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Multidisciplinary Clinic Dedicated to Treating Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome: Presenting Characteristics of the First 47 Consecutive Patients

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Abstract

Background: Abrupt, dramatic onset obsessive-compulsive disorder (OCD) and/or eating restriction with at least two coinciding symptoms (anxiety, mood dysregulation, irritability/aggression/oppositionality, behavioral regression, cognitive deterioration, sensory or motor abnormalities, or somatic symptoms) defines pediatric acute-onset neuropsychiatric syndrome (PANS). Descriptions of clinical data in such youth are limited.

Methods: We reviewed charts of 53 consecutive patients evaluated in our PANS Clinic; 47 met PANS symptom criteria but not all met the requirement for ''acute onset.'' Patients meeting full criteria for PANS were compared with patients who had a subacute/insidious onset of symptoms.

Results: Nineteen of 47 (40%) patients in the study had acute onset of symptoms. In these patients, autoimmune/inflammatory diseases and psychiatric disorders were common in first-degree family members (71% and 78%, respectively). Most acute-onset patients had a relapsing/remitting course (84%), prominent sleep disturbances (84%), urinary issues (58%), sensory amplification (66%), gastrointestinal symptoms (42%), and generalized pain (68%). Inflammatory back pain (21%) and other arthritis conditions (28%) were also common. Suicidal and homicidal thoughts and gestures were common (44% and 17%, respectively) as were violent outbursts (61%). Group A streptococcus (GAS) was the most commonly identified infection at onset (21%) and during flares (74%). Rates of the abovementioned characteristics did not differ between the acute-onset group and the subacute/insidious-onset groups. Low levels of immunoglobulins were more common in the subacute/insidious-onset group (75%) compared with the acute-onset group (22%), but this was not statistically significant ($p = 0.06$).

Conclusions: In our PANS clinic, 40% of patients had acute onset of symptoms. However, those with and without acute onset of symptoms had similar symptom presentation, rates of inflammatory conditions, somatic symptoms, and violent thoughts and behaviors. GAS infections were the most commonly identified infection at onset and at symptom flares. Because of the wide variety of medical and psychiatric symptoms, youth with PANS may require a multidisciplinary team for adequate care management.

Introduction

PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME (PANS) is a condition characterized by the abrupt, dramatic onset of obsessive-compulsive disorder (OCD) or eating restriction accompanied by equally abrupt and severe comorbid neuropsychiatric symptoms, which include anxiety, emotional lability, depression, irritability, aggression, oppositionality, deterioration in school performance, behavioral (developmental) regression, sensory amplification, movement abnormalities, sleep disturbance, and urinary frequency (Brimberg et al. 2012). PANS is felt to be caused by infection, inflammation, or some other trigger that is associated with a brain response that leads to these symptoms (Swedo et al. 2012; Chang et al. 2015; Murphy et al. 2014). In an effort to organize etiologic research and treatment trials for this disorder, we started the Stanford PANS Clinic, an interdisciplinary clinic designed to evaluate and treat youth with suspected PANS. Many of these children have been extremely ill with destructive rage outbursts, debilitating compulsions, motor and vocal tics, school dysfunction, and multiple psychiatric hospitalizations. As little precedence exists to guide treatment, our interventions are based on those thought to be useful in pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS) (Garvey et al. 1999; Perlmutter et al. 1999; Snider et al. 2005; Murphy et al.

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2014) and related conditions such as acute rheumatic fever, post-infectious/reactive arthritis, and Sydenham chorea. In an effort to increase knowledge about this condition, we report here on the first 53 patients evaluated in the Stanford Children's PANS Clinic.

Methods

Pediatric referrals and parents desiring evaluation for a child were referred to our intake coordinator who did the initial screening of patients. Forty-seven of 53 patients who were ultimately evaluated in PANS clinic met research criteria for diagnosing PANS, except for the criteria for acuity of onset. Patients who had an abrupt onset of symptoms were compared with patients who did not have an abrupt onset of symptoms. We reviewed the results from clinical evaluations, patient questionnaires, PANS Impairment Scale (Table S1), and Caregiver Burden Inventory (Fig. S1) (see online supplementary material at http://www.liebertonline.com/jcap).

Clinical evaluations

Patients underwent standard psychiatric (with K.C., M.T.) and medical evaluation (with J.F.), results of which were recorded in the electronic medical record (EMR).

