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Factors Associated with Symptom Persistence in PANS: Part II—Presenting Features, Medical Comorbidities, and IVIG Treatment History

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Abstract

Objective: Individuals with Pediatric Acute Onset Neuropsychiatric Syndrome (PANS) experience neuropsychiatric symptoms following an infection or other trigger. Although PANS is typically described as relapsing-remitting, a large community-based 2017 study revealed a range of courses. The present study examined clinical predictors of symptom persistence, measured as *% days symptom-free*, in this same sample.

Methods: A 146-question online survey gathered histories (infections and other triggers, medical and developmental comorbidities), symptomatology, interventions, and outcomes (including school functioning) of PANS patients. Multivariate analyses were applied to examine associations between these variables and *% days symptom-free* across the disease course.

Results: Among the 646 subjects included, significant relationships were found between greater symptom persistence and higher rates of medical comorbidities (especially rashes, headaches, chronic sinusitis, frequent diarrhea, and immune deficiencies), developmental diagnoses, and respondent-perceived developmental lags. Subjects with greater symptom persistence were significantly more likely to report PANS exacerbations associated with infections in close contacts, vaccinations, environmental triggers, and exacerbations of comorbidities and were more likely to report PANS recurrences triggered by Epstein Barr Virus, mycoplasma, and sinus infections. More persistent PANS was also associated with significantly higher frequencies of certain symptoms (sleep disturbance, urinary incontinence, muscle pain, brain fog, sensory defensiveness, irritability, and aggression-related symptoms), less effectiveness of intravenous immunoglobulin in combating symptoms, and more difficulty attending school.

Conclusions: Our results suggest high symptom persistence in PANS to be associated with more pervasive medical and neuropsychiatric symptoms. Differences in symptom persistence are associated with both intrinsic (e.g., immune competence) and extrinsic (e.g., infections, treatment) factors. Because extrinsic factors are potentially modifiable, it is critical that providers be aware of current guidelines on PANS evaluation and treatment.

Keywords: PANDAS, PANS, course, outcomes, Clinical Presentation

Introduction

Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) is characterized by obsessive-compulsive symptoms and/or restricted food intake, as well as neuropsychiatric and somatic symptoms including anxiety, emotional lability, depression, irritability, aggression, oppositional behaviors, behavioral regression, sleep disturbances, urinary frequency, sensory or motor abnormalities, and deterioration in school performance (Swedo et al., 2012). Onset and exacerbations often follow infections, frequently with *Streptococcus pyogenes* (termed Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus: PANDAS), but can also be triggered by environmental factors. Consensus guidelines on evaluation (Chang et al., 2015) and intervention (Swedo et al., 2017) provide a standard approach to this condition, including behavioral support (Thienemann et al., 2017), immunomodulatory therapies (Frankovich et al., 2017), and management of infections (Cooperstock et al., 2017).

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The frequency and duration of PANS exacerbations vary widely across affected patients. Although generally considered a relapsing-remitting illness (Cooperstock et al., 2017), complete relief of symptoms between exacerbations is not always achieved (Gromark et al., 2022). In a 34-patient cohort followed by clinician assessment over 2-5 years, 2 patients were classified as remitted, 20 as relapsing–remitting, and 12 as having a chronic-static/progressive course (Gromark et al., 2022). Compared to those with relapsing-remitting or remitted disease, levels of IL-1-β, TNF-α, and IgM were significantly elevated in patients who experienced chronic symptoms, suggesting a more inflammatory state. Similarly, in a large-scale survey sample of 698 cases, 19% had experienced PANS symptoms every day since onset, while 19% had been asymptomatic more than 75% of days (Calaprice et al., 2017). However, no large-scale study to date has attempted to identify what clinical or treatment-related features differentiate individuals with persistent versus intermittent symptoms. Understanding potential risk factors for symptom persistence might empower providers to take preventive measures to prevent chronic disease. Moreover, in other autoimmune neurological diseases, for example, multiple sclerosis and neuropsychiatric lupus (Bates, 2011; Schwartz et al., 2019), patients experiencing different disease courses respond differently to therapeutic interventions; thus, understanding the range of courses experienced by PANS patients may aid our understanding of variability in therapeutic response.

In 2017 and 2018, Calaprice and colleagues described the symptoms, course, medical and family histories, and treatment experiences of 698 patients with PANS, the largest survey cohort to date (Calaprice et al., 2018; Calaprice et al., 2017). Although the authors reported briefly that receiving sufficient antibiotic treatment to resolve the infection associated with PANS onset was associated with lower probability of recurrence, a thorough investigation of factors associated with symptom persistence was beyond the scope of the original analyses.

The current study further analyzes presentation, treatment, and medical history traits associated with PANS symptom persistence, as measured by the respondent-reported *% days symptom-free*. We hypothesized that more persistent PANS symptoms could reflect a state of chronic, systemic immune activation and that this would be reflected in associations between symptom persistence and (1) higher rates of comorbid inflammatory conditions (specifically allergies, chronic sinusitis, musculoskeletal pains, rashes, recurrent high fevers, and/or asthma) and immune deficiencies, (2) a stronger tendency for PANS symptoms to flare in response to a range of pathogens and other immune-activating environmental triggers, and (3) lack of effective immunomodulatory treatment. We further hypothesized that more persistent disease would be associated with poorer outcomes, including more numerous symptoms and functional difficulties.

Methods

Data capture

As noted in our companion article (Calaprice-Whitty et al., 2023):

A 146-question, retrospective online survey gathered data regarding PANS, medical, and family history; symptomatology; and medical and nonmedical interventions and outcomes. Instrument development is detailed in Calaprice et al. (2017). The study was approved by the University at Buffalo Social and Behavioral Sciences Institutional Review Board. Participants were recruited from PANS and OCD-related organizational websites, emails, conferences, and radio shows, as well as through posters sent to PANS-treating providers. As part of the consent process before accessing the survey, respondents were required to certify that they were at least 18 years old and either the parents or legal guardians of children with PANS or PANDAS or had PANS/PANDAS themselves. Although no documentation was required from the medical record, each respondent was specifically asked if the subject had been diagnosed by a physician, and survey access was automatically prevented if the answer was not ''yes.'' The type of physician who made the diagnosis was requested. The specific diagnostic criteria for PANS were provided as a reference (detailed in companion article).

