JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume XX, Number XX, 2017

Pp. 1–12
DOI: 10.1089/cap.2016.0105

Original Article

A Survey of Pediatric Acute-Onset Neuropsychiatric Syndrome Characteristics and Course

Denise Calaprice, PhD,[1] Janice Tona, PhD, OTR,[2]
Ellisa Carla Parker-Athill, MD,[3] and Tanya K. Murphy, MD, MS[3,4]

Abstract

Objective: To date, studies in the area of pediatric acute-onset neuropsychiatric syndrome (PANS; including pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection [PANDAS] and pediatric infection-triggered neuropsychiatric disorder [PITAND]) have been relatively small and hence unable to comprehensively address questions of disease heterogeneity (e.g., by age, gender), comorbidities, and progression. In this study, we investigated an internet survey sample to more fully characterize the phenotypic traits; medical, family, and developmental history; functional challenges; and clinical course associated with PANS.

Methods: Six hundred and ninety-eight patients with clinical diagnoses of PANS were included in this study. Participants, who included parents and legal guardians (for minors) or the PANS patients themselves (for those ages 18 and older), were asked to complete a 146-question survey designed to ascertain medical, developmental, and family history; PANS symptomatology; medical and nonmedical interventions for PANS; PANS course; PANS outcomes; and access to PANS care.

Results: Our results agree with previous findings concerning the core symptoms of PANS as well as its male predominance (65% in this survey) and infection-triggered onset, thus validating the study population. Infection was implicated as the primary inciting factor in 65% of patients; 54% of patients reported an association with group A streptococcus specifically. The results of this survey also revealed new findings, including a surprisingly strong impact of gender and pubertal status on symptom course and chronicity, a high rate of medical comorbidity suggesting generalized immune dysfunction, a profound impact of PANS episodes on functional status, and a role for early resolution of infection through antibiotic treatment in disease course.

Conclusions: This study serves as the first survey of its size to provide insight into the global clinical picture and range of phenotypes of PANS patients. Significant results included the impact of gender and pubertal status on phenotype, affirmation of the role of the immune system in PANS pathology, and the role of timely resolution of infection in clinical outcomes. Understanding how PANS presents in a broad population-based sample, within the limitations of a self-selected and administered online survey, is an important step toward improving diagnosis, creating more targeted treatment options, educating the clinical and research community, and generating hypotheses for future prospective research.

Keywords: obsessive-compulsive disorder, Pediatric Acute-Onset Neurosychiatric Syndrome, pediatric autoimmune neuropsychiatric disorder associated with streptococcus, Tourette's and Tic disorder

Introduction

Historical perspective

The purpose of the present study was to characterize the global clinical picture and range of phenotypes of pediatric acute-onset neuropsychiatric syndrome (PANS) in a large sample. As reflected in studies performed to date, children with PANS experience a sudden onset of obsessive-compulsive behaviors and/or restricted eating following infectious, environmental, or metabolic triggers (Swedo et al. 2012). While this particular disorder is recently named, the link between infection and neuropsychiatric symptoms has been understood since the early 1900s (Murphy et al. 2010b; Hornig 2013; Khandaker et al. 2014), and researchers have continued to identify syndromes in which neuropsychiatric symptoms appear to be immune mediated. Included among these are pediatric infection-triggered neuropsychiatric disorder (PITAND) (Allen et al. 1995), in which sudden-onset obsessive-compulsive disorder (OCD) and tics follow bacterial or viral infection, and the

[1]PANDAS Network, Menlo Park, California.
[2]Department of Rehabilitation Science, University at Buffalo, Buffalo, New York.
Departments of [3]Pediatrics and [4]Psychiatry, University of South Florida, St. Petersburg, Florida.

subset of PITAND called pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS), in which children appear to exhibit neuropsychiatric symptoms as a specific autoimmune response to group-A streptococcal (GAS) infections in a model similar to that of Sydenham's chorea (SC).

A description of 50 children who met criteria for PANDAS was published in 1998 (Swedo et al. 1998). Interestingly, these children were reported to experience neuropsychiatric symptom exacerbations in temporal association not only with GAS infection but also with exposure to a wide variety of other infections. Despite this fact, the association with GAS became the focus of most research in subsequent years, unfortunately rendering some studies difficult to interpret as non-GAS triggers of acute-onset symptoms were often not examined (Kurlan et al. 2008). Confusion and controversy ensued, and in an attempt to clarify matters, experts convened at the National Institutes of Health in 2010 and agreed on criteria for PANDAS (requiring sudden onset associated with GAS infection) and PITAND (a broader category encompassing other infections). Both of these diagnoses then fell under a newer umbrella category called PANS, which also allowed for environmental or metabolic changes as symptom triggers (Fig. 1). To qualify for a diagnosis of PANS, children must present with (1) a dramatic onset of OCD and/or severely restricted food intake that is not better explained by a known neurologic or medical disorder, such as SC, lupus, or Tourette's Disorder, and (2) at least two of the following additional symptoms: anxiety; emotional lability and/or depression; irritability, aggression, and/or severely oppositional behaviors; behavioral (developmental) regression; deterioration in school performance; sensory or motor abnormalities; and/or somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency.

A significant fraction of children with PANS have low levels of immunoglobulins, a disorder that is otherwise rare, in addition to autoantibodies (Frankovich et al. 2015; Murphy et al. 2015a). Medical intervention for children with PANS has therefore included immunomodulatory treatments such as intravenous immunoglobulins (IVIGs) (Allen et al. 1995; Perlmutter et al. 1999; Kovacevic et al. 2015), therapeutic plasmapheresis, or plasma exchange (Allen et al. 1995; Perlmutter et al. 1999; Latimer et al. 2015), as well as antibiotics (Snider and Swedo 2004; Murphy et al. 2015a), with mixed reports on efficacy in relieving symptoms.

Purpose

All PANS and PANDAS studies to date have examined small (i.e., 25–100 participants), generally geographically localized samples of patients who have met restrictive eligibility criteria for clinical research. Although these studies have allowed for the establishment of a basic disease description, they have been too small to address questions of disease heterogeneity (e.g., by age, gender), comorbidities, and progression. This study employed an online survey to gather information about a large widespread sample of PANS patients to more fully characterize the phenotypic traits; medical, family, and developmental history; functional challenges; and clinical course associated with PANS; as well as to capture experiences with interventions, access to medical care, and challenges to quality of life. This study was designed to be hypothesis generating, in that we sought to uncover patterns and trends in all of these areas that could be the subject of future prospective studies of this disease.

This was a broad study with multiple research questions, some of which will be addressed in additional articles. Specifically, for this article, we sought to determine the following:

(1) At what ages and with what signs, symptoms, and severity does PANS typically present?
(2) How rapidly does the initial PANS episode typically commence, and with what triggers (infections and other conditions) is onset typically associated?
(3) What fraction of patients have recurrences beyond the initial episode, and what triggers are typically associated with recurrences? Does the probability or severity of recurrences depend upon whether and how the initial episode was treated?