Laboratory workup

All patients underwent evaluation for Group A streptococcus (GAS) (throat culture, perianal culture [if there were symptoms of redness, pain, or itching], antistreptolysin O [ASO], and anti-deoxyribonuclease B [DNase B]) at presentation to PANS clinic or flare after being established in PANS clinic. GAS infection was indicated if culture was positive and antistreptococcus antibodies were outside the expected range for age (Kaplan et al. 1998). Mycoplasma titers were ordered by the primary medical doctor (PMD) or Stanford PANS Clinic staff if the patient had a chronic cough, tonsillitis, or sinusitis and/or had had close contact with someone who had these symptoms. We attempted to order an antinuclear antibodies (ANA) test and a histone antibody test on every patient for workup of primary lupus and drug-induced lupus, given the high prevalence of OCD in patients with lupus (Slattery et al. 2004) and concern for lupus cerebritis. We attempted to evaluate thyroid antibodies in all patients with behavior regression and/or hallucinations, given the association of these symptoms with steroid responsive encephalitis associated with thyroiditis (SREAT) (Mahmud et al. 2003). We obtained tissue-transglutaminase (TTG) antibodies in all patients with abdominal complaints (pain, bloating, flatulence, diarrhea), arthritis, and/or unexplained weight loss or failure to gain weight. Autoimmune encephalitis and paraneoplastic antibody panels were sent on all patients with psychosis, memory impairment, cognitive impairment, and a deteriorating course. Summary of physical and occupational therapy reports, neurological consults, and phone calls to school teachers/nurses were recorded in the medical record as per routine.

Record review

Treating clinicians (J.F., M.T., K.C.) reviewed medical records including those from primary care physicians and urgent care visits.

Patient questionnaire

Caregivers completed an extensive intake questionnaire, which required severity scoring of psychiatric and somatic symptoms (including a pain questionnaire). Detailed medical history, including infections and infectious exposures, past medical history, and family history was also elicited by this questionnaire.

PANS Impairment Scale

The PANS Impairment Scale is a parent-rated scale of impairment from PANS symptoms that generates scores ranging from 0 to 50 (see Supplementary Table 1). The PANS Impairment Scale was developed by Dr. James Leckman and his colleagues at Yale and the National Institute of Mental Health (personal communication).

Caregiver Burden Inventory

All parents completed the Caregiver Burden Inventory (see Supplementary Fig. 1) to assess the level of family stress and burden of the illness (Novak and Guest 1989). Retrospective review of patient medical records was approved by the Stanford Panel on Human Subjects Institutional Review Board. Difference in means was evaluated with the student t test. Difference in proportions was evaluated with the χ^2 test. This was an exploratory study, and no corrections for multiple comparisons were performed.

Results

Psychiatric symptoms started acutely (≤ 3 days) in 40%, subacutely (3 days–8 weeks) in 31%, and insidiously (>8 weeks) in 29%. In patients with subacute onset, the mean time for all the PANS symptom criteria to be met was 3.9 weeks. When the timing of onset was unclear and/or each symptom onset spanned >8 weeks, patients were classified as having had an insidious symptom onset. Patients meeting full research criteria for PANS (i.e., meeting the required symptoms and ''abrupt'' onset) were compared with the non-PANS cohort (i.e., those who satisfied the symptom criteria but did not have ''abrupt'' onset).

The mean age at onset for the acute-onset group (PANS group) was 9.6 years (SD 3.5) and for the subacute/insidious-onset group (non-PANS group) it was 7.7 years (SD 2.9). The age at presentation to our clinic for the PANS group was 11.8 years (range = 5–17) and for the non-PANS group it was 10.3 years (range = 3–17) (Table 1). Most patients in our cohort were male (77%). Preexisting but low-level neuropsychiatric symptoms were common in both the acute-onset and subacute/insidious-onset groups (71% and 63%, respectively) and included sensory disturbance (11% and 14%), attention disorder (0% and 14%), hyperactivity (0% and 14%), anxiety (16% and 14%), behavior problems (0% and 21%), learning disorder (16% and 7%), irritability/anger (5% and 7%), mood disorder (5% and 18%), OCD (11% and 7%), movement disorder (5% and 4%), fine motor difficulties (16% and 18%), gross motor difficulties (5% and 11%), and autism spectrum (21% and 4%). Psychiatric disorders and autoimmune diseases in first-degree family members were commonly reported by parents in both groups (Table 1).

Course of illness is reported in Table 2. Most PANS and non-PANS patients (89%) had a relapsing/remitting course and 74% generally returned to baseline after flares, as determined by parents and psychiatrists (M.T. and K.C.). Three patients had a chronic static course: One patient was admitted to a psychiatric facility shortly after presentation because of extreme violence, and the other two eventually developed choreic movements. Of these two patients with chronic static course and choreic movements, one had a definitive GAS infection and the other did not have evidence of GAS and had undetectable ASO and anti-DNase B antibodies

Table 1. Demographics of 47 Consecutive Patients Evaluated in Our Stanford Pediatric Acute-Onset Neuropsychiatric Syndromes (PANS) Clinic Who Met Symptom Criteria for PANS, but Only the Acute-Onset Group Met Full Criteria for PANS

Patient demographics and medical history	*Total cohort* (n = *47*)	*Acute-onset (PANS group)* (n = *19*)	*Subacute/insidious-onset (not PANS group)* (n = *28*)	*Significance* (p *value*)
Mean age at full symptom onset	8.5 (SD = 3.3)	9.6 (SD = 3.5)	7.7 (SD = 2.9)	0.05
Mean age at presentation to PANS clinic	10.9 (SD = 3.7)	11.8 (SD = 4.0)	10.3 (n = 27, SD = 3.4)	0.18
Male	36/47 (77%)	14/19 (74%)	22/28 (78%)	0.70
Preexisting neuropsychiatric disorder in patient (n = 44)	29/44 (66%)	12/17 (71%)	17/27 (63%)	0.83
First degree family member with history of psychiatric illness (n = 27)	21/27 (78%)	7/9 (78%)	14/18 (78%)	0.53
First degree family member with history of autoimmune disease or inflammatory disorder (n = 45)	30/45 (67%)	12/17 (71%)	18/28 (64%)	0.53