Data analysis

As noted in our companion article (Calaprice-Whitty et al., 2023):

Of the 753 surveys submitted, 55 were considered to contain illogical or incomplete information that rendered the data unreliable based on predefined logic checks (for example, dates reflecting illogical event sequences, clinical features inconsistent with demographics); any instance of unreliable information rendered the entire record ineligible for inclusion, leaving 698 records for analysis. The outcome variable *% days symptom-free* (ordinal numeric categories selected by respondents) was used as the marker of disease persistence. Specifically, the question asked: *''During the period from initial onset of PANS symptoms to the present, approximately what percentage of the patient's days have been symptom-free (treated or untreated)?''* The possible responses were: (a) None, patient has had symptoms every day; (b) 1%–10% of days have been symptom free; (c) 10%–25% of days have been symptom free; (d) 26%–50% of days have been symptom free; (e) 51%–75% of days have been symptom free; (f) 76%–99+% of days have been symptom free; (g) Patient was too young during much of this period to tell; or (h) Don't remember. ''Don't remember'' responses (g and h) were excluded, leaving 646 records for analysis. Categories b and c were combined.

For all variables, responses of ''don't recall'' were excluded from analyses. Ordinal logistic regression models were used for categorical variables and MANOVA for continuous variables. There was a significant relationship between age and *% days symptom-free* (L-R $\chi^2 = 15.87$, $p = 0.003$), so all statistical analyses controlled for this variable. Neither sex (L-R $\chi^2 = 1.96$, $p = 0.74$) nor length of illness (L-R $\chi^2 = 2.26$, $p = 0.69$) bore significant relationships to *% days symptom-free*, thus were not included as factors. When case numbers were too small to support the multivariable models (conservatively set at <40, Peduzzi et al., 1996), only descriptive statistics are provided (represented by NP = Not Performed in tables). To provide the most conservative estimates of statistical significance, Bonferroni corrections for multiple tests were applied where applicable, with results indicated in the table footnotes and text. The JMP® statistical program was used to perform all data analyses.

Results

The demographic and disease-history characteristics of the sample for this analysis are described in the companion to this article (Calaprice-Whitty et al., 2023).

% days symptom-free by inciting agents

There were no significant relationships between *% days symptom-free* and whether an inciting infection was identified at onset (suspected or confirmed in 92%–95% of subjects across persistence categories) or whether the inciting infection was Streptococcus (50%–

Table 1. Inciting Agents for Episodes by Symptom Persistence in Pediatric Acute Onset Neuropsychiatric Syndrome (% Giving This Response/[*N*])

	No days symptom-free	*1%–25% days symptom-free*	*26%–50% days symptom-free*	*51%–75% days symptom-free*	*>75% days symptom-free*	*Estimate (95% CI)*	*L-R* χ^2	p
Was the first episode of PANS associated in time with an infection?						0.03 (0.01 to 0.06)	0.06	0.97
No	5% (5)	8% (13)	6% (6)	5% (5)	6% (7)			
Suspect so, but unsure	24% (26)	24% (39)	22% (21)	21% (21)	25% (29)			
Yes	72% (78)	68% (110)	72% (70)	74% (73)	69% (79)			
What was the associated infection at the time of initial PANS episode? [%confirmed (n)/%suspected (n)]								
Streptococcus	40% (50)/10% (12)	48% (87)/5% (9)	51% (54)/6% (6)	48% (53)/8% (9)	50% (60)/8% (10)	–0.10 (–0.34 to 0.13)/ 0 (–0.38 to 0.38)	2.06	0.36
Cold	9% (11)/2% (3)	4% (8)/3% (6)	7% (7)/6% (6)	5% (6)/3% (3)	5% (6)/2% (3)			NP
Mononucleosis/EBV	5% (6)/2% (2)	2% (4)/1% (2)	4% (4)/2% (2)	3% (3)/1% (1)	2% (2)/0% (0)			NP
Influenza	1% (1)/4% (5)	3% (5)/3% (5)	1% (1)/3% (3)	3% (3)/1% (1)	0% (0)/2% (2)			NP
Mycoplasma	8% (10)/4% (5)	4% (8)/2% (4)	11% (12)/3% (3)	5% (5)/6% (6)	7% (9)/4% (5)	0.08 (–0.35 to 0.51)/ –0.15 (–0.68 to 0.38)	0.36	0.84
Sinusitis	10% (12)/3% (3)	8% (14)/4% (8)	12% (13)/6% (6)	5% (6)/3% (3)	5% (6)/3% (4)	0.24 (–0.16 to 0.63)/ –0.11 (–0.59 to 0.38)	2.06	0.36
Gastrointestinal illness	5% (6)/1% (1)	4% (7)/2% (3)	5% (5)/2% (2)	3% (3)/0% (0)	2% (2)/1% (1)			NP
Lyme disease	5% (6)/3% (4)	2% (4)/2% (3)	3% (3)/1% (1)	1% (1)/3% (3)	1% (1)/2% (2)			NP
Lyme coinfection	6% (7)/2% (3)	1% (2)/1% (2)	3% (3)/0% (0)	0% (0)/4% (4)	1% (1)/2% (2)			NP
Other infection	7% (9)/3% (4)	7% (12)/2% (3)	6% (6)/3% (3)	11% (12)/4% (4)	4% (5)/2% (3)			NP
What infectious agents have been associated with episodes/exacerbations beyond the first?								
Streptococcus	57% (59)	57% (94)	60% (58)	71% (73)	59% (54)	0.11 (–0.04 to 0.26)	2.02	0.16
Cold	26% (27)	39% (64)	42% (41)	32% (33)	23% (21)	–0.07 (–0.23 to 0.08)	0.87	0.35
Mononucleosis/EBV	15% (15)	9% (15)	11% (11)	4% (4)	5% (5)	–0.28 (–0.55 to –0.02)	4.36	0.04
Influenza	17% (18)	21% (34)	31% (30)	15% (15)	16% (15)	–0.04 (–0.22 to 0.15)	0.15	0.70
Mycoplasma	35% (36)	29% (48)	33% (32)	23% (24)	16% (15)	–0.21 (–0.37 to –0.04)	6.22	0.01‡
Sinus infection	32% (33)	33% (55)	32% (31)	25% (26)	19% (17)	–0.19 (–0.35 to –0.03)	5.20	0.02
Does the patient appear to react with PANS symptoms to… (% Yes [N])								
…infections in family members or friends with which he/she has frequent contact, even in the absence of a clear infection in the patient?	80% (63)	81% (104)	78% (60)	73% (57)	59% (55)	–0.37 (–0.56 to –0.17)	13.78	0.0002***
…vaccinations?	52% (56)	60% (39)	48% (24)	52% (28)	30% (17)	–0.27 (–0.48 to –0.06)	6.46	0.01*
…environmental triggers such as particular foods, additives, allergens, weather, lighting, etc.?	71% (59)	71% (89)	58% (42)	56% (47)	37% (35)	–0.44 (–0.62 to –0.27)	26.33	<0.0001***
When the patient experiences a PANS exacerbation are there medical conditions that flare at the same time?								
Yes, always	23% (29)	20% (35)	11% (12)	12% (13)	10% (12)		11.86	0.003**
Yes, sometimes	27% (34)	38% (66)	48% (50)	45% (49)	28% (33)			

‡Bonferroni-corrected $p < 0.10$.
*Bonferroni-corrected $p < 0.05$.
**Bonferroni-corrected (or not needed) $p < 0.01$.
***Bonferroni-corrected $p < 0.001$
EBV, Epstein Barr Virus; NP, not performed due to small number of cases.
PANS, Pediatric Acute Onset Neuropsychiatric Syndrome.