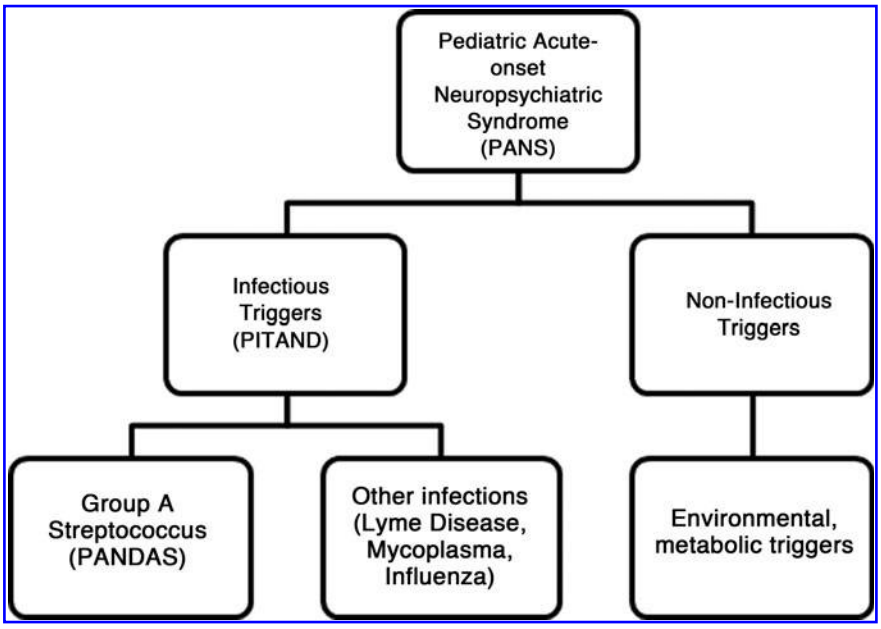

FIG. 1. PANS hierarchy. PANS, Pediatric Acute-Onset Neuropsychiatric Syndrome. Adapted from Swedo et al. (2012).

(4) Among those who experience recurrences, what is the typical frequency and severity, and how do episodes change over time? Does this depend on age and/or sex?
(5) Are any personal or family medical history factors common among patients with PANS?

Methods

Participant recruitment

A wide net was cast in informing potential participants about the study. Following approval from the Social and Behavioral Sciences Institutional Review Board (SBSIRB) at the University at Buffalo, a description of the study was posted on the websites of the PANDAS Network (http://pandasnetwork.org) and the International Obsessive-Compulsive Disorder Foundation (IOCDF; www.ocfoundation.org), along with a link to the survey (hosted at Vovici: www.vovici.com). E-mail invitations were sent to families in the PANDAS Network database, and information about the survey was included in their monthly e-mail newsletters. The survey was also discussed during an internet-based radio show (RadioPandas) and at the Northeastern PANDAS/PANS Parent conference. In addition, postcards and posters describing the study were sent to all healthcare providers known to provide services to children with PANS/PANDAS.

The participant pool was then narrowed as part of the survey process. To access the survey questions, individuals had to be at least 18 years of age and either the parents or legal guardians of at least one minor child diagnosed by a physician as having PANS (including PANDAS or PITAND) or PANS patients themselves. No documentation was examined to confirm the presence of key criteria; however, the following definition of and information about the disorder were offered as part of the survey introduction before the e-consent process:

''For the purposes of this survey, PANS is considered to be Pediatric Acute-Onset Neuropsychiatric Syndrome, which is a disorder in which children experience a sudden and severe onset of obsessive-compulsive thoughts and behaviors along with other symptoms that are thought to be precipitated by an infection, environmental trigger, or metabolic disorder. The disorder is described by Swedo and colleagues (2012) and descriptions can be found here http://intramural.nimh.nih.gov/pdn/PANDAS-to-PANS2012.pdf We consider PANS to include PANDAS, which is Pediatric Acute-Onset Neuropsychiatric Disorder Associated with Strep, and PITAND, which is Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorder. Therefore, when we use the term 'PANS' we mean PANS, PANDAS, and/or PITAND.''

In addition, an IRB-approved electronic informed consent form built into the survey system had to be completed; contact information for study staff was provided in the e-consent form so that questions could be answered before the decision to participate. Participants were not compensated.

Survey instrument

To ensure that the questions were clinically meaningful and constructed so as to maximize correct understanding, the survey instrument was developed by a pediatric psychiatrist with expertise in PANS (T.K.M.) and a clinical research consultant with expertise in survey design (D.C.) and was then reviewed by an occupational therapist with expertise in PANS (J.T.), a PANS parent advocate with no clinical or scientific training, and an epidemiologist, as well as by the IRB. The instrument consisted of 146 questions designed to ascertain medical, developmental, and family history; PANS symptomatology; medical and nonmedical interventions for PANS; PANS course; PANS outcomes; and access to PANS care. A mix of multiple-choice and open-ended questions was used, and conditional logic was applied so that participants only answered questions that pertained to the patient's clinical history (i.e., questions that were logically irrelevant based on answers to previous questions were omitted from the participant's view of the survey). For multiple-choice questions relating to, for example, pubertal status and symptom severity, detailed guidelines were provided (e.g., for puberty based on Tanner's criteria for pubic hair, breast/testicular enlargement, attainment of full adult height) to standardize, as much as possible, the manner in which participants responded. The survey required 20–40 minutes to complete.

Statistical analyses

All data analyses were performed using the JMP® statistical program. Before data analysis, predefined logic checks were performed on the data to clean the sample of records with illogical or incomplete information that called the quality of the reporting into question and/or that rendered the associated data uninterpretable. Through this process, we arrived at a sample of 698 surveys (derived from 753 total submitted surveys) considered to have complete and reliable information. Because participants were not required to answer every question in the survey, the actual number of patients for which information is reported varies by question. For the analyses presented below, patient age was approximated by subtracting the year of birth from the year of survey completion.

Results

Demographic characteristics

Ninety-five percent of surveys were completed by mothers of minor patients; 4% were completed by fathers; and <1% were completed by each of other primary caregivers and patients themselves (ages 18 and over only). The sample comprised 698 patients, 64% of whom were males and 34% of whom were females (sex was not reported for 9 patients) (Table 1). Patients ranged in age from under 2 to 38 years, with a median age of 11, and 80% between ages 7 and 17. Boys in this sample were on average significantly younger than girls (11.4 vs. 12.4 years, $F = 6.34$, $df = 1$, $p = 0.01$) and were significantly more likely to be prepubertal ($\chi^2 = 43.7$, $df = 2$, $p < 0.0001$). Ninety-two percent of the patients currently resided in the United States; 45 states and the District of Columbia were represented, with the largest fractions of patients deriving from California, New York, and Virginia (7% each).

The median age of PANS symptom onset was 8 years for female patients (mean 8.1) and 7 years for males (mean 7.1); median ages at diagnosis were 9 and 10, respectively (Table 1). The sex difference in mean age at onset was significant ($F = 12.59$, $df = 1$, $p = 0.0004$) and remained so when age at survey was included in the model ($F = 7.93$, $df = 1$, $p = 0.005$). Eighty percent of patients were diagnosed between the ages of 5 and 15. Of note, postpubertal patients in this sample had on average been symptomatic for 3.8 years (median 1.5 year) before diagnosis, compared with 2.2 years (median 1 year) for patients currently in puberty and 1.1 (median 0.5 years) for the prepubescent portion of the sample ($F = 3.76$, $df = 2$, $p < 0.0001$).