Difference in means was evaluated with the student t test. Difference in proportions was evaluated with the χ^2 test.

despite having known household contacts with GAS. These two latter patients were included in the overall analysis because OCD symptoms predominated in the clinical picture and the choreic movements were not interfering with the patient's activities of daily living. Two patients were classified as having a progressive course: One patient was thought to have an illness resembling, but not definitively, lupus cerebritis (positive ANA, positive antiphospholipid antibodies [β 2-glycoprotein antibodies], thrombocytopenia [platelets less than 100,000/mm $\times$3, in the absence of offending drugs]). The other patient was eventually diagnosed with autoimmune encephalitis caused by chronic, deteriorating speech and cognition (in addition to the OCD and other psychiatric symptoms), nonspecific autoimmune markers, and dramatic responsiveness to high dose intravenous corticosteroids. Both of these latter patients demonstrated complete response (returned to baseline) with aggressive immunosuppression and relapse when weaned from immunosuppression.

The prevalence of psychiatric symptoms is reported in Table 3. Anxiety was the most prevalent symptom and anorexia was the least common. All patients met the required secondary symptom criteria, but only 40% had an abrupt onset qualifying them for the diagnosis of PANS. Only 17% had documented evidence of GAS infections (within 12 weeks prior to or during presentation) and/or elevated streptococcal titers at presentation as well as having acute-onset of symptoms. Most patients had not been evaluated for streptococcus infection prior to or at presentation and, therefore, GAS status was unknown. Symptom severity scores and caregiver burden scores were highly elevated.

Patients had a high rate of somatic symptoms (sleep disturbances, urinary frequency and enuresis, gastrointestinal symptoms) and sensory amplification (hyperacusis, photophobia, generalized pain), the details of which are reported in Table 4. Patients also had high rates of suicidality, aggressive ideation, violent behavior, and psychosis (see Table 4).

All patients underwent a medical evaluation including a full history and physical examination at intake and at each follow up evaluation. The most common immunological and rheumatological examination findings (reported in Table 5) indicated a high rate of axial skeletal pain and conditions relating to inflammatory arthritis. Six patients were thought to have arthritis triggered by an infection (reactive arthritis) based on the pattern and timing of symptoms and the limited course of arthritis. The remainder had a clinical picture of mild but persistent arthritis, and met clinical criteria for enthesitis-related arthritis, spondyloarthritis, or psoriatic arthritis; in these cases, it was unclear as to whether or not the arthritis was infection triggered. Hematological and immunological abnormalities are also reported in Table 5, but should be interpreted with caution, because blood samples were retrospectively reviewed and it is possible that infections may have skewed the results, as laboratory blood draws were typically obtained at the time of a deterioration in clinical status. The most common motor findings in the PANS and non-PANS groups included simple tics (21% and 32% respectively), complex tics (5% and 4% respectively), chorea (5% and 7% respectively), and choreiform movements (11% and 0% respectively).

Table 2. Course of Psychiatric Illness in 47 Consecutive Patients Evaluated in Our Stanford Pediatric Acute-Onset Neuropsychiatric Syndromes (PANS) Clinic Who Met Symptom Criteria for PANS, but Only the Acute-Onset Group Met Full Criteria for PANS

Course of disease	*Total cohort* (n = *47*)	*Acute-onset (PANS group)* (n = *19*)	*Sub-acute/ insidious-onset (not PANS group)* (n = *28*)	*Significance**
Relapsing/remitting course of those relapsing/remitting (n = 42),	42 (89%)	16 (84%)	26 (93%)	0.60
Generally returned to baseline after flares	31 (74%)	12 (75%)	19 (73%)	0.71
Generally worsened to baseline after flares	8 (19%)	3 (19%)	5 (19%)	0.71
Unclear or variable return to baseline	3 (6%)	1 (6%)	2 (8%)	
Chronic course (symptoms persist at same level)	2 (5%)	1 (7%)	1 (4%)	0.60
Progressive course (symptoms worsen over time)	3 (8%)	2 (13%)	1 (4%)	0.60

*Difference in proportions was evaluated with the χ^2 test.

