8 | 42.1 | 7[c] | 41.2 | 0.955 |
| Change in food intake | 9 | 47.4 | 4 | 22.2 | 0.109 |
| Irritability | 15 | 78.9 | 8 | 44.4 | 0.031 |
| Oppositional defiant behavior | 13 | 68.4 | 4 | 22.2 | 0.005[b] |
| Mood swings | 16 | 84.2 | 8 | 44.4 | 0.011[b] |
| Inattention | 14[c] | 77.8 | 0 | 0.0 | 0.000[b] |
| Hyperactivity | 10 | 52.6 | 2 | 11.1 | 0.007[b] |
| Impulsivity | 14 | 73.7 | 4 | 22.2 | 0.002[b] |
| Abnormal hand or finger movements | 8 | 42.1 | 0 | 0.0 | 0.002[b] |
| Change in gait | 4 | 21.1 | 1 | 5.6 | 0.168 |
| Decline in handwriting | 11[c] | 61.1 | 0 | 0.0 | 0.000[b] |
| Decline in school performance | 16[c] | 88.9 | 5 | 27.8 | 0.000[b] |
| Decline in school attendance | 5 | 26.3 | 7[c] | 41.2 | 0.345 |

[a]Two parents did not complete the PANDAS Questionnaire.
[b]PANDAS significantly different from non-PANDAS based on family-wise Bonferroni correction.
[c]One subject is missing this item.

with PANDAS. Similarly, Swedo et al. (1998) found that only 20% of children with PANDAS engaged others in their rituals. This may be because children with non-PANDAS OCD compared with children with PANDAS demonstrate an insidious onset of symptoms. In the non-PANDAS participants, subthreshold symptoms may have been present for months before the "onset" of the initial episode. With the insidious onset, the parents may have been gradually accommodating to the children's subthreshold symptoms, even before their children were diagnosed with OCD. Thus, in non-PANDAS children, there is a greater likelihood of families supporting or maintaining the symptoms. Parents may be actively involved in their children's OCD symptoms by unknowingly reinforcing their offspring's compulsive behaviors (e.g., giving verbal reassurance or "helping" their children to wash clothing perceived to be contaminated) (Geller 2010). Family accommodation of OCD symptoms has been found to be common in pediatric OCD (Storch et al. 2007; Peris et al. 2008).

In the present study, PANDAS participants were more likely to have had their tonsils and adenoids removed compared with the children with non-PANDAS OCD. This is presumably due to recurrent streptococcal and other upper respiratory infections. In a recent study of children with PANDAS ($n = 41$) compared with children with non-PANDAS tics and/or OCD ($n = 68$), the PANDAS group was more likely to have a history of streptococcal infections before age 7 and a history of tonsillectomies/adenoidectomies (Murphy 2009). The increase in tonsillectomy reported here may be related to increased rates of GAS infections in PANDAS children, which has been described in previous case–control studies (Kurlan et al. 2008). A recent study showed that PANDAS children have significantly lower levels of immunoglobulin A, the major immunoglobulin involved in defense against mucosal pathogens such as GAS (Kawikova et al. 2010).

There were no significant differences in antistreptococcal antibody titers between the two groups during exacerbation episodes, but the findings are in the expected direction with PANDAS compared with non-PANDAS children demonstrating higher ASO and anti-DNAse B titers. Further, a prospective longitudinal study that compared PANDAS versus non-PANDAS OCD/tic disorder cases reported that many clinical exacerbations in PANDAS children are not temporally associated with GAS (Kurlan et al. 2008). Another factor associated with exacerbations in PANDAS children is high levels of psychosocial stress (Lin et al. 2010).

Urinary urgency, hyperactivity, impulsivity, and deterioration in handwriting are characteristics that were significantly more likely to occur in children with PANDAS during their initial episode of neuropsychiatric illness, based upon parental report. There is some evidence to suggest that the etiology of these differentiating symptoms relates to the basal ganglia. The finding of urinary urgency in the PANDAS group is consistent with a study that found a greater likelihood of compulsive/frequent urination in PANDAS children ($n = 41$) compared with non-PANDAS children ($n = 68$) (Murphy 2009). Similarly, a prospective study found that 58% (7 of 12) of PANDAS subjects exhibited daytime urinary urgency, frequency, and wiping behaviors without a urinary tract infection (Murphy and Pichichero 2002). Neuronal control of urination has been shown to be dependent upon basal ganglia function in animal studies, and striatal dopamine levels in particular (Yamamoto et al. 2005, 2009). This is of interest in PANDAS, as emerging evidence supports that antineuronal antibodies in PANDAS may be directed against dopamine receptors (Cunningham, pers. comm., 2010). Also, neuroimaging studies suggest that dopaminergic and volumetric abnormalities in the striatum may play a role in symptoms of hyperactivity and impulsivity (Carmona et al. 2009; Bédard et al. 2010).