Table 1. Demographic Characteristics and Age of Onset

	Total	*Females*	*Males*
N (%)	698 (Sex not reported for 9 respondents)	239 (34%)	450 (64%)
Age (years)			
Mean	11.8	12.4	11.4
Median	11	12	11
Range	Under 2–38	Under 2–31	3–38
Pubertal status, % (*N*)			
Prepubertal	52 (357)	39 (92)	59 (262)
In puberty	33 (229)	34 (81)	32 (143)
Postpubertal	15 (107)	27 (65)	9 (41)
Age at onset of PANS symptoms (years), % (*N*)			
Mean	7.5	8.1	7.1
Median	7	8	7
Range	<1 to 18	<1 to 18	<1 to 17
Distribution	<3: 4 (26)	<3: 4 (8)	<3: 4 (17)
	3–11: 85 (537)	3–11: 80 (178)	3–11: 85 (355)
	12–15: 11 (71)	12–15: 14 (31)	12–15: 10 (39)
	16–18: 1 (9)	16–18: 2 (4)	16–18: 1 (5)
Age at PANS diagnosis (years)			
Mean	9.5	10.1	9.2
Median	9	10	9
Range	<1 to 36	<1 to 31	<1 to 36
Lag between age at onset of symptoms and age at diagnosis, mean years (*N*)			
Prepubertal patients	1.1 (328)	0.8 (86)	1.2 (239)
Patients in puberty	2.2 (206)	1.8 (71)	2.5 (131)
Postpubertal patients	3.8 (94)	3.3 (55)	4.7 (38)

PANS, Pediatric Acute-Onset Neuropsychiatric Syndrome.

Developmental/medical and family histories

Developmental diagnoses were common in the sample: 60% of males and 40% of females carried at least one such diagnosis (sex difference: $\chi^2 = 20.4$, df = 1, $p < 0.0001$; Table 2). Of these, attention-deficit/hyperactivity disorder (ADHD) and sensory integration disorder were reported most commonly. Several developmental diagnoses were significantly more common among males than among females, including autism spectrum disorders ($\chi^2 = 28.6$, df = 1, $p < 0.0001$), ADHD ($\chi^2 = 8.15$, df = 1, $p = 0.004$), handwriting disorder ($\chi^2 = 8.29$, df = 1, $p = 0.004$), and speech delays ($\chi^2 = 5.00$, df = 1, $p = 0.03$).

Generalized issues with immune dysfunction were evident from the patients' medical histories (Table 3). The majority of patients were reported to suffer from frequent and/or chronic infections (73%) and allergies (55%), and inflammatory conditions such as chronic sinusitis (39%), joint conditions (38%), eczema (37%), and asthma (27%) were also common. A history of scarlet fever was reported for 15% of patients and rheumatic fever for 4%, although a rheumatic fever diagnosis is exclusionary for PANS. A surgical history was uncommon, except that 36% of the patients had histories of tonsillectomy and/or adenoidectomy.

Immune status (i.e., healthy vs. deficient) had been assessed by diagnostic testing for 431 of the patients. Among these, more than half (53%) were reported to have some form of immunocompromised state. Twenty-five percent reported an immune deficiency diagnosis (most commonly hypogammaglobulinemia [total IgG below normal limit; *N* = 46], but IgG subclass and IgA deficiencies were also common) and an additional 22% reported IgG values in the low-normal range. Six percent of patients had low white blood cell counts.

Table 2. Developmental Diagnoses of Pediatric Acute-Onset Neuropsychiatric Syndrome Patients

Response	*All* (N = *586*), % (N)	*Female* (N = *186*), % (N)	*Male* (N = *391*), % (N)
Attention-Deficit/hyperactivity disorder	25 (149)	18 (34)	29 (114)
Sensory integration disorder	18 (104)	13 (25)	20 (78)
Learning disability	13 (78)	13 (25)	14 (53)
Speech delay	13 (77)	9 (16)	15 (59)
Autism spectrum disorder	12 (73)	3 (5)	17 (65)
Handwriting disorder (dysgraphia)	12 (73)	7 (13)	15 (59)
Other	8 (49)	8 (14)	9 (35)
Math disorder (dyscalculia)	6 (34)	6 (12)	6 (22)
Reading disorder (dyslexia)	4 (25)	5 (9)	4 (16)
Visioperceptual disorder	4 (24)	3 (6)	5 (18)
Coordination disorder	4 (23)	4 (7)	4 (16)
No developmental issues	46 (269)	60 (111)	40 (155)

Table 3. Medical and Family Histories of Pediatric Acute-Onset Neuropsychiatric Syndrome Patients, Parents, and Grandparents (N=624–664)

Condition	*PANS patients, % (N)*	*Maternal history, % (N)*	*Paternal history, % (N)*	*Grandparental history, % (N)*
PANS	100 (698)	4 (28)	1 (9)	1 (9)
Frequent or chronic infection	73 (485)	10 (68)	3 (19)	4 (29)
Allergies	55 (361)	43 (289)	30 (201)	28 (187)
Frequent sore throats	51 (317)	NA	NA	NA
Headaches	48 (313)	NA	NA	NA
Frequent ear infections	44 (288)	NA	NA	NA
Frequent urination	41 (271)	NA	NA	NA
Other chemical or food intolerances or sensitivities	40 (264)	NA	NA	NA
Chronic sinusitis	39 (255)	NA	NA	NA
Joint conditions/pain	38 (246)	NA	NA	NA
Rheumatoid arthritis	NA	4 (26)	1 (7)	17 (112)
Osteoarthritis	NA	5 (31)	2 (15)	26 (172)
Eczema	37 (248)	17 (113)	11 (77)	13 (84)
Unexplained rashes/bumps	37 (244)	NA	NA	NA
Muscle conditions/muscle pain	34 (218)	NA	NA	NA
Frequent constipation	33 (217)	NA	NA	NA
Eye conditions (including need for glasses)	32 (206)	NA	NA	NA
Pneumonia	32 (207)	NA	NA	NA
Dermatologic (skin conditions)	29 (190)	15 (98)	8 (56)	11 (73)
Asthma	27 (176)	16 (106)	11 (71)	16 (109)
Colic	26 (167)	NA	NA	NA
Underweight	24 (158)	NA	NA	NA
Other digestive conditions	23 (149)	NA	NA	NA
Recurrent high fevers	22 (142)	NA	NA	NA
Frequent diarrhea	21 (134)	NA	NA	NA
Irritable bowel syndrome	NA	14 (93)	6 (43)	13 (86)
Neurological issues (other than PANS)	17 (106)	4 (24)	1 (7)	5 (33)
Fibromyalgia	NA	7 (45)	0 (2)	9 (62)
Psychiatric disorder, childhood onset	NA	5 (32)	3 (21)	3 (18)
Psychiatric disorder, adult onset	NA	6 (38)	4 (28)	13 (90)
Scarlet fever	15 (98)	7 (46)	2 (11)	8 (56)
Numerous dental caries	15 (98)	NA	NA	NA
Heart condition/heart murmur	14 (91)	15 (98)	4 (30)	34 (228)
Overweight	14 (93)	NA	NA	NA
Anemia	13 (81)	16 (108)	1 (8)	8 (56)
Delayed growth	13 (82)	NA	NA	NA
Head injury	10 (65)	NA	NA	NA
Hypothyroid	7 (47)	16 (106)	4 (25)	18 (123)
Lung conditions	6 (36)	NA	NA	NA
Kidney/bladder conditions	6 (39)	NA	NA	NA
MRSA skin infections	6 (38)	NA	NA	NA
Celiac disease	5 (33)	NA	NA	NA
Rheumatic fever	4 (24)	3 (17)	1 (7)	14 (96)
Hematologic (blood conditions)	4 (27)	2 (11)	1 (4)	5 (34)
Other endocrine (including diabetes)	3 (22)	5 (35)	4 (24)	31 (208)
Hyperthyroid	1 (9)	3 (21)	1 (4)	6 (40)
Cancer	0 (2)	3 (23)	2 (16)	49 (327)
Immune deficiency	NA	4 (29)	1 (9)	2 (11)
Lupus	NA	2 (11)	0 (0)	3 (21)
Multiple sclerosis	NA	1 (4)	0 (1)	1 (7)
Crohn's/ulcerative colitis	NA	1 (6)	2 (11)	5 (34)
Developmental disorder	NA	1 (4)	1 (4)	0 (3)
Tourette's	NA	1 (4)	0 (1)	1 (5)