Table 3. Frequency of Each Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) Symptom Criteria in 47 Consecutive Patients

	Fraction of patients meeting each of these PANS criteria (n = *47*)	*Acute-onset (PANS group)* (n = *19*)	*Sub-acute/ insidious-onset (not PANS group)* (n = *28*)	*Significance**
Major PANS criteria				
Obsessive compulsive disorder	44 (94%)	17 (90%)	27 (96%)	0.09
Eating restriction	13 (28%)	9 (47%)	4 (14%)	0.03
Minor PANS criteria (new or highly escalated)				
Anxiety	43 (92%)	18 (95%)	25 (89%)	0.51
Mood disorder	42 (89%)	18 (95%)	24 (86%)	0.23
Irritability/aggression	39 (83%)	15 (79%)	24 (86%)	0.83
Behavioral regression	29 (62%)	11 (58%)	18 (64%)	0.71
Deterioration in academics	37 (79%)	16 (84%)	21 (75%)	0.44
Sensory/motor abnormalities	43 (92%)	18 (95%)	25 (89%)	0.40
Somatic symptoms	40 (85%)	17 (90%)	23 (82%)	0.83
Patients meeting symptom criteria (at least 1 major and 2 minor)	47 (100%)	19 (100%)	28 (100%)	
Patients meeting PANDAS criteria	8 (17%)	8 (42%)	0 (0%)	
Mean PANS Severity Score during presentation of worst flare (supplementary table) ($n = 32$)	41 (range = 14–50, SD = 12)	44 (range = 20–50, SD = 9)	39 (range = 14–50, SD = 13)	0.22 ($t = 1.27$, $df = 30$)
Mean Caregiver Burden Inventory (CGB) (supplementary figure) ($n = 22$)	45 (SD = 21)	51 (SD = 24)	42 (SD = 20)	0.38 ($t = 0.91$, $df = 20$)

*All statistics are Pearson χ^2 except the last two (PANS Severity Score and Caregiver Burden Score), which are both independent sample t tests.
PANDAS, pediatric autoimmune neuropsychiatric disorder associated with streptococcus.

In patients with psychosis ($n = 11$) and/or chronic, static, or progressive courses ($n = 5$), we obtained paraneoplastic and autoimmune encephalitis antibody panels (Mayo Medical Laboratory), and all but one was negative. The one positive paraneoplastic antibody found was low titer and did not match the patient's clinical phenotype; therefore, it was considered a nonspecific finding and not relevant to the patient's illness.

We attempted to collect data on reported infections and illnesses thought to be associated with the psychiatric illness; however, this type of data collection has significant limitations (outlined in the Discussion); therefore, the following data should be interpreted with caution and should only be used to plan future prospective studies. An illness within 3 weeks prior to or during the development of the first PANS symptom was commonly reported in patients with PANS and non-PANS OCD (84% and 93% respectively). The primary symptoms of the illness included fever (47% and 25% respectively), sore throat (42% and 14% respectively), upper respiratory infection (URI) symptoms (5% and 18% respectively), myalgias and/or arthralgias (11% for both cohorts), sinusitis (11% and 0% respectively), otitis media (5% and 4% respectively), rash (5% and 4% respectively), gastroenteritis symptoms (11% and 4% respectively), headache (0% and 4% respectively), and fatigue (0% and 4% respectively). Documented GAS infection within 12 weeks of development of psychiatric symptoms, was found in PANS and non-PANS groups at presentation (21% vs. 61%) and with at least one major flare (74% vs. 39%). Positive mycoplasma immunoglobulin (Ig)M (not confirmed with polymerase chain reaction ([PCR]) was found at the time of presentation (5% vs. 7%) or with at least one flare (26% vs. 18%); however, this test was only ordered on patients with suspected clinical symptoms of mycoplasma infection. Other illnesses reported within 3 weeks prior to or during presentation included: Sinusitis and/or otitis media (5), impetigo (1), dental infection (1), vaccine (1), anaphylactic reaction (1), and acute-onset hip pain requiring hospitalization (2). Other illnesses reported within 3 weeks prior to or during major flares included: Otitis media and/or sinusitis (19), urinary tract infection (1), anaphylactic reaction (1), mononucleosis (1), pneumonia (1), impetigo (1), and arthritis/inflammatory disease flare (1). In 16% of the PANS group and 21% of the non-PANS group, parents did not feel that illnesses preceded neuropsychiatric deteriorations. However, in 63% of PANS patients and 61% of non-PANS patients, parents reported that all or most deteriorations were preceded by an infection. This was subjective data collected from our parent questionnaire; there were no clear dates or timeline information of infection and subsequent flares. Parents also reported a high rate of sinopulmonary infections and/or recurrent tonsillitis on the medical history form in both the PANS and non-PANS groups (47% and 44% respectively).

Discussion

Forty-seven patients evaluated in the Stanford Children's PANS Clinic had prominent OCD and/or eating restriction and significant comorbid psychiatric symptoms including anxiety, mood disorders, behavior regression, academic deteriorations, sensory, and somatic symptoms. All these patients met secondary symptom criteria for PANS (Table 3), whereas a smaller but clinically important fraction (40%) met full criteria for PANS by having symptoms starting abruptly. The minority of patients (17%) met criteria for PANDAS. However, many patients without a history of preceding GAS had not been evaluated fully for streptococcal disease (i.e., throat culture, perianal cultures, ASO, and anti-DNase B antibodies) prior to or during their initial presentation, and we suspect that PANDAS was underdiagnosed in our cohort.