58% confirmed or suspected across persistence categories) (Table 1). Few subjects reported infections other than Streptococcus to have incited the first episode. However, individuals with greater symptom persistence were more likely to report recurrences triggered by Epstein Barr Virus (EBV) (L-R $\chi^2 = 4.36$, unadjusted $p = 0.04$, Bonferroni-corrected $p =$ ns), mycoplasma (L-R $\chi^2 = 6.22$, unadjusted $p = 0.01$, Bonferroni-corrected $p < 0.10$), and/or sinus infections (L-R $\chi^2 = 5.20$, unadjusted $p = 0.02$, Bonferroni-corrected $p =$ ns).

Patients with greater symptom persistence were also significantly more likely to report PANS exacerbations in response to environmental triggers (such as particular foods, additives, allergens, weather, and lighting; L-R $\chi^2 = 26.33$, $p < 0.0001$, Bonferroni-corrected $p < 0.001$), vaccinations (L-R $\chi^2 = 6.46$, $p = 0.01$, Bonferroni-corrected $p < 0.05$), and infections in frequent contacts even in the absence of personal infection (L-R $\chi^2 = 13.78$, $p = 0.0002$, Bonferroni-corrected $p < 0.001$). There was a statistically significant relationship between more persistent PANS symptoms and a tendency for symptoms to flare in conjunction with comorbid medical conditions (L-R $\chi^2 = 11.86$, $p = 0.003$).

% days symptom-free by medical comorbidities

Medical comorbidities that were most strongly associated with more persistent symptoms included unexplained rashes (L-R $\chi^2 = 11.17$, $p = 0.0008$, Bonferroni-corrected $p < 0.01$), eczema (L-R $\chi^2 = 7.53$, $p = 0.006$, Bonferroni-corrected $p < 0.05$), chronic sinusitis (L-R $\chi^2 = 7.62$, $p = 0.006$, Bonferroni-corrected $p < 0.05$), headaches (L-R $\chi^2 = 10.31$, $p = 0.001$, Bonferroni-corrected $p < 0.05$), and frequent diarrhea (L-R $\chi^2 = 7.47$, $p = 0.005$, Bonferroni-corrected $p < 0.10$) (Table 2). There was no significant difference between groups in frequencies of sore throats, pneumonia, ear infections, or scarlet fever. Among those whose immune competence had been evaluated, subjects with more persistent symptoms were more likely to have identified immunologic abnormalities (L-R $\chi^2 = 5.88$, $p = 0.05$), although deficiencies were common across the board (16% to 38% across persistence categories). Of those who reported immune deficiencies, small N's for specific diagnoses prevented strong conclusions, but there were notably high rates of Total IgG deficiency (56%) and of IgG4 subclass deficiency (38%) in subjects with the most persistent symptoms.

% days symptom-free and treatment with intravenous immunoglobulin

The use of intravenous immunoglobulin (IVIG) was quite common (19%–38%) across symptom-persistence categories (Table 3). Those with more persistent symptoms were more likely to have been treated with IVIG (L-R $\chi^2 = 8.11$, $p = 0.004$) but there was no clear relationship between *% days symptom-free* and the IVIG protocol used. There was a significant positive relationship between *% days symptom-free* and the effectiveness of IVIG at ameliorating PANS symptoms (L-R $\chi^2 = 16.40$, $p = 0.0009$).

% days symptom-free by functional performance and developmental history

There was a strong relationship between symptom persistence and difficulty functioning in the classroom setting, which derived largely from the tendency of those with more persistent symptoms to miss school for periods of more than 1 week at a time (Table 4).

There was a strong correlation between lower symptom persistence and *absence* of a developmental diagnosis (L-R $\chi^2 = 12.78$, $p = 0.0004$); only 38%–39% of those with <25% of days symptom-free, but 68% of those with 75%–99% of days symptom-free, had no such history. The range of diagnosed developmental conditions reported was broad, with only autism significantly more prevalent with higher symptom persistence once Bonferroni corrections were applied (L-R $\chi^2 = 11.19$, $p = 0.0008$, Bonferroni-corrected $p < 0.01$). However, clear correlations existed between higher symptom persistence and greater frequencies of respondent-perceived developmental ''lags'' relative to peers in every area examined (Bonferroni-corrected $p < 0.001$ for: verbal, spatial, artistic, other creative, athletic, social, mathematical, memory, fine motor, and gross motor abilities; Bonferroni-corrected $p < 0.01$ for empathy and reading). Across all symptom-persistence categories, the most common perceived deficits were in fine motor skills (29%–55% across persistence categories) and social abilities (20%–54%). Lags in other areas were uncommon in individuals with low symptom persistence (3%–12%), but quite common in the more persistently symptomatic groups (23%–55%).

% days symptom-free by PANS symptomatology

The PANS symptomatology of subjects with more persistent symptoms included significantly higher frequencies of mood symptoms (especially irritability: L-R $\chi^2 = 12.29$, $p = 0.0005$, Bonferroni-corrected $p < 0.05$), cognitive and perceptual symptoms (especially sensory defensiveness [L-R $\chi^2 = 17.55$, $p < 0.0001$, Bonferroni-corrected $p < 0.01$] and brain fog [L-R $\chi^2 = 10.51$, $p = 0.001$, Bonferroni-corrected $p < 0.05$]), aggression-related behavior symptoms (L-R χ^2 range 11.54–27.10, $p < 0.0001$ to .0007, Bonferroni-corrected $p < 0.05$ to <0.01), sleep symptoms (L-R χ^2 range 14.85–19.18, $p < 0.0001$ to .0001, Bonferroni-corrected $p < 0.01$), urinary issues (L-R χ^2 range 6.98–11.14, $p = 0.004$ to 0.0008, Bonferroni-corrected p ns to <.05), fatigue (L-R $\chi^2 = 7.34$, $p = 0.007$, Bonferroni-corrected $p =$ ns), and muscle pain (L-R $\chi^2 = 15.70$, $p < 0.0001$, Bonferroni-corrected $p < 0.01$) (Table 5). There were no significant differences across symptom-persistence groups in rates of tics, eating-related symptoms, or most forms of anxiety.