MRSA, methicillin-resistant Staphlococcus aureus; NA, not assessed; PANS, Pediatric Acute-Onset Neuropsychiatric Syndrome.

Autoimmune conditions were common among patients' first-degree relatives, particularly among mothers, 20% of whom were reported to have at least one serious autoimmune diagnosis (multiple sclerosis, Crohn's, PANS, lupus, rheumatoid arthritis, and/or hypothyroidism; Table 3). Rheumatic fever was reported in 3% of mothers and 1% of fathers, and 14% of patients had at least one grandparent with this diagnosis. Twelve percent of PANS patients (N=78) had at least one sibling with PANS. Interestingly, no psychiatric diagnoses were reported among first-degree relatives for the majority of PANS patients. A childhood-onset psychiatric

history was reported for only 5% of mothers and 3% of fathers, and an adult-onset psychiatric history was reported for only 6% of mothers and 4% of fathers.

Presenting characteristics of PANS

For the vast majority of patients (88%), disease onset was sudden, defined as ramping up to a concerning level within 3 days either from a starting point of no symptoms (for 64%) or in the context of existing symptoms or developmental issues (for 24%). Four percent of the patients were too young at the onset of symptoms to discern (parents reported at first assuming patients were just experiencing terrible twos, e.g.). For only 8% of patients, a gradual onset was reported.

The lives of the patients in this study were seriously impacted by their presenting episodes. For most, initial PANS episodes were severe (defined as rendering patients unable to perform age-typical activities; 30%) or incapacitating (defined as rendering patients unable to perform basic tasks of daily living; 27%). Nearly all of the remaining patients were moderately affected by their initial episodes, that is, unable to perform age-typical activities in a normal manner. Among patients whose caregivers could recall ($N=624$), the initial episodes lasted more than 12 weeks for 49% and between 2 and 12 weeks for nearly all of the remainder (44%).

For 70% of patients whose caregivers could recall ($N=623$), the initial PANS episode was associated in time with a confirmed infection (defined as at the same time as or shortly preceding or following a clinical diagnosis of an infection); for an additional 24%, an infection was suspected, but not confirmed. Among those who reported this association, GAS was the infection most likely to have been confirmed (54%, $N=314$) or suspected (8%, $N=49$), followed distantly by sinusitis (unspecified agent; 10% confirmed, 4% suspected), mycoplasma (8%, 4%), colds (7%, 4%), and a variety of other infections confirmed in 5% or fewer of respondents each. Lyme disease (*Borrelia burgdorferi*) was confirmed or suspected in 33 patients (5%), and Lyme coinfection was confirmed or suspected in 26 (4%).

For those with confirmed or suspected GAS, specific methods of ascertainment were requested by the survey and could include rapid strep test (75%, $N=267$ tested), culture (81% of 194 tested), other culture (e.g., perianal, vaginal, skin; 72% of 22 tested), anti-streptolysin O antibody (ASO) (84% of 147 tested), streptozyme (85% of 33 tested), and/or anti-DNAse B (88% of 118 tested). In total, 88% of these subjects (321 who gave specific data) reported a positive rapid strep test, throat culture, or other culture. Interestingly, even among those in whom streptococcus was confirmed by other methods, only 89% of those for whom ASO was tested ($N=122$) had elevated titers; elevated titers were found in 94% of those with apparently healthy (or untested) immunity ($N=86$), but only 77% of the immune deficient subset ($N=26$) and 70% of the subset with low-normal IgG ($N=10$). Ninety percent of patients with infection-associated onset reported receiving antibiotics for the infection, with 59% seeing a resolution of infection and 31% seeing a resolution of PANS symptoms following this intervention.

Although the survey did not specifically ask about this, it was quite common for respondents to report in the comment field of this section of the survey that symptom onset was associated with multiple immune challenges at the same time or in quick succession, that is, multiple coinfections, infection plus vaccination, and/or infection plus allergic reaction.

Nearly half of patients (48%) never experienced a complete return to the pre-episode state after the initial episode. Those who achieved complete resolution of the initial inciting infection with antibiotic treatment were significantly more likely to completely return to the pre-episode state when compared with patients who did not have complete resolution of their infection (62% vs. 49%; $\chi^2=4.73$, $\mathrm{df}=1$, $p=0.03$; analysis excludes patients still receiving antibiotic treatment for the initial episode or for whom antibiotic treatment status/result was unknown).

PANS recurrences

Eighty-seven percent of patients had experienced at least one episode of PANS beyond the presenting episode. The probability of recurrence was significantly lower among those who had achieved complete resolution of infection with antibiotic treatment for the initial episode (84%) when compared with those who had not (92%; $\chi^2=4.99$, $\mathrm{df}=1$, $p<0.03$). When recurrences were triggered by infections, GAS was by far the agent most likely to have been confirmed (60% of patients) or suspected (36%) as the inciting infection for at least one recurrence. A significant percentage of patients were reported to have experienced recurrences in response to colds (30%), sinusitis (29%), mycoplasma (28%), influenza (20%), Epstein–Barr virus (EBV; 10%), and a variety of other infections (e.g., pneumonia, coxsackie, varicella, and MRSA). Additionally, 74% were reported to experience PANS symptoms following contact with infected family members or friends, even in the absence of apparent infection in the patient.

Although recurrences were frequently associated with infections (85% endorsed at least one recurrence with an infection association), most patients (61%) experienced at least some that were not. These patients were reported to experience PANS flares in response to a variety of environmental exposures, including particular foods, additives, allergens, weather/season (with winter being the worst), and lighting. When asked about flares in response to vaccines, many participants were not able to comment since they either could not recall or the patients did not receive regular vaccinations. Of the 300 patients for whom information was available, vaccines appeared to precipitate a flare of PANS symptoms in half ($N=150$). Although participants were not specifically asked to name the triggering vaccination(s), 23% mentioned flu vaccines in the open-ended comment field in this section of the survey. Some patients had not been vaccinated since the PANS diagnosis, either because the subject had not come up or, more commonly, because of fears or guidance from medical practitioners that vaccines might lead to symptom flares.