The age of onset in our cohort was older compared with the mean age reported in prior reports of youth with PANS and PANDAS

Table 4. Somatic Symptoms, Violence, and Psychosis Reported in the Clinical Charts of 47 Consecutive Patients Presenting to the Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) Clinic

*Ancillary symptoms – new or highly escalated at time of psychiatric symptom presentation or major flare**	*Total cohort* (n = *47*)	*Acute-onset (PANS group)* (n = *19*)	*Subacute/insidious-onset (not PANS group)* (n = *28*)	*Significance*
Sleep disturbance	39 (83%)	16 (84%)	23 (82%)	0.85
General fatigue	34 (72%)	11 (58%)	23 (82%)	0.07
Not feeling rested in morning	27 (57%)	9 (47%)	18 (64%)	0.25
Urinary complaints (polyuria, enuresis, other)	21 (45%)	11 (58%)	10 (36%)	0.12
Weight loss	26 (55%)	12 (63%)	14 (50%)	0.47
Gastrointestinal symptoms	18 (38%)	8 (42%)	10 (36%)	0.44
Weakness with or without exercise intolerance	41 (87%)	16 (84%)	25 (89%)	0.28
Headaches	5 (11%)	2 (11%)	3 (11%)	0.68
Sensory amplification				
Hypersensitivity to touch	30 (64%)	13 (68%)	17 (61%)	0.41
Hyperacusis	21 (45%)	10 (53%)	11 (39%)	0.20
Photophobia	28 (60%)	13 (68%)	15 (54%)	0.24
Hypersensitivity to smell or taste	35 (74%)	14 (74%)	21 (75%)	0.59
Generalized pain	31 (66%)	13 (68%)	18 (64%)	0.77
Violence questionnaire and/or structured interview.	(*n* = 42)	(*n* = 18)	(*n* = 24)	
Any suicidality	17 (40%)	8 (44%)	9 (38%)	0.23
Suicidal ideation	17 (40%)	8 (44%)	9 (38%)	
Gestures	6 (14%)	2 (11%)	4 (17%)	
Intent	1 (2%)	1 (6%)	0 (0%)	
Any homicidality	8 (19%)	3 (17%)	5 (21%)	0.85
Homicidal Ideation	8 (19%)	3 (17%)	5 (21%)	
Gestures	4 (10%)	1 (6%)	3 (13%)	
Intent	0 (0%)	0 (0%)	0 (0%)	
Injury/damage from violence	25 (60%)	11 (61%)	14 (58%)	0.64
Self	15 (36%)	6 (33%)	9 (38%)	
Others	18 (43%)	7 (39%)	11 (46%)	
Objects	21 (50%)	8 (44%)	13 (54%)	
Life-threatening violence	6 (14%)	2 (11%)	4 (17%)	0.15
Psychosis (hallucinations)	11 (26%)	4 (22%)	7 (29%)	0.41

*These ancillary symptoms were either new or highly escalated at or following presentation or major flare of the psychiatric illness. Data were obtained through patient questionnaires and patient interviews. We assessed suicidality, homicidality, violence, injury, and psychosis through patient questionnaires and structured interviews.

(Swedo et al. 1998; Bernstein et al. 2010; Murphy et al. 2012, 2015), we believe that our result reflects an inaccurate estimate because of the small patient population studied. Additionally, many patients reported earlier and milder PANS-like episodes, but we did not adjust the age of onset for undocumented psychiatric deteriorations, even though we believe that these earlier episodes may have been the first presentation of the PANS illness.

The co-occurrence of psychiatric symptoms from a number of diagnostic categories is not unique to PANS (Table 3). For example, non-PANS pediatric OCD is often associated with tics, mood disorders, anxiety disorders, and attention-deficit/hyperactivity disorder (ADHD) (Peterson et al. 2001; O'Rourke et al. 2011; Gomes de Alvarenga et al. 2012; Selles et al. 2014). Taken out of the PANS context, many of our patients could otherwise be diagnosed with multiple psychiatric disorders. OCD symptoms in our PANS group were severe, and similar to those in children with non-PANS OCD. Many spent multiple hours each day performing compulsive activities, and many of our patients reported violent imagery that was severe and persistent. In most cases, the violent imagery was a source of anxiety (especially separation anxiety). Depressed mood (including full depressive episodes) and mood lability were common. Patients and families frequently reported patient suicidal and homicidal ideation, gestures, and intent (Table 4). Impulsive dangerous behavior, such as attempting to jump out of moving cars and out of windows, was common. Patients were also reported to exhibit violence toward themselves, family members, and/or objects. No person died or was hospitalized as a result of injury. Psychotic symptoms were also reported in some patients including auditory and visual hallucinations.

Preexisting neuropsychiatric symptoms – such as anxiety, ADHD symptoms, and mood difficulties – were common in both the acute- and subacute-onset groups of patients in our cohort, but these symptoms were usually subclinical, and did not cause significant impairment. It is possible that this premorbid pathology was the sequela of previous, undetected infections and/or inflammatory reactions. Therefore, the finding of preexisting neuropsychiatric symptoms should not dissuade clinicians and researchers from considering the possibility of PANS and looking into infectious and inflammatory triggers.

