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Special Section: Update on PANS

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Factors Associated with Symptom Persistence in PANS: Part I—Access to Care

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Abstract

Objective: Pediatric acute-onset neuropsychiatric syndrome (PANS) presents with abrupt neuropsychiatric symptoms, often after an immunologic trigger. A 2017 survey of 698 subjects found diagnostic delays to be associated with recurrences, suggesting that timely care impacts course. This secondary analysis explores the impact of barriers to care on symptom persistence.

Methods: A 146-question online survey gathered history, symptomatology, intervention, and outcome data from subjects with PANS. Multivariate analyses examined associations between symptom persistence over the entire reported disease course, measured as *% days symptom-free* over reporting periods averaging approximately 4 years, and access-to-care history, reflected in availability of medical expertise and affordability of care. The impacts of time from symptom onset to treatment and effectiveness of initial antibiotics were also examined.

Results: Among the 646 subjects analyzed, greater symptom persistence was associated with longer intervals between symptom onset and treatment ($F = 4.43$, $p = 0.002$). Thirty-four percent of subjects with the least symptom persistence (>75% symptom-free days), versus 13% of those with the most (symptoms every day), had been diagnosed by the first practitioner seen (likelihood ratio [L-R] $\chi^2 = 36.55$, $p < 0.0001$, for comparison across all groups). Diagnosis and treatment had *not* been impeded by lack of access to expertise for 52% of subjects with the least persistent symptoms, versus 22% of those with the most (L-R $\chi^2 = 22.47$, $p < 0.0001$). Affordability had *not* impacted diagnosis and treatment for 76% of subjects with the least persistent symptoms, versus 42% of those with the most (L-R $\chi^2 = 27.83$, $p < 0.0001$). The subjects whose PANS symptoms resolved with antibiotic treatment of the inciting infection experienced less symptom persistence than others ($\chi^2 = 23.27$, $p = 0.0001$). More persistently symptomatic subjects were more likely to have discontinued intravenous immunoglobulin (IVIG) treatment for access-to-care reasons.

Conclusions: Unimpeded access to care for PANS is associated with more symptom-free days over reporting periods averaging approximately 4 years. Difficulty reaching expert providers, missed opportunities for diagnoses, and financial limitations may worsen outcomes. Practitioners, particularly primary providers, should adhere to published diagnostic and treatment guidelines promptly upon presentation.

Keywords: PANDAS, PANS, access to care, disparities in care, outcomes

Introduction

Individuals with pediatric acute-onset neuropsychiatric syndrome (PANS) experience myriad neuropsychiatric symptoms, frequently after infectious or inflammatory triggers (Swedo et al., 2012). Pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS) is a subset of PANS triggered by Group A streptococcus. Manifestations of PANS include obsessive-compulsive symptoms and/or restricted food intake, along with anxiety, emotional lability, depression, irritability, aggression, oppositional behaviors, behavioral regression, deterioration in school performance, psychosis, sensory and/or motor abnormalities, and sleep and/or urinary irregularities (Pavone et al., 2020; Swedo et al., 2012). Although onset is characteristically abrupt, acuity can be difficult to ascertain in very young patients, patients with existing neurobehavioral conditions, or patients with

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long-standing disease; thus, most PANS clinics recognize a minority of cases with subacute onset that are identical in other aspects to acute-onset cases and respond similarly to treatment (Frankovich et al., 2015). While the prevalence of PANS is not well defined, it was found in 5% of 134 youth in an obsessive-compulsive disorder specialty clinic (Jaspers-Fayer et al., 2017).

Recent consensus guidelines have established a standard approach