Of the 298 patients whose initial episodes were not associated with streptococcal infections and for whom later infection-triggered episodes were reported, 63% had experienced episodes associated with varying levels of streptococcal confirmation or with suspected streptococcus. Thus, PANDAS appears commonly to emerge in patients who initially present with non-GAS triggers. Similarly, of the 363 patients whose initial episodes were associated with streptococcal infections, 55% of those reporting later episodes and who could recall triggers ($N=300$) stated that at least some episodes did not appear to be associated with infections at all, and many reported infectious triggers other than GAS, most commonly colds (32%), sinusitis (29%), mycoplasma (24%), and influenza (23%).

Episode severity was reported to have changed over time for the vast majority (70%) of patients, although there was division as to whether these changes represented worsening (26%) or improvement (44%). Thirty percent reported no change in severity, including 7% who also reported no changes in the character of

symptoms, and 23% who reported some change in the character of symptoms. Similarly, the duration of episodes was reported to have changed for most patients (76%), although again there was division as to whether these changes represented lengthening (31%) or shortening (45%). In the open-ended comment field associated with this section of the survey, most improvements were attributed to successful management strategies. (Participant-reported success of various treatment strategies will be the subject of a future publication.)

PANS symptoms and impact on functional status

Patients varied considerably in the severity and nature of their symptomatology. At least 75% had some history of generalized anxiety, obsessive-compulsive symptoms, mood lability, irritability, excessive worry, rages/meltdowns, sadness, sensory defensiveness, handwriting deterioration, defiance, and/or fatigue, although only a small percentage of patients experienced these symptoms chronically (Table 4). Tics were experienced by more than half of patients and psychotic or manic symptoms by more than one-third. Somatic symptoms such as stomach, muscle, and joint pain had also been experienced by a majority of the patients. The average severity of most PANS symptoms was in the moderate range. Anxiety and other mood symptoms were on average more severe than were somatic or functional symptoms such as stomach, muscle, and joint pain.

As can be seen in Table 5, the lifetime frequencies of most symptoms were not substantially different in postpubescent compared with prepubescent patients, suggesting that most symptoms appear at least episodically from an early age. Important exceptions included panic attacks and self-injurious behavior, which had been experienced by significantly more postpubescent than prepubescent patients (panic attacks: 71% vs. 46%, $\chi^2 = 18.96$, df = 1, $p < 0.0001$; self-injurious behavior: 55% vs. 35%, $\chi^2 = 12.97$, df = 1, $p < 0.001$). Additionally, postpubescent patients were characterized by higher levels of symptom severity and chronicity compared with others. In the prepubescent subset, at least one-quarter of the patients experienced chronic generalized anxiety (34% of females, 29% of males) and/or chronic OCD symptoms (31% of females, 22% of males) (Table 5). In the postpubescent subset, in contrast, the fraction with chronic generalized anxiety was 62% among females and 32% among males, and approximately half reported chronic OCD (49% of females; 54% of males). Females in this age group were more likely to report chronicity of psychiatric symptoms than were males, with at least one-quarter also reporting each of chronic excessive worry (44%), irritability (42%), chronic mood lability (35%), sadness (34%), fatigue (33%), insomnia (33%), social anxiety (27%), and specific phobias (26%). Males were more likely to report chronicity of a slightly different set of symptoms, with at least one-quarter reporting chronic handwriting deterioration (31%), irritability (28%), rage/meltdowns (26%), insomnia (26%), and loss of math skills (26%).

The overall burden of disease as reflected in this survey was great, but patients varied widely in the level of impact suffered (Tables 6 and 7). At the extremes, 19% of patients were reported to have had no symptom-free days since PANS onset, while 19% were asymptomatic for more than 75% of days. At some point during the course of the disease, nearly half of patients (46%) had experienced an incapacitating episode and an additional 31% had experienced at least one severe episode (Table 6); postpubescent patients were significantly more likely to have suffered severe or incapacitating episodes than were those in prepubescence ($\chi^2 = 10.9$, df = 1, $p = 0.01$; effect of duration of illness was also statistically significant in the multivariate model, but age was not). In fact, typical (''average'') episodes were severe or incapacitating for most postpubescent patients, but most prepubescent patients generally experienced

Table 4. Pediatric Acute-Onset Neuropsychiatric Syndrome Symptoms: Frequency and Average Severity ($N = 652$–686)

	Any history, % (N)	*Chronic,* % (N)	*Average severity,*[a] % (N)
General anxiety	96 (655)	37 (252)	5.5
Obsessive-compulsive symptoms	94 (645)	34 (230)	5.4
Mood lability (moodiness)	90 (602)	22 (145)	5.2
Irritability	89 (598)	20 (135)	5.1
Excessive worry	87 (588)	25 (170)	5.2
Rage/meltdowns	84 (563)	13 (88)	5.3
Sadness	83 (552)	14 (96)	4.6
Sensory defensiveness (e.g., to sound, light, clothing)	79 (534)	23 (152)	4.7
Handwriting deterioration	76 (508)	18 (121)	5.0
Defiance	75 (501)	13 (89)	4.9
Fatigue	75 (499)	20 (130)	5.1
Specific phobias	74 (489)	17 (110)	5.0
Tics—motor (other than eye)	71 (474)	12 (80)	4.5
Bizarre thoughts or behavior	69 (461)	8 (54)	4.5
Insomnia	67 (450)	16 (105)	4.7
Hyperactivity	66 (437)	13 (83)	4.6
Loss of math skills	66 (435)	14 (95)	4.8
Stomach/abdominal pain	64 (426)	12 (83)	4.1
Brain fog/confusion	64 (427)	13 (87)	4.8
Social anxiety (very shy)	63 (421)	16 (109)	4.4
Aggression toward others	59 (398)	5 (35)	4.1
Panic attacks	57 (378)	8 (55)	4.8
Nightmares	57 (374)	5 (34)	3.7
Tics—vocal	57 (378)	10 (66)	4.3
Frequent urination	56 (367)	8 (52)	4.4
Joint pain	53 (353)	10 (65)	3.7
Tics—eyes	50 (334)	10 (65)	4.0
Restrictive eating, eating fears, fear of weight gain	48 (320)	9 (58)	4.5
Loss of appetite	48 (314)	6 (38)	4.1
Muscle pain	47 (308)	7 (44)	3.7
Self-injurious behavior	40 (264)	4 (24)	3.8
Bed-wetting (after potty training complete)	38 (256)	5 (33)	4.1
Night terrors	37 (245)	3 (19)	4.0
Speech disfluencies (e.g., stuttering, stammering)	37 (240)	5 (30)	3.7
Mania/hypomania (grandiose or high behavior or feelings)	37 (247)	5 (31)	4.1
Hallucinations/hearing or seeing things that are not there	36 (233)	4 (23)	3.9
Daytime urinary incontinence (peeing in pants), after potty training has been complete	31 (202)	3 (20)	3.6
Encopresis (soiling), after potty training	13 (84)	1 (9)	3.5
Mutism (no speaking at all)	12 (77)	2 (10)	4.5
Bulimia/binge eating	8 (52)	1 (8)	4.1

[a]Scale of 1 = minimal to 10 = very severe/incapacitating.