Most patients had a relapsing/remitting course (89%) and the minority (11%) had a chronic static or progressive course, which may be suggestive of a different illness. In general, the course of most autoinflammatory diseases – which are driven by abnormalities of the innate immune system – tend to be relapsing and remitting, whereas autoimmune diseases (driven by the adaptive immune system; i.e., T cells and B cells) are typically chronic or progressive (Masters et al. 2009). In addition to autoinflammatory diseases, postinfectious inflammatory diseases (i.e., acute rheumatic

Table 5. Rheumatological and Immunological Evaluation in 47 Consecutive Patients Evaluated in Our Stanford Pediatric Acute-Onset Neuropsychiatric Syndromes (PANS) Clinic Who Met Symptom Criteria for PANS, but Only the Acute-Onset Group Met Full Criteria for PANS

Medical evaluations	*Fraction (%) of patients with medical finding* (n = *47*)	*Acute-onset (PANS group)* (n = *19*)	*Subacute/ insidious-onset (not PANS group)* (n = *28*)	*Significance between PANS and not PANS groups**
Reported neck and/or, back and/or sacroiliac joint pain.	19/47 (40%)	5/19 (26%)	14/28 (50%)	0.56
Patients meeting criteria for inflammatory back pain	10/47 (21%)	4/19 (21%)	6/28 (21%)	0.45
Patients having at least one episode consistent with reactive arthritis or persistent arthritis (enthesitis-related arthritis, spondyloarthropathy- related arthritis, or psoriatic arthritis).	13/47 (28%)	6/19 (32%)	7/28 (25%)	0.61
Transient erythematous flat rashes	6/47 (13%)	0/19 (0%)	6/28 (21%)	0.03
Elevated inflammatory markers ESR/CRP	3/43 (7%)	0/17 (0%)	3/26 (12%)	0.15
Rheumatology/autoimmune markers				
ANA (>1:160 titer)	7/43 (16%)	5/18 (28%)	2/25 (8%)	0.19
Antihistone antibodies (>1.0 Eliza)	6/41 (15%)	4/16 (25%)	2/25 (8%)	0.27
Antithyroid antibodies[a]	3/41 (7%)	2/16 (13%)	1/25 (4%)	0.11
Tissue-transglutaminase antibodies	4/37 (11%)	1/14 (7%)	3/23 (13%)	0.38
More than one disease- associated autoantibody	7/44 (16%)	4/18 (22%)	3/26 (12%)	0.40
Paraneoplastic/autoimmune encephalitis panel (Mayo Medical Laboratory) positive	1/16 (6%)	0/5 (0%)	1/3 (33%)	0.16
Hematological abnormalities on at least one laboratory examination (presentation or flare)				
Monocytosis	20/47 (43%)	9/19 (47%)	11/28 (39%)	0.58
Eosinophilia	14/47 (30%)	8/19 (42%)	6/28 (21%)	0.13
Neutropenia	3/47 (6%)	2/19 (11%)	1/28 (4%)	0.34
Anemia	7/47 (15%)	3/19 (16%)	4/28 (14%)	0.89
Immunoglobulin (Ig) analyses				
Low IgG levels	6/21 (29%)	1/7 (14%)	5/14 (36%)	0.41
Low IgA levels	5/21 (24%)	1/7 (14%)	4/14 (29%)	0.31
Low IgM levels	6/21 (29%)	1/7 (14%)	5/14 (36%)	0.21
Any hypogammaglobulinemia above	11/23 (48%)	2/9 (22%)	9/14 (64%)	0.06
Elevated IgE	2/14 (14%)	0/5 (0%)	2/9 (22%)	0.08
Low vitamin D	4/42 (10%)	2/16 (13%)	2/26 (8%)	0.66

[a]Thyroperoxidase antibodies and/or thyroglobulin antibodies.
*Difference in proportions evaluated with Pearson χ^2 test.
ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibodies.

fever and reactive arthritis) also follow a relapsing/remitting course with accumulative damage with each flare eventually leading to progressive disease in some cases (for example, cardiac valve damage in the case of acute rheumatic fever). Further research is needed to map the illness course in PANS patients, and correlate with infections and immunological phenotypes.

Autoimmune and other inflammatory diseases were reported to be prevalent in first-degree family members of our patients with and without PANS. This is consistent with what has been reported for family members of youth with PANDAS (Murphy et al. 2010). Both the PANS and non-PANS patients themselves frequently demonstrated coexisting autoimmune and/or inflammatory diseases, most commonly inflammatory back pain (21%), reactive or persistent arthritis (28%), and presumed celiac disease (11%). Patients with presumed celiac disease had high titers of TTG antibodies, and reported improvement of gastrointestinal symptoms on a gluten-free diet; however, these patients/families did not pursue confirmatory endoscopy/biopsy, because of the severity of the psychiatric illness. The rate of ANA positivity in our PANS cohort (28%) was higher than that reported in healthy children (Hilario et al. 2004; Malleson et al. 2010; Satoh et al. 2012; Sperotto et al. 2014), but may have reflected recent infections. Although antihistone and antithyroid antibody titers were higher than those expected based on our laboratory's reference ranges, these reference ranges were not age matched to our cohort; therefore, we cannot draw definitive conclusions from these data. As all laboratory blood tests were performed during presentation or relapse of disease, immunological and hematological abnormalities (Table 5) may have reflected aberrations secondary to recent infections. More research into specific and reproducible (through time) immunological deviations and presence of concurrent infections are necessary before drawing conclusions from these data.