When present, the severity of mood, cognitive, and behavior symptoms was also generally greater for subjects with greater symptom persistence; symptoms with the most significant differences in maximum severity across groups (unadjusted $p \leq 0.001$) included fatigue (ranging from 7.8 on a scale of 1–10 for the most persistent group to 6.1 for the most intermittent group, $F = 8.03$, $p < 0.0001$), irritability (8.1 vs. 6.6, $F = 7.65$, $p < 0.0001$), mood lability (8.0 vs. 6.6, $F = 5.70$, $p = 0.0002$), aggression toward others (6.9 vs. 5.1, $F = 4.54$, $p = 0.001$), and bizarre thoughts and behavior ($F = 4.85$, $p = 0.0008$; full data available upon request).

Discussion

Our findings reveal compelling associations between the persistence of PANS symptoms as measured by respondent-reported *% days symptom-free* and subjects' medical comorbidities, inciting infections for recurrences, responses to environmental triggers, and IVIG treatment experiences. Increased symptom persistence in our study was also associated with more pervasive debility in a wide range of realms, including more problematic neuropsychiatric and behavioral symptoms, cognitive and perceptual symptoms, sleep symptoms, urinary issues, fatigue, pain, and developmental issues, as well as an inability to attend school even with accommodation. Although it is not possible to assert causality for the associations revealed in this observational study, the life-altering consequences of persistent symptoms make it important to explore all potential opportunities to shift patients toward more intermittent symptoms

Table 2. Medical Comorbidities by Symptom Persistence in Pediatric Acute Onset Neuropsychiatric Syndrome (% Reporting This Condition/[*N*])

Condition	*No days symptom-free*	*1%–25% days symptom-free*	*26%–50% days symptom-free*	*51%–75% days symptom-free*	*>75% days symptom-free*	*Estimate (95% CI)*	*L-Rχ^2*	p
Which best describes the patient's immune status? (before IVIG treatment, if applicable)[a]							5.88	0.05
Apparently healthy immunity	46% (34)	45% (49)	38% (24)	53% (36)	66% (53)			
Low-normal IgG	23% (17)	23% (25)	16% (10)	25% (17)	13% (10)			
Immune deficient	22% (16)	29% (32)	38% (24)	21% (14)	16% (13)			
Type of immune deficiency (among those who reported immune deficiency; select all that apply)								
Total IgG below limit of normal (BLN)	56% (9)	44% (14)	52% (13)	47% (7)	23% (3)		1.49	0.22
IgG1 BLN	13% (2)	6% (2)	4% (1)	7% (1)	8% (1)			NP
IgG2 BLN	19% (3)	9% (3)	4% (1)	27% (4)	8% (1)			NP
IgG3 BLN	6% (1)	3% (1)	4% (1)	7% (1)	23% (3)			NP
IgG4 BLN	38% (6)	13% (4)	4% (1)	0	23% (3)			NP
Inadequate Prevnar response	19% (3)	9% (3)	12% (3)	13% (2)	54% (7)			NP
IgA BLN	19% (3)	22% (7)	44% (11)	13% (2)	23% (3)			NP
Likely autoimmune/inflammatory conditions								
Allergies	51% (59)	58% (99)	55% (54)	66% (70)	46% (49)	0.01 (–0.14 to 0.15)	0.01	0.91
Asthma	23% (27)	27% (48)	23% (23)	32% (34)	23% (26)	0.04 (–0.12 to 0.20)	0.28	0.60
Sinusitis, chronic	47% (54)	39% (67)	41% (40)	36% (37)	26% (28)	–0.21 (–0.36 to –0.06)	7.62	0.006*
Eczema	51% (60)	35% (62)	35% (35)	42% (45)	27% (29)	–0.21 (–0.35 to –0.06)	7.53	0.006*
Unexplained rashes/bumps	44% (51)	44% (76)	40% (40)	36% (37)	22% (23)	–0.25 (–0.40 to –0.10)	11.17	0.0008**
Recurrent high fevers	25% (29)	23% (40)	26% (26)	25% (26)	11% (12)	–0.17 (–0.34 to 0)	3.93	0.05
Joint conditions/pain	44% (52)	40% (68)	47% (47)	32% (33)	25% (27)	–0.19 (–0.34 to –0.04)	6.29	0.01
Muscle conditions/pain	37% (42)	39% (68)	37% (37)	30% (31)	22% (24)	–0.17 (–0.32 to –0.02)	4.65	0.03
Celiac disease	8% (9)	6% (10)	5% (5)	4% (4)	3% (3)			NP
Infection-related conditions								
Frequent sore throats	56% (65)	49% (82)	51% (46)	57% (54)	42% (45)	–0.08 (–0.23 to 0.07)	1.16	0.28
Pneumonia	36% (42)	31% (54)	34% (33)	33% (35)	21% (22)	–0.13 (–0.28 to 0.02)	2.75	0.10
Frequent ear infections	44% (52)	45% (77)	49% (49)	44% (46)	33% (36)	–0.09 (–0.24 to 0.05)	1.56	0.21
MRSA (Methicillin-Resistant *Staphylococcus Aureus*) skin infections	3% (4)	5% (9)	4% (4)	8% (8)	6% (6)	0.18 (–0.14 to 0.49)	1.19	0.28
Scarlet fever	13% (16)	13% (22)	22% (22)	17% (18)	13% (13)	0.03 (–0.16 to 0.23)	0.12	0.73
Rheumatic fever	5% (6)	4% (7)	4% (4)	3% (3)	3% (3)			NP
Other								
Headaches	54% (63)	58% (102)	42% (42)	43% (45)	34% (37)	–0.24 (–0.39 to –0.09)	10.31	0.001*
Concussion	6% (7)	4% (7)	3% (3)	2% (2)	12% (12)	0.27 (–0.08 to 0.64)	2.24	0.13
Chemical or food intolerances or sensitivities	37% (44)	48% (83)	31% (30)	44% (48)	33% (36)	–0.06 (–0.21 to 0.08)	0.70	0.40
Frequent constipation	35% (41)	40% (70)	36% (35)	25% (26)	24% (26)	–0.18 (–0.34 to –0.03)	5.60	0.02
Frequent diarrhea	28% (33)	25% (44)	17% (17)	15% (16)	16% (17)	0.25 (–0.43 to –0.07)	7.47	0.006‡
Celiac disease	8% (9)	6% (10)	5% (5)	4% (4)	3% (3)			NP
Colic	26% (30)	29% (50)	26% (25)	24% (25)	23% (25)	–0.07 (–0.23 to 0.10)	0.63	0.43
Underweight	29% (34)	28% (49)	29% (29)	18% (19)	15% (16)	–0.22 (–0.38 to –0.05)	6.57	0.01
Overweight	20% (23)	17% (29)	11% (11)	12% (12)	7% (8)	–0.27 (–0.48 to –0.05)	6.01	0.01