TABLE 5. PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME SYMPTOMS IN PREPUBERTAL (N=246–256 MALES; 82–91 FEMALES) AND POSTPUBERTAL PATIENTS (N=56–63 FEMALES; 37–41 MALES), BY SEX

	Any history				*Chronic*				*Average severity*[a]			
	Prepubertal		*Postpubertal*		*Prepubertal*		*Postpubertal*		*Prepubertal*		*Postpubertal*	
	F, % (N)	*M*, % (N)	*F*, % (N)	*M*, % (N)	*F*, % (N)	*M*, % (N)	*F*, % (N)	*M*, % (N)	*F*	*M*	*F*	*M*
General anxiety	98 (88)	93 (237)	98 (60)	100 (41)	34 (31)	29 (74)	62 (38)	32 (13)	5.4	5.3	5.8	5.8
Obsessive-compulsive symptoms	93 (85)	91 (231)	97 (61)	98 (40)	31 (28)	22 (55)	49 (31)	54 (22)	5.3	5.0	5.6	6.0
Mood lability (moodiness)	95 (84)	93 (232)	87 (52)	85 (35)	26 (23)	14 (35)	35 (21)	22 (9)	5.0	5.0	5.6	4.9
Irritability	93 (80)	88 (221)	92 (55)	85 (34)	12 (10)	12 (29)	42 (25)	28 (11)	4.8	5.0	5.6	5.0
Excessive worry	96 (85)	84 (213)	90 (53)	85 (33)	34 (30)	17 (44)	44 (26)	21 (8)	5.2	5.0	5.5	5.2
Rage/meltdowns	87 (75)	87 (220)	82 (50)	79 (31)	9 (8)	9 (23)	23 (14)	26 (10)	4.9	5.1	5.6	5.4
Sadness	80 (70)	80 (200)	90 (53)	75 (30)	14 (12)	8 (20)	34 (20)	20 (8)	4.6	4.4	5.1	5.0
Sensory defensiveness	78 (68)	80 (203)	78 (47)	77 (30)	24 (21)	17 (44)	22 (13)	23 (9)	4.9	4.5	5.2	4.8
Handwriting deterioration	65 (57)	80 (201)	64 (38)	79 (31)	8 (7)	13 (33)	15 (9)	31 (12)	4.1	5.0	4.1	6.1
Defiance	72 (63)	78 (198)	73 (44)	64 (25)	10 (9)	11 (29)	15 (9)	18 (7)	4.5	4.9	4.9	5.5
Fatigue	75 (65)	66 (163)	75 (46)	87 (33)	16 (14)	12 (29)	33 (20)	13 (5)	5.0	4.5	5.9	5.1
Specific phobias	87 (42)	67 (28)	72 (77)	70 (166)	24 (21)	12 (30)	26 (15)	18 (7)	5.0	4.8	5.3	5.2
Tics—motor (other than eye)	55 (48)	76 (190)	52 (31)	80 (32)	10 (9)	12 (31)	12 (7)	15 (6)	4.1	4.8	4.7	4.4
Bizarre thoughts or behavior	67 (58)	69 (173)	69 (41)	72 (28)	5 (4)	6 (15)	15 (9)	10 (4)	4.4	4.1	5.4	5.2
Insomnia	65 (58)	59 (147)	69 (42)	74 (28)	9 (8)	10 (25)	33 (20)	26 (10)	4.3	4.6	5.5	6.0
Hyperactivity	61 (52)	80 (199)	46 (26)	43 (17)	7 (6)	18 (45)	9 (5)	5 (2)	3.8	5.1	4.4	4.8
Loss of math skills	62 (51)	59 (147)	63 (38)	74 (29)	7 (6)	8 (19)	22 (13)	26 (10)	4.0	4.6	5.3	5.8
Stomach/ abdominal pain	75 (66)	59 (149)	67 (41)	44 (17)	19 (17)	10 (26)	13 (8)	3 (1)	4.3	4.1	4.8	4.0
Brain fog/ confusion	52 (45)	61 (150)	69 (43)	65 (26)	7 (6)	9 (21)	19 (12)	13 (5)	4.2	4.4	5.4	4.9
Social anxiety (very shy)	63 (55)	58 (147)	65 (40)	71 (27)	19 (17)	10 (24)	27 (17)	21 (8)	3.9	4.1	5.2	4.9
Aggression toward others	63 (55)	62 (157)	48 (29)	53 (21)	5 (4)	4 (9)	8 (5)	5 (2)	3.8	4.1	4.4	3.8
Panic attacks	58 (52)	42 (106)	71 (42)	70 (28)	12 (11)	4 (9)	22 (13)	15 (6)	4.8	4.6	5.8	5.2
Nightmares	62 (53)	57 (143)	56 (34)	49 (19)	4 (3)	6 (15)	7 (4)	0 (0)	3.4	4.1	3.7	4.2
Tics—vocal	44 (38)	67 (164)	37 (23)	64 (25)	8 (7)	12 (29)	8 (5)	10 (4)	4.6	4.5	3.8	3.7
Frequent urination	60 (52)	55 (137)	48 (28)	37 (14)	7 (6)	6 (16)	12 (7)	5 (2)	4.5	4.4	4.7	4.8
Joint pain	49 (43)	50 (124)	55 (33)	32 (12)	9 (8)	4 (10)	15 (9)	8 (3)	3.6	3.3	3.9	4.1
Tics—eyes	40 (35)	58 (144)	38 (22)	60 (24)	7 (6)	13 (32)	10 (6)	13 (5)	3.8	4.3	4.5	3.7
Restrictive eating, eating fears, fear of weight gain	56 (49)	40 (101)	51 (31)	41 (16)	9 (8)	6 (15)	10 (6)	10 (4)	4.8	4.3	4.9	4.6
Loss of appetite	49 (42)	47 (116)	53 (30)	42 (16)	4 (3)	4 (10)	12 (7)	5 (2)	4.6	3.8	4.8	4.1
Muscle pain	42 (36)	42 (105)	56 (33)	32 (12)	9 (8)	3 (8)	14 (8)	5 (2)	4.1	3.4	3.7	4.2
Self-injurious behavior	32 (28)	36 (90)	59 (36)	50 (20)	2 (2)	1 (3)	15 (9)	3 (1)	3.3	3.3	4.8	4.8
Bed-wetting (after potty training has been complete)	38 (33)	46 (117)	22 (13)	26 (10)	6 (5)	6 (16)	2 (1)	3 (1)	3.3	4.4	5.7	5.4
Night terrors	32 (28)	39 (98)	31 (18)	38 (15)	5 (4)	3 (7)	3 (2)	0 (0)	3.7	4.1	4.7	5.5
Speech disfluencies (e.g., stuttering, stammering)	27 (23)	39 (99)	32 (19)	43 (16)	3 (3)	4 (10)	7 (4)	3 (1)	4.5	3.4	3.8	3.7

(*continued*)

Table 5. (Continued)