In addition to the high reported prevalence of autoimmune disease in family members, psychiatric disorders were frequently reported in first-degree relatives. This ''dual vulnerability'' to autoimmune disease and psychiatric illness is not a novel finding, as it parallels prior reports in PANDAS, depression, Tourette's syndrome, autism, schizophrenia, and other psychiatric disorders (Morer et al. 2008; Leckman and Vaccarino 2014; Stagi et al. 2014). Recent genetic findings in Tourette's syndrome, autism, and schizophrenia may further support this dual vulnerability theory (Gesundheit et al. 2013; Postal and Appenzeller 2014; Stringer

et al. 2014). Families may share genes that lead to a propensity for immune dysfunction and psychiatric dysfunction, or to a mechanism that links the two. It is an intriguing possibility that relatives may have experienced an unrecognized PANS-like illness as youth, initiating their psychiatric illnesses, which are now seen as ''garden variety'' and idiopathic. Although this is speculation on our part, we feel that the presence of psychiatric illness in family members should not dissuade clinicians and researchers from considering the diagnosis of PANS.

Infections are postulated to be a trigger for PANS (Swedo et al. 2010). Except for GAS, no infections have been definitively linked to PANS. Our data set is limited, because of recall bias and limited workup surrounding the presentation and flares prior to coming to our PANS clinic. Therefore, we are not able to draw any conclusions, at this time, regarding the role of infections in triggering disease presentation and flares in either the PANS and/or the non-PANS group.

Based on parent inquiry, most parents reported that illnesses generally preceded neuropsychiatric deteriorations in both groups. Although many had reported GAS pharyngitis, others had unknown or unclear illnesses. Workup for GAS infection was often not pursued at the initial presentation of OCD, presumably because of the lack of awareness and guidelines to help clinicians perform workups for medical illness at the onset of OCD. Additionally, GAS may be missed by using a rapid streptococcus test only, by using a throat culture that is improperly collected, or by failing to detect GAS in another location, such as the perianal area. Additionally, it was previously found that 27% of healthy children did not mount an ASO and anti-DNase B antibody response (Shet et al. 2003). As GAS infections in youth are common and possibly coincidental in this population, it is also difficult to establish causality in those patients who test positive. However, there has been a substantial body of literature linking GAS infections with OCD, eating restriction, and movement disorders including chorea and tics (Husby et al. 1976; Swedo et al. 1989, 1993, 1998; Mercadante et al. 2000; Leonard and Swedo 2001; Kirvan et al. 2003; Hoffman et al. 2004; Singer et al. 2004; Kirvan et al. 2006, 2007; Murphy et al. 2007; Yaddanapudi et al. 2010; Brimberg et al. 2012; Lotan et al. 2014; Toufexis et al. 2014; Williams and Swedo 2014).

We are not fully able to interpret our mycoplasma data, because IgM serology has poor positive predictive value (52%) (Chang et al. 2014); we hope to further explore this possible infectious trigger with more specific testing in the future (mycoplasma PCR). Mycoplasma has been reported to be a possible etiologic pathogen in striatal encephalitis, but not specifically acute-onset OCD (Candler and Dale 2004; Dale and Brilot 2012).

Although many parents report a possible association between infections and onset or flare of psychiatric symptoms, it is difficult to know if these infections are coincidental or are in the causal pathway. As discussed, we believe that there are adequate published data to support the connection between preceding GAS infections as an etiologic trigger for acute-onset OCD, certain movement abnormalities, and possibly eating restriction (Swedo et al. 1998; Leonard and Swedo 2001; Toufexis et al. 2014; Williams and Swedo 2014) but it is not known whether other infections are also in the causal pathway and whether GAS infections play a role for patients who are not described as having acute-onset symptoms. Well-designed prospective studies are needed to better explore connections between infections and psychiatric deteriorations. In addition to acute rheumatic fever and reactive arthritis, the connection among infections, autoimmunity, and immune dysfunction is postulated in many autoimmune diseases including lupus (Esposito et al. 2014; Nelson et al. 2014) and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (Sanders et al. 2004). The infection itself may not be the primary problem, but rather the inflammatory sequelae that develop after the infection is cleared.

Patients' laboratory examinations revealed a high rate of hematological and immunological deviations (Table 5), including depressed immunoglobulins; the clinical significance remains unknown, however, and may be more relevant to preceding illnesses. Prospective studies are needed to determine the relevance of the immunophenotypes described in this report, with more detailed analysis including measurements repeated through time with correlation to infections and psychiatric symptom flares.