(*continued*)

TABLE 2. (CONTINUED)

Condition	*No days symptom-free*	*1%–25% days symptom-free*	*26%–50% days symptom-free*	*51%–75% days symptom-free*	*>75% days symptom-free*	*Estimate (95% CI)*	*L-R*χ^2	p
Hypothyroid	9% (10)	10% (17)	7% (7)	4% (4)	3% (3)	–0.30 (–0.58 to –0.02)	4.30	0.04
Hyperthyroid	1% (1)	2% (4)	4% (4)	0	0	–0.25 (–0.82 to 0.30)	0.83	NP
Delayed growth	14% (16)	15% (25)	16% (16)	10% (10)	7% (7)	–0.16 (–0.37 to 0.05)	2.18	0.14
Anemia	14% (16)	14% (25)	14% (14)	9% (9)	10% (10)	–0.35 (–0.37 to 0.07)	1.82	0.18
Kidney/bladder	9% (11)	8% (13)	2% (2)	7% (7)	5% (5)			NP
Numerous dental caries	17% (19)	19% (32)	14% (14)	16% (16)	10% (11)	–0.11 (–0.31 to 0.09)	1.22	0.27
Heart condition/heart murmur	14% (16)	12% (22)	13% (13)	17% (18)	16% (17)	0.09 (–0.11 to 0.30)	0.81	0.37

†Bonferroni-corrected $p < 0.10$.
*Bonferroni-corrected $p < 0.05$.
**Bonferroni-corrected $p < 0.01$.
[a]Excludes subjects with "low white count."
IVIG, intravenous immunoglobulin; NP, not performed due to small expected N per cell.

and more durable remissions. Encouragingly from this perspective, symptom persistence appears to be impacted by potentially modifiable variables, including infectious and environmental exposures, although intrinsic factors such as a genetic vulnerability to immune dysfunction also likely play a role.

In general, the specific comorbidities and symptoms that were more often reported for subjects with more persistent PANS symptoms are common in many rheumatologic conditions, that is, pain (headaches, musculoskeletal), immune deficiencies, dermatologic and sinus issues, digestive concerns, fatigue, irritability, and brain fog (Dickerson et al., 2007; Groven et al., 2018; Hansen et al., 2020; Kogan et al., 2020). Subjects with more persistent symptoms did not, however, suffer higher rates of allergies or asthma. It is conceivable that these common conditions are more likely to be treated on a consistent basis with systemic anti-inflammatory medications and that such medications may in turn mitigate PANS symptoms; the relationships between comorbid conditions, medications, and PANS symptoms deserve further exploration.

Greater symptom persistence was also associated in our sample with symptom reactivity to a wider range of immune stimuli, including infections in cohabitants, vaccinations, and environmental irritants, as well as with infections that are often persistent, for example, chronic sinus infections and EBV, and with flares in comorbid conditions. These observations suggest that, in contrast to subjects with more intermittent disease, persistently symptomatic PANS subjects may suffer a more consistently active inflammatory response. Peripheral inflammation has known negative effects on cognitive function and emotional processing, with potential mechanisms including disruption of the blood–brain barrier and activation of pro-inflammatory cytokines, T/B cells, and monocytes (Bauer and Teixeira, 2019; Bollen et al., 2017; Huang et al., 2021; Miller, 2020; Platt et al., 2017; Van Erp et al., 2022; Yarlagadda et al., 2009). The greater levels of immune compromise, lower responsiveness to the initial antibiotic course, and broader range of infectious triggers associated with symptom persistence in our sample also suggest that the ratio of immune challenge to immune competence may play a role in symptom persistence. Whether some patients may benefit from increased antibiotic dosing or duration requires further study.

The muted response to IVIG treatment in subjects with more persistent PANS symptoms is also of interest in this context. In our sample, subjects with greater symptom persistence were more likely to have received IVIG, possibly because of their more problematic PANS symptoms and/or their higher rates of relatively pervasive immune deficiency. In other chronic inflammatory disorders, including multiple sclerosis, lupus, and rheumatoid arthritis, IVIG treatment is reserved for clearly relapsing-remitting, refractory, or special cases (e.g., pregnancy), as the benefits for chronic cases generally do not outweigh the liabilities (Dalakas, 2004; Hoffman and Enk, 2019; Katz-Agranov et al., 2015; Mulhearn and Bruce, 2015; Shoenfeld and Katz, 2005; Sorensen, 2003). Instead, standard treatment for chronic cases relies on corticosteroids, DMARDS (Disease Modifying Anti-Rheumatic Drugs), B-cell suppressors, and/or cytokine inhibitors to provide more consistent suppression of the inflammatory state than periodic IVIG can achieve.

Children with chronic/persistent PANS possess many clinical features found in other chronic rheumatic conditions such as lupus, psoriatic arthritis, and ankylosing spondylitis, all of which are also seen at elevated frequencies in PANS patients and/or first-degree relatives (Calaprice et al., 2017; Chan et al., 2020; Fernell et al., 2021; Frankovich et al., 2015; Murphy et al., 2010). In fact, 28% of

Table 3. IVIG Treatment by Symptom Persistence in Pediatric Acute Onset Neuropsychiatric Syndrome (% Reporting This Condition/[*N*])

	No days symptom-free	*1%–25% days symptom-free*	*26%–50% days symptom-free*	*51%–75% days symptom-free*	*>75% days symptom-free*	*L-R* χ^2	p
Use of IVIG (% Yes)	38% (47)	31% (55)	28% (29)	31% (34)	19% (22)	8.11	0.004**
IVIG treatment program						16.53	0.35
Single treatment	45% (21)	42% (23)	32% (9)	32% (11)	64% (14)		
Recurrent based on PANS symptoms	19% (9)	27% (15)	32% (9)	41% (14)	18% (4)		
Regularly scheduled, 2–5 weeks	21% (10)	11% (6)	21% (6)	11% (4)	14% (3)		
Regularly scheduled, 6–12 weeks	13% (6)	13% (7)	7% (2)	6% (2)	0		
Other	2% (1)	7% (4)	7% (2)	9% (3)	5% (1)		
IVIG effectiveness						16.40	0.0009***
Very effective	34% (15)	42% (21)	44% (12)	59% (20)	86% (18)		
Somewhat effective	34% (15)	24% (12)	30% (8)	15% (5)	14% (3)		
Not very effective	14% (6)	16% (8)	7% (2)	0	0		
Effective at first, but then lost effect	18% (8)	18% (9)	18% (5)	26% (9)	0		

Bonferroni-corrections not needed:
**$p < 0.01$.
***$p < 0.0001$.
PANS, Pediatric Acute Onset Neuropsychiatric Syndrome.

patients meeting PANS criteria at Stanford's clinic developed chronic arthritis confirmed by MRI or ultrasound, often years later (Ma et al., 2023). Interestingly, it is not uncommon for psychiatric symptomatology, including OCD, to antedate development of the physical manifestations of autoimmune illnesses such as Sjogrens and inflammatory bowel disease (Ananthakrishnan et al., 2013; Chang et al., 2021; Walker et al., 2008). These observations suggest the need for long term follow-up of PANS patients to determine risk of developing additional rheumatologic conditions and for research into the role of DMARDS, B-cell suppressors, and cytokine inhibitors in treating persistent PANS.