	Any history				*Chronic*				*Average severity*[a]			
	Prepubertal		*Postpubertal*		*Prepubertal*		*Postpubertal*		*Prepubertal*		*Postpubertal*	
	F, % (N)	*M*, % (N)	*F*, % (N)	*M*, % (N)	*F*, % (N)	*M*, % (N)	*F*, % (N)	*M*, % (N)	*F*	*M*	*F*	*M*
Mania/hypomania (grandiose or high behavior or feelings)	38 (33)	32 (79)	40 (24)	44 (17)	3 (3)	4 (10)	3 (2)	0 (0)	4.1	3.9	4.9	4.2
Hallucinations/ hearing or seeing things that are not there	31 (27)	31 (76)	41 (24)	43 (16)	1 (1)	3 (8)	7 (4)	3 (1)	4.0	3.9	4.9	3.5
Daytime urinary incontinence (peeing in pants) after potty training has been complete	36 (31)	35 (85)	12 (7)	13 (5)	5 (4)	4 (10)	0 (0)	0 (0)	3.2	3.8	5.0	2.0
Encopresis (soiling), after potty training	9 (8)	16 (39)	10 (6)	8 (3)	1 (1)	1 (3)	0 (0)	0 (0)	4.3	3.7	1.8	2.3
Mutism (no speaking at all)	10 (9)	8 (19)	21 (12)	8 (3)	0 (0)	1 (2)	5 (3)	0 (0)	4.2	3.6	6.0	4.0
Bulimia/binge eating	2 (2)	5 (13)	12 (7)	11 (4)	0 (0)	0 (1)	5 (3)	3 (1)	6.0	4.0	5.0	3.4

[a]Scale of 1 = minimal to 10 = very severe/incapacitating.

mild to moderate episodes (Table 7). Interestingly, prepubescent males were reported to have severe or incapacitating episodes less often than were prepubescent females, but among postpubescent patients, the opposite was true (Table 7).

Only 23% of patients had been able to perform adequately in a typical preschool/classroom setting without special accommodation (including 29% of prepubertal patients; 17% of pubertal patients; and 15% of postpubertal patients), while 35% reported needing to miss at least a week of school at a time during exacerbations (27% prepubertal; 43% in puberty; 45% postpubertal), and 9% reported not having attended school at all during exacerbations (7% prepubertal; 10% in puberty; 12% postpubertal). Thirty-three percent of patients were able to attend school only with special accommodations. The effect of pubertal status on school functioning (i.e., ability to attend school with/without special accommodations) related to PANS symptoms was highly significant ($\chi^2 = 31.79$, $p < 0.0001$).

Discussion

Although several attempts have been made to characterize the PANS phenotype, the existing body of research has been limited by small sample sizes, restrictive eligibility criteria, and other methodological challenges, leading to an inconsistent and generally incomplete picture of this condition. This situation has impacted patients in a profoundly negative way as clinicians have struggled to identify and appropriately treat affected patients, while patients and caregivers have been left to search for answers through the internet and family-organized support groups. This study, the first in-depth survey of PANS ever conducted, sought to begin to

Table 6. Impact of Worst Episode on the Functional Status of Pediatric Acute-Onset Neuropsychiatric Syndrome Patients

Pubertal status	*Sex of patient*	*Incapacitating, % (N)*	*Severe, % (N)*	*Moderate, % (N)*	*Mild, % (N)*	*Responses*
All	All	46 (278)	31 (184)	19 (118)	4 (25)	592
Prepuberty	Female	31 (23)	39 (29)	27 (20)	4 (3)	75
	Male	33 (76)	36 (82)	25 (58)	6 (14)	230
In puberty	Female	60 (39)	25 (16)	11 (7)	5 (3)	65
	Male	54 (70)	30 (39)	13 (17)	2 (3)	129
Postpuberty	Female	68 (38)	18 (10)	11 (6)	4 (2)	56
	Male	68 (25)	14 (5)	19 (7)	0 (0)	37

Incapacitating: interferes with ability to perform basic tasks of daily living; Mild: noticeable to a casual observer, but does not interfere with normal performance of age-typical activities; Moderate: interferes with normal performance of age-typical activities; Severe: unable to perform age-typical activities.

Table 7. Impact of Average Episode on the Functional Status of Pediatric Acute-Onset Neuropsychiatric Syndrome Patients

Pubertal status	*Sex*	*Incapacitating, % (N)*	*Severe, % (N)*	*Moderate, % (N)*	*Mild, % (N)*	*Minimal, % (N)*	*Responses*
All	All	6 (35)	19 (119)	44 (268)	26 (156)	5 (29)	593
Prepuberty	Female	7 (5)	15 (11)	41 (31)	35 (26)	3 (2)	75
	Male	2 (4)	10 (23)	49 (112)	34 (78)	6 (13)	230
In puberty	Female	9 (6)	22 (14)	40 (26)	18 (12)	11 (7)	65
	Male	8 (10)	22 (29)	46 (60)	20 (26)	4 (5)	130
Postpuberty	Female	9 (5)	38 (21)	41 (23)	9 (5)	4 (2)	56
	Male	14 (5)	43 (16)	24 (9)	19 (7)	0 (0)	37

Incapacitating: interferes with ability to perform basic tasks of daily living; Mild: noticeable to a casual observer, but does not interfere with normal performance of age-typical activities; Moderate: interferes with normal performance of age-typical activities; Severe: unable to perform age-typical activities.

remedy this situation by providing insight into both the typical global clinical condition and range of phenotypes of PANS patients. Since many PANS patients are still searching for a proper diagnosis well into the course of the disorder, an important aspect of this research was to examine changes in phenotype with pubertal status and progression. It is the hope of the authors that an improved understanding of the spectrum of phenotypes will lead to greater consideration of the possibility of PANS when children and adolescents present with psychiatric symptoms.

The results of this survey reinforced previously published observations, while also further defining the typical phenotype and highlighting important groups of patients who might present atypically. Known core features of PANS reflected in the survey results included a predominance of males and a sudden and prepubertal onset of symptoms associated with some type of trigger, most commonly a confirmed infection. Similar to Murphy et al. (2015a), GAS infection was noted as the inciting agent in more than half of patients, although many also reported that exacerbations had been precipitated by other infections and environmental triggers. Of the PANS primary criteria, nearly all survey respondents reported OCD symptoms and about half reported food restriction/weight issues. A wide range of other previously reported symptoms (Murphy et al. 2015b) was also reported in this sample, with at least three-quarters of patients reported to have experienced irritability, excessive worry, rage/meltdowns, sadness, sensory defensiveness, handwriting deterioration, defiance, and/or fatigue. Similar to other studies (Murphy et al. 2015b; Tona et al. 2017), the reported impairment from this constellation of symptoms was high.

The pathophysiology of PANS is presumed to involve immune dysfunction, particularly a role for autoantibodies with neuropsychiatric impacts. However, the results of this survey demonstrate that immune dysfunction in PANS patients is typically not restricted to this mechanism, but in fact quite pervasive. Seventy-three percent of PANS patients were reported to suffer from frequent and/or chronic infections, and of the 431 patients who had been tested for immune competence, more than half reported some form of immunocompromised state, most commonly including low immunoglobulin levels. For comparison, only $\sim$1/1200 people in the general U.S. population are believed to suffer from primary immune deficiency (Boyle and Buckley 2007). The majority of patients were also reported to suffer from additional autoimmune and inflammatory conditions, including allergies, chemical and food sensitivities, eczema, joint conditions and pain, and asthma.