Patients in our cohort had severe and often life-impairing somatic symptoms including sleep disturbances, urinary symptoms (often extreme polyuria) not attributable to infections, sensory amplification (hyperacusis, photosensitivity, hyperosmia, sensitivity to touch), and generalized pain (Table 4). Corroboration with neuroimaging findings may help elucidate whether brain circuits involved in these symptoms overlap with brain circuits thought to be involved with OCD and eating restriction. Patient report of weakness and exercise intolerance may reflect general deconditioning or secondary effect of fatigue, pain, and depressed mood.

Although most of these patients did not report pain to their parents and/or primary care physicians, the results of our physical examination, clinical interview, and pain questionnaire demonstrate that most patients (68% in the PANS group and 64% in the non-PANS group) actually do *experience* pain, including ''shooting pains,'' limb pains, joint pain, and/or tender myofascial points. Many patients (26% of PANS group and 50% of the non-PANS group) reported neck, and/or back, and/or sacroiliac pain (Table 5). Furthermore, 21% of patients in both cohorts met criteria for the diagnosis of inflammatory back pain (age of onset <40 years, insidious onset, improvement with exercise, no improvement with rest, and pain at night that improved upon getting up and moving around) (Sieper et al. 2009). The diagnosis of inflammatory back pain clinically indicates the need for further work-up (including imaging, which is often, but not always, normal in early stages), anti-inflammatory medications, and monitoring by a rheumatologist.

Limitations

This study has several limitations. Potential limitations included reliance on parental history and recall, the small number of patients, possible missed infections (discussed previously), and ascertainment bias. In retrospective studies, recall bias and lack of detailed medical records surrounding the onset of illness may lead to misclassification of patients. Many patients presented to our clinic years after their initial symptom onset; therefore, the history was subject to recall bias, especially with regard to timing of onset and history of infections. Although reliance on parent recall is a potential weakness, we did obtain medical records to substantiate parent report. However, medical record documentation was sometimes vague with regard to the onset timing. Additionally, patients were not always evaluated by their pediatrician in the time period surrounding onset, and GAS screening was not performed in the majority of patients at presentation. Therefore, GAS infection and subsequent PANDAS are possibly underreported.

Future studies will attempt to use more stringent inclusion criteria to minimize the possibility of recall bias and, ideally, follow at-risk children prospectively. Although in our sample the

acute-onset group did not differ significantly from the subacute- or insidious-onset groups in this initial analysis of medical and psychiatric characteristics, this study may have been underpowered to find differences. Additionally, the immune function studies we performed were screening tests. Certainly more detailed immunophenotyping should be done in order to evaluate immune differences between these groups, which may or may not explain the differences in onset presentation (acute vs, subacute/insidious). Future larger studies with more detailed data correlated with more in-depth immunophenotyping may suggest differences that further distinguish the two types. Ascertainment bias may have followed from the tremendous impact of the illness on these children. These patients suffered from severe psychiatric, behavioral, and physical symptoms, which was reflected in the high impairment scores and the high degree of caregiver burden reported by the parents (Table 3). It is conceivable that medical health professionals and families caring for severely impaired patients sought medical attention at our clinic more readily than they did for more moderately or mildly impaired patients. As awareness of PANS grows, perhaps the profile of the population will change.

Conclusion

Patients presenting to our PANS clinic had grave psychosocial impairment assessed through the PANS Impairment Scale and the Caregiver Burden (both available in the online article at www.liebert.com/jcap), but only 40% of the patients met full PANS criteria by having symptoms starting abruptly. In addition to OCD, anxiety, mood disorder, cognitive deterioration, and the other symptoms previously described to comorbid with PANS, patients coming to our clinic also had high rates of violence and psychosis. Due to the multidisciplinary nature of our clinic, patients had evaluations for pain, rheumatic conditions, and immunodeficiency. We cannot conclude definitely on the rates of these comorbid immune-related conditions since there is a strong ascertainment bias with regards to the patient population that chose to be evaluated in our clinic. Larger and more in-depth studies are needed to understand the immune system in patients with PANS and PANS-like illnesses.

Clinical Significance

Children presenting with acute-onset of OCD symptoms or restricted eating should be carefully evaluated for PANS, as they often have medical comorbidities and severe psychosocial impairment. Steps should be taken to evaluate for underlying infections and inflammatory illnesses per guidelines established by the 2013 PANS Consensus Conference (Chang et al. 2015). Caregivers may seek evaluation of PANS and/or PANDAS, but not all of these cases will meet the full PANS and PANDAS criteria requiring that symptoms develop and reach maximum intensity over a 24–36 hour period. Primary care and psychiatric professionals may be helped by knowing that some children with subacute or insidious onset of neuropsychiatric symptoms resemble those with *bona fide* PANDAS and PANS in many ways. If clinicians suspect a PANDAS or PANS-like illness, evaluation of infections, especially GAS, and inflammatory diseases may result in diagnostic insights that otherwise would not occur when encountering severe psychiatric symptoms.

Disclosures

Dr. Chang is an unpaid consultant for Bristol–Myers Squibb, GlaxoSmithKline (GSK), and Lilly. He is on the Data and Safety Monitoring Board for Sunovion. In the past 2 years, he has received research support from GSK and Merck. The other authors have nothing to disclose.

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