In our sample, developmental concerns were present even in significant minorities of those with low-symptom persistence, while the majority of those with highly persistent symptoms carried one or more developmental diagnoses and suffered high rates of respondent-perceived developmental lags relative to peers in every functional realm probed. Possible explanations for these associations are that PANS and developmental issues share a common pathophysiologic mechanism; that they share common risk factors; or that either condition predisposes a child for the other (e.g., social skills lag due to loss of opportunities to develop such skills during PANS exacerbations, Tona et al., 2017). Our survey did not inquire whether developmental diagnoses were rendered before or after the PANS diagnosis; thus, it is also possible that, because of diagnostic overshadowing (i.e., an individual's new symptoms are attributed to the previously-diagnosed condition rather than being investigated independently, thought to occur often in mental health conditions; The Joint Commission, 2022), individuals with preexisting developmental disorders may not have received prompt workups at PANS onset, resulting in delayed diagnosis and treatment and leading to a more persistent course (Calaprice-Whitty et al., 2023). In any case, our findings point to the importance of inquiring about developmental concerns during PANS evaluations.

Our findings also suggest the potential utility of interventions to improve occupational participation. Occupational therapists may identify opportunities to accommodate deficits during exacerbations and assist with ''catch up'' development as exacerbations subside (Tona and Posner, 2011). Ultimately, further research exploring the root cause of the association between PANS and developmental issues, as well as research examining the effectiveness of occupational therapies, could help professionals develop appropriate interventions to promote skill development.

The results of this study underscore the recommendations for clinical evaluation from the 2013 PANS Consensus Conference (Chang et al., 2015), which called for inquiring about a history of rashes over the past 6 months and for serologic testing relevant to potential rheumatologic diagnoses if a rash, joint pain, fatigue, or elevated inflammatory markers are seen. In our sample, such symptoms correlate with higher PANS symptom persistence and may support the provider not only in differential diagnosis but also in risk-stratifying patients to consider for more aggressive treatment. Our findings also support Chang et al.'s recommendation to maintain a low index of suspicion to screen for immune deficiencies. Immune abnormalities are so commonplace in the PANS population that universal screening may even be warranted, including not only measurement of total immunoglobulins but also of IgG subclasses and specific antibody deficiencies that may be detected by inadequate response to multivalent pneumococcal vaccination; any of these may be clinically relevant to the ability to clear a specific infection and to the development of autoimmunity (Jefferis and Kumararatne, 1990; Morell, 1994).

This study has the weaknesses associated with any retrospective observational survey, including that participants are self-selected and diagnoses are self-reported. With respect to self-selection, respondents who represent more serious cases may be more engaged with PANS patient communities and hence more likely to respond to solicitations for research participation; thus it is possible that our sample skews in this direction and is not representative of the PANS population as a whole. On the flipside, however, it is also possible that respondents who represent more serious cases may find it more burdensome to participate in research activities with no expected personal benefit; thus our sample may also skew the other way. The fact that no benefit whatsoever was offered to subjects to complete the lengthy survey would be expected to minimize participation by those not meeting diagnostic criteria. Although each of these factors may play some role in shaping our sample, the fact

Table 4. Developmental Comorbidities by Symptom Persistence in Pediatric Acute Onset Neuropsychiatric Syndrome (% Reporting This Condition/[*N*])

Condition	*No days symptom free*	*1%–25% days symptom-free*	*26%–50% days symptom-free*	*51%–75% days symptom- free*	*>75% days symptom-free*	*Estimate (95% CI)*	*L-R* χ^2	p
Have the patient's PANS symptoms interfered with his/her ability to function adequately in a typical preschool/classroom setting?							28.23	<0.0001****
No	13% (16)	22% (39)	23% (24)	22% (23)	39% (44)			
Attends with accommodations	29% (35)	30% (52)	39% (41)	31% (33)	33% (37)			
Misses periods of ≥1 week	52% (63)	37% (64)	28% (29)	39% (42)	19% (21)			
Does not attend during exacerbations	7% (8)	11% (19)	10% (11)	8% (9)	9% (10)			
Developmental diagnoses								
No developmental diagnosis	38% (41)	39% (63)	52% (46)	44% (40)	68% (63)	0.28 (0.13 to 0.43)	12.78	0.0004***
Specific developmental diagnoses								
Autism	22% (23)	14% (22)	9% (8)	7% (6)	8% (7)	−0.40 (−0.64 to −0.17)	11.19	0.0008**
ADHD	29% (31)	29% (46)	27% (24)	22% (20)	15% (14)	−0.18 (−0.36 to −0.01)	4.54	0.03
Learning disability	15% (16)	17% (28)	10% (9)	14% (13)	8% (7)	−0.11 (−0.34 to 0.11)	0.99	0.32
Dysgraphia	11% (12)	17% (28)	9% (8)	12% (11)	8% (7)	−0.08 (−0.31 to 0.15)	0.48	0.48
Dyscalculia	7% (8)	8% (13)	7% (6)	6% (5)	0			NP
Dyslexia	3% (3)	5% (8)	3% (3)	4% (4)	5% (5)			NP
Visuoperceptual disorder	4% (4)	7% (11)	1% (1)	1% (1)	5% (5)			NP
Speech delay	17% (18)	11% (18)	11% (10)	14% (13)	10% (9)	−0.12 (−0.35 to 0.11)	0.97	0.32
Coordination disorder	4% (4)	6% (10)	2% (2)	2% (2)	2% (2)			NP
Sensory integration disorder	20% (21)	22% (36)	17% (15)	11% (10)	11% (10)	0.21 (−0.41 to −0.01)	4.33	0.04
Do you feel that the patient lags behind his/her peers in any of the areas below? % Yes (N)								
Verbal abilities	27% (31)	23% (39)	15% (15)	12% (13)	7% (8)	−0.40 (−0.59 to −0.21)	17.41	<0.0001***
Spatial abilities	30% (36)	23% (38)	13% (13)	16% (17)	7% (8)	−0.42 (−0.60 to −0.23)	19.04	<0.0001***
Artistic abilities	32% (37)	29% (49)	14% (14)	13% (14)	11% (12)	−0.53 (−0.76 to −0.31)	21.86	<0.0001***
Other creative abilities	23% (27)	14% (23)	10% (10)	8% (8)	3% (3)	−0.53 (−0.76 to −0.31)	21.86	<0.0001***
Athletic abilities	43% (50)	36% (59)	33% (33)	28% (29)	9% (10)	−0.41 (−0.57 to −0.26)	26.85	<0.0001***
Social abilities	53% (63)	54% (92)	36% (35)	36% (38)	20% (22)	−0.42 (−0.57 to −0.27)	31.15	<0.0001***
Empathy	23% (27)	23% (37)	16% (16)	13% (14)	6% (6)	−0.37 (−0.56 to −0.18)	14.64	0.0001**
Mathematical abilities	37% (43)	39% (66)	29% (30)	28% (30)	11% (12)	−0.33 (−0.49 to −0.17)	16.23	<0.0001***
Reading	31% (37)	33% (57)	26% (25)	24% (25)	12% (13)	−0.28 (−0.44 to −0.12)	11.57	0.0007**
Memory	28% (33)	27% (46)	16% (16)	16% (16)	5% (5)	−0.43 (−0.62, −0.25)	21.20	<0.0001***
Fine motor (inc handwriting)	55% (64)	51% (90)	38% (39)	38% (40)	29% (33)	−0.31 (−0.46 to −0.17)	17.86	<0.0001***
Gross motor	39% (46)	29% (48)	27% (26)	18% (19)	11% (12)	−0.40 (−0.58 to −0.24)	23.39	<0.0001***