Deterioration in handwriting was reported in 61% of PANDAS children compared with none of the non-PANDAS children. Abnormal movements of the fingers and hands that were present in 42% of the PANDAS children and none of the OCD children may contribute to this finding. The significant decline in handwriting is seemingly not explained by motor tics because of the absence of a significant difference in motor tic severity between groups. Change in handwriting is of particular interest in PANDAS, as acute damage to the putamen significantly affects handwriting ability (Pullicino et al. 1994; Capone et al. 2009). Decline in handwriting has been suggested as an objective measure for tracking symptom severity in PANDAS patients (Snider and Swedo 2004). Further, inattention and deterioration of handwriting may be factors contributing to the reported significant decline in school performance in the PANDAS group. Decline in school performance has been previously reported in PANDAS children (Swedo et al. 1998).

MRI analyses of PANDAS patients have demonstrated inflammation of basal ganglia structures during acute periods of illness and subsequent reductions in basal ganglia volumes following successful immunomodulatory therapy (Elia et al. 2005). The present study suggests that particular motor and/or cognitive abnormalities (i.e., deterioration in handwriting, urinary urgency, hyperactivity, and impulsivity), which are hypothesized to be dependent upon basal ganglia function, are overrepresented in PANDAS children compared with children with non-PANDAS OCD. Although it is unclear if these symptoms represent basal ganglia dysfunction or damage due to autoimmune antibodies in PANDAS children, this association deserves further study.

Symptoms of separation anxiety, inattention, mood swings, and oppositional defiant behavior were also significantly more common during their initial episode of neuropsychiatric illness in the children with PANDAS compared with children with non-PANDAS OCD. A significantly higher percentage of children in the non-PANDAS group (33%) met criteria for separation anxiety disorder compared with the PANDAS group (5%). However, significantly more children with PANDAS (74%) compared with non-PANDAS (39%) had separation anxiety as an associated symptom during their sentinel episode of neuropsychiatric illness. As PANDAS children had only a 5% rate of separation anxiety disorder, the finding that 74% showed separation anxiety during their initial episode of illness demonstrates a dramatic change in this symptom dimension during the onset of PANDAS. Separation anxiety and oppositional behaviors were described by Swedo et al. (1998) in their description of 50 children with PANDAS. Similarly, the sudden onset of severe, age-inappropriate separation anxiety was present in 42% (5 of 12) of PANDAS children in another study (Murphy and Pichichero 2002). Case studies also report sudden-onset separation anxiety, mood instability, and inattention in children with PANDAS (Perlmutter et al. 1998; Elia et al. 2005; Mabrouk and Eapen 2009).

A limitation of the present study is that the association of GAS with exacerbations of neuropsychiatric symptoms was assigned retrospectively by review of pediatric records and Medical History Questionnaire for episodes prior to the research assessments. The study design also raises the possibility of recall bias, in that for most initial episodes the parents retrospectively reported the associated symptoms. Further, the blinding of independent evaluators was likely not successful in many cases because of the nature of the symptoms that the participants were describing. In addition, future studies should evaluate ancillary neuropsychiatric symptoms from

the children's perspectives, as well as from the parents' perspectives. Although our sample size is relatively small, PANDAS is a rare condition, and this study directly compares children with PANDAS and children with non-PANDAS OCD.

## Conclusion

This study demonstrates that children with PANDAS display unique clinical characteristics compared with children with childhood-onset OCD beyond the etiological association with GAS infections. This study systematically analyzes these associated symptoms and co-morbid psychiatric disorders in PANDAS children with respect to their childhood-onset OCD counterparts. The results suggest that differentiation between PANDAS and non-PANDAS is not possible based upon the types of obsessions and compulsions or overall severity of OCD, but may be based upon the presence of associated PANDAS symptoms including urinary urgency, hyperactivity, impulsivity, abnormal hand and finger movements, and decline in handwriting, among others. Although the association of these symptoms with PANDAS must be validated through additional research, use of these symptoms in the diagnosis of PANDAS will aid in the differentiation of PANDAS children for research and clinical purposes and ultimately guide our understanding and treatment of this disorder.

## Disclosures

Drs. Bernstein, Victor, and Williams and Ms. Pipal have no conflicts of interest or financial ties to disclose.

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