Similar to previous reports (Murphy et al. 2010a; Dalsgaard et al. 2015), high rates of autoimmune disorders were also reported among first-degree relatives, notably affecting 20% of patients' mothers. In these studies, over 20% of mothers were reported to have serious autoimmune diagnoses, while the national average among women is closer to 12.5% (Fairweather and Rose 2004). Although this suggests the possibility of maternal effects during fetal development, the difference between mothers and fathers may also be due to the fact that the vast majority of those completing the survey were mothers and/or the generally higher rates of autoimmune disease in females compared with males. In keeping with the possible role of a particular vulnerability to GAS infections in PANS patients, rheumatic fever was reported much more commonly among mothers (3%) and grandparents (14%) of the patients in this survey than would be expected given that the average incidence of rheumatic fever (RF) in developed communities is <5/100,000 population (World Health Organization 2004). In contrast, the reported rate of a family history of psychiatric disorders was surprisingly low.

The survey results also highlighted presentations that may be less typical and hence less likely to achieve prompt diagnosis. For example, a significant minority of patients experienced a gradual onset of symptoms, and for an additional subset, onset occurred at such a young age that its acuteness was difficult to ascertain. These subsets warrant further investigation. The high rate of background developmental comorbidities, particularly in boys, may also cloud the acuteness of onset in many patients. Further frustrating evaluation of the acute-onset criterion for diagnosis is the level of chronicity of some psychiatric symptoms within this population: at least one-quarter of the patients in this sample experienced chronic generalized anxiety, OCD symptoms, and/or excessive worry, and in the postpubescent subset, the majority experienced psychiatric symptoms chronically. Postpubescent females were more likely to report chronicity of mood and anxiety symptoms than were males and generally experienced such symptoms with greater severity, whereas males were more likely to report chronicity and severity of irritability, rage/meltdowns, and functional symptoms such as handwriting deterioration and loss of math skills. The reasons for increased chronicity in the postpubescent subset are unknown, but may include increased awareness of symptoms, coinfection influences (e.g., Epstein Barr Virus), hormonal effects, or the natural course of the disorder. Postpubescent patients in this sample had also sustained a longer lag between first symptoms and diagnosis than other groups, suggesting the possibility that increased chronicity may result from delays in diagnosis and treatment and/or the reverse.

Complicating diagnosis further, 11% of the patients in this study had nonelevated ASO titers, even when GAS infections had been confirmed by other means. Although this result is not surprising given this population's relatively high rate of failure to produce typical antibody responses to infections and prior evidence

suggesting that many youth with a documented GAS infection fail to demonstrate elevated streptococcal titers (Kaplan et al. 1971; Johnson et al. 2010), it may lead to inappropriate rejection of a PANDAS diagnosis even in the context of an acute-onset psychiatric episode and suspected GAS infection when the expected ASO elevations are not observed. Further blurring the picture for clinicians expecting PANS patients to demonstrate clean associations between infectious triggers and acute episodes, most patients also reported that symptoms could be triggered by environmental contributors, including specific foods, weather changes, exposures to infected friends or family members, and vaccines. These observations may speak to the general role of immune activation (as opposed to simply infection) in symptomatology and disease course since all of these triggers are known to impact levels of inflammatory cytokines in susceptible individuals in a manner similar to that seen with infection.

Despite these challenges, the importance of prompt diagnosis is critical. Not only can prompt diagnosis and treatment lead to short-term resolution of symptoms, but it may also impact the course of disease in the long term. Although most patients in this survey never completely returned to their preonset state after the initial PANS episode, those who achieved complete resolution of the initial inciting infection with antibiotic treatment had a significantly higher probability of remission than did those whose inciting infection was not resolved with antibiotic treatment and were also significantly less likely to experience recurrences. Given the very high rate of functional impairment seen in PANS patients, particularly as they progress into the critical teen years, the importance of early identification and intervention cannot be overstated.

Limitations

This study possessed several limitations, most significant of which may be the reliance on participant recall and lack of clinical confirmation of diagnosis and medical features, as well as ascertainment bias as parents of children whose symptoms are resolved were less likely to find this survey. Additionally, pubertal status and symptom and episode severity ratings were based on participant interpretations, and although detailed guidelines were provided to assist with classification, some lack of consistency in interpretation of these guidelines may have impacted some of the observations.

Conclusions

This survey was the first to provide insight into the range of PANS phenotypes seen in a large, community-based sample. Findings regarding the impacts of gender and pubertal status, medical comorbidities, and the role of timely resolution of infection in clinical outcomes should support improved diagnosis and treatment, and serve to generate hypotheses for future prospective research.

Clinical Significance

This study, while exploratory, has important clinical implications for the diagnosis and treatment of patients with PANS. Although the results reported herein support current diagnostic criteria, including the sudden and severe onset of OCD and/or tic symptoms, the co-occurrence of other neuropsychiatric and developmental symptoms and comorbidities, and an infection-mediated onset, they also highlight common features that go beyond the current diagnostic criteria to create a more global picture of the condition that may aid in differential diagnosis. These include a high rate of generalized immune dysfunction, including both deficiencies and autoimmunity; an increased rate of familial, and particularly maternal, autoimmunity and rheumatic fever (but low rates of familial neuropsychiatric pathology); a high rate of chronicity in symptom course particularly among postpubescent patients; and the responsiveness of symptoms to a wide range of environmental and infectious insults. Given the high incidence in this population of immune deficiencies, allergies, and sensitivities, along with the likelihood of PANS flares with infections and exposures, a medical evaluation (Chang et al. 2015) should be considered for patients in whom a PANS diagnosis is confirmed or suspected.

While it is appreciated by a small percentage of clinicians that timely antibiotic intervention and eradication of the inciting infection are integral in the treatment of PANS, this study, for the first time, highlights the importance of such treatment in the long-term clinical picture of PANS. Although PANS is typically recurrent with some chronic features, the data reported herein suggest that early and aggressive treatment of infection may decrease both the likelihood of residual symptoms and the likelihood of recurrence, potentially preventing the high levels of functional impairment seen particularly in the postpubertal years. Having increased vigilance for new infections and exposure to GAS is likely also helpful to minimize the impact of recurrence of PANS symptoms.

Several trends identified in this survey would benefit from additional research. The impact of early diagnosis and treatment on disease course is clearly an area that deserves further study, as is the impact of noninfectious symptom triggers, including vaccinations. Family history studies using more comprehensive techniques for family assessment would also be of interest, in particular to examine the possibility of maternal effects. Future publications based on this survey will focus on experiences with specific traditional and alternative treatment modalities and on access to care and the clinical and functional impacts thereof.

Acknowledgments

The authors would like to thank PANDAS Network for their support in survey review and study execution, Heather Lindstrom, PhD, for support in protocol development, and the participating families.

Disclosures

T.K.M. reports grants from Auspex Pharmaceuticals, National Institute of Mental Health, Shire Pharmaceuticals, Pfizer, Inc., F. Hoffmann-La Roche Ltd., AstraZeneca Pharmaceuticals, Centers for Disease Control, Massachusetts General Hospital, Sunovion Pharmaceuticals, Neurocrine Biosciences, Psyadon Pharmaceuticals, and PANDAS Network and personal fees from International OCD Foundation, Tourette Syndrome Association. All other authors have no competing financial interests.

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Address correspondence to:
Tanya K. Murphy, MD, MS
Department of Pediatrics
Rothman Center for Neuropsychiatry
University of South Florida
Box 7523, 880 6th Street South
St. Petersburg, FL 33701

E-mail: tmurphy@health.usf.edu