**Bonferroni-corrected $p < 0.01$.
***Bonferroni-corrected or not needed, $p < 0.001$.
****Bonferroni not needed, $p < 0.0001$.
NP = not performed.

Table 5. Frequency of Pediatric Acute Onset Neuropsychiatric Syndrome Symptoms by Symptom Persistence Category in Pediatric Acute Onset Neuropsychiatric Syndrome (% Reporting This Symptom/[*N*])

	No days symptom-free (N = *124*)	*1%–25% days symptom-free* (N = *179*)	*26%–50% days symptom-free* (N = *105*)	*51%–75% days s ymptom-free* (N = *110*)	*>75% days symptom-free* (N = *118*)	*Estimate (95% CI)*	*L-R* χ^2	p
Anxiety symptoms								
General anxiety	96% (117)	98% (175)	94% (97)	95% (104)	95% (112)	–0.05 (–0.40 to 0.32)	0.06	0.81
Obsessive compulsive symptoms	94% (117)	95% (170)	94% (99)	90% (99)	93% (110)	–0.12 (–0.40 to 0.16)	0.70	0.40
Specific phobias	76% (90)	80% (140)	66% (65)	74% (79)	68% (77)	–0.13 (–0.29 to 0.03)	2.56	0.11
Excessive worry	87% (105)	91% (160)	85% (88)	86% (93)	82% (95)	–0.14 (–0.35 to 0.07)	1.65	0.20
Social anxiety	71% (87)	64% (112)	59% (60)	68% (73)	49% (56)	–0.19 (–0.34 to –0.04)	6.51	0.01
Panic attacks	67% (80)	54% (95)	49% (49)	62% (67)	47% (53)	–0.12 (–0.27 to 0.02)	2.78	0.10
Mood symptoms								
Mood lability	90% (110)	94% (163)	90% (94)	92% (99)	78% (90)	–0.38 (–0.62 to –0.13)	9.28	0.002‡
Irritability	88% (107)	94% (165)	92% (95)	92% (99)	73% (84)	–0.42 (–0.66 to –0.19)	12.29	0.0005*
Sadness	85% (105)	85% (146)	79% (78)	87% (94)	73% (84)	–0.16 (–0.35 to 0.03)	2.80	0.09
Cognitive & perceptual symptoms								
Loss of math skills	67% (80)	69% (119)	69% (70)	68% (72)	53% (59)	–0.13 (–0.28 to 0.03)	2.50	0.11
Brain fog/confusion	67% (81)	74% (129)	66% (66)	64% (69)	46% (52)	–0.25 (–0.41 to –0.10)	10.51	0.001*
Sensory defensiveness (e.g., to sound, light, clothing)	85% (105)	83% (144)	78% (81)	81% (87)	63% (72)	–0.37 (–0.55 to –0.20)	17.55	<0.0001**
Behavior symptoms								
Rage/meltdowns	86% (104)	88% (155)	84% (87)	87% (95)	69% (79)	–0.34 (–0.54 to –0.14)	11.54	0.0007*
Aggression toward others	61% (74)	64% (113)	66% (67)	61% (66)	38% (43)	–0.27 (–0.42 to –0.13)	13.43	0.0002**
Self-injurious behavior	56% (68)	44% (76)	38% (38)	35% (37)	21% (24)	–0.39 (–0.54 to –0.24)	27.10	<0.0001**
Defiance	74% (90)	82% (144)	79% (81)	80% (87)	56% (63)	–0.27 (–0.44 to –0.10)	9.37	0.002‡
Hyperactivity	61% (73)	73% (126)	75% (75)	68% (73)	53% (59)	–0.15 (–0.31 to 0)	3.65	0.06
Somatic symptoms								
Fatigue	82% (99)	77% (131)	75% (76)	78% (83)	61% (69)	–0.23 (–0.40 to –0.06)	7.34	0.007
Frequent urination	63% (75)	58% (100)	57% (57)	50% (54)	44% (49)	–0.21 (–0.36 to –0.07)	8.44	0.004
Daytime urinary incontinence	37% (45)	33% (57)	31% (31)	28% (30)	20% (22)	–0.27 (–0.43 to –0.11)	11.14	0.0008*
Bed-wetting	38% (46)	46% (80)	41% (42)	32% (34)	28% (32)	–0.20 (–0.34 to –0.05)	6.98	0.008
Joint pain	61% (72)	54% (93)	63% (64)	46% (49)	41% (46)	–0.20 (–0.34 to –0.06)	7.43	0.006
Muscle pain	59% (71)	49% (85)	53% (53)	39% (42)	30% (33)	–0.29 (–0.44 to –0.15)	15.70	<0.0001**
Movement and speech								
Tics – eyes	51% (62)	53% (90)	55% (57)	56% (58)	43% (49)	–0.04 (–0.19 to 0.10)	0.39	0.53
Tics – motor (other than eye)	68% (82)	71% (125)	72% (75)	72% (76)	77% (89)	0.12 (–0.04 to 0.27)	2.19	0.14
Tics – vocal	55% (66)	61% (107)	59% (58)	64% (67)	46% (53)	–0.09 (–0.24 to 0.05)	1.61	0.20
Speech dysfluencies (e.g., stuttering, stammering)	40% (48)	43% (72)	31% (32)	35% (37)	29% (32)	–0.17 (–0.32 to –0.02)	5.25	0.02
Mutism	15% (18)	13% (22)	5% (5)	12% (13)	8% (9)	–0.18 (–0.41 to 0.05)	2.25	0.13
Handwriting deterioration	77% (95)	78% (138)	73% (74)	75% (80)	69% (79)	–0.11 (–0.28 to 0.05)	1.85	0.17

(*continued*)

TABLE 5. (CONTINUED)

	No days symptom-free (N = *124*)	*1%–25% days symptom-free* (N = *179*)	*26%–50% days symptom-free* (N = *105*)	*51%–75% days s ymptom-free* (N = *110*)	*>75% days symptom-free* (N = *118*)	*Estimate (95% CI)*	*L-R* χ^2	p
Psychotic symptoms								
Bizarre thoughts or behavior	69% (83)	75% (129)	68% (69)	72% (78)	60% (70)	0.11 (–0.27 to 0.04)	2.08	0.15
Hallucinations	42% (42)	41% (69)	30% (30)	36% (39)	27% (30)	–0.15 (–0.30 to 0)	3.98	0.05
Mania/hypomania	43% (52)	43% (75)	37% (37)	37% (39)	28% (31)	–0.17 (–0.32 to –0.03)	5.42	0.02
Sleep symptoms								
Insomnia	70% (85)	79% (139)	63% (65)	65% (69)	50% (57)	–0.30 (–0.46 to –0.15)	14.85	0.0001**
Nightmares	64% (64)	63% (109)	56% (57)	54% (57)	39% (44)	–0.29 (–0.43 to –0.14)	15.38	<0.0001**
Night terrors	44% (53)	46% (79)	34% (34)	30% (31)	22% (25)	–0.33 (–0.48 to –0.18)	19.18	<0.0001**
Eating and digestive								
Restrictive eating, eating fears, fear of weight gain	49% (60)	50% (88)	48% (48)	50% (53)	41% (46)	–0.05 (–0.19 to 0.09)	0.53	0.47
Bulimia/binge eating	7% (8)	8% (14)	10% (10)	8% (8)	4% (4)	–0.05 (–0.32 to 0.21)	0.16	0.68
Loss of appetite	51% (60)	51% (88)	46% (46)	53% (55)	37% (41)	–0.12 (–0.26 to 0.03)	2.58	0.11
Stomach/Abdominal pain	68% (84)	67% (115)	63% (64)	58% (62)	56% (64)	–0.17 (–0.32 to –0.03)	5.37	0.02
Encopresis	15% (18)	13% (22)	12% (12)	10% (11)	6% (7)	–0.25 (–0.48 to –0.03)	5.16	0.02

‡Bonferroni-corrected $p < 0.10$.
*Bonferroni-corrected $p < 0.05$.
**Bonferroni-corrected $p < 0.01$.

that our sample characteristics are consistent with those seen in practice-based studies of PANS (e.g., gender and age distribution, time to diagnosis, range of acuity of onset, symptom frequencies, recurrence rates) suggests our sample to be representative of the general PANS population that participates in research (Frankovich et al., 2015; Johnson et al., 2019; Lepri et al., 2019; Murphy et al., 2015).

It is also possible that recall bias plays a role in a few of our findings. For example, caregivers of subjects with more persistent symptoms may be more likely to track or recall events that led to symptom exacerbations or may be more focused on tracking individual symptoms or functional deficits as they occur. To mitigate this effect, we offered, in the survey, ''don't recall'' or ''don't know'' options for every question so that respondents who could not recall clearly did not feel compelled to guess, and we then excluded such responses from the analysis. Indeed, if recall biases such as these were in play, we would expect their effect to be most apparent for more subtle events or symptoms that might escape the notice of less-focused caregivers. Instead, the most pronounced differences were observed in symptoms that are likely to be memorable to all, for example, aggression, urinary incontinence, pain, sleep problems such as night terrors and nightmares, and diagnoses of developmental disorders.

In contrast, a major strength of our survey format is that it achieves a large broad sample otherwise not possible for an uncommon disease. This naturalistic study represents ''real world'' community medicine and not simply the experience of PANS specialty clinic populations, thus serving to confirm the generalizability of studies of those populations. Our naturalistic data may also be hypothesis-generating for prospective studies. For example, we urge future research on the intersection between PANS and other rheumatologic illnesses, as well as prospective studies of disease modifying anti-rheumatic drugs (DMARDS) in PANS patients at high risk of further autoimmunity. Such research should include long-term follow-up of both medically-supervised and community-based cohorts and consideration of the hypothesis that PANS may in fact represent an early and/or subsyndromal presentation of a rheumatologic condition.

Future research may also consider the relationship between *% symptom-free days* and disease course according to classical rheumatologic classifications, that is, relapsing-remitting vs. chronic. Although the measure *% symptom-free days* shows, importantly, what proportion of time a person feels and functions normally (and does in fact correlate in our sample with function, for example, the ability to attend school), it does not entirely distinguish between individuals with frequent short flares and those with few or single long bouts. The effectiveness of programs focusing on occupational engagement is another area deserving of further investigation. Finally, research relevant to the identification and avoidance or management of a variety of infections and inflammatory triggers could help in the development of strategies to prevent more persistent and pervasive disease manifestations.

Conclusion and Clinical Significance

The present study sheds light on the wide-ranging experiences of PANS subjects in a large community sample and identifies features associated with symptom persistence. Specifically, subjects experiencing greater PANS symptom persistence also reported higher rates of: medical comorbidities, including rashes, pain (head, muscle, joint), digestive concerns, chronic sinusitis, and immune deficiencies; symptom exacerbations in association with infections in close contacts, vaccinations, a variety of environmental triggers, flares of comorbid medical conditions, and infections with EBV, mycoplasma, or ''sinus infections''; developmental diagnoses and respondent-perceived developmental lags; and difficulties attending school. They were also more likely to receive IVIG but less likely to find it effective. Together with our companion article, the results presented here suggest that both intrinsic and extrinsic factors, including exposures and access to interventions, may influence the symptom persistence experienced by individual patients. Adherence to published assessment and treatment recommendations may improve disease course, with pervasive benefits on health, function, and quality of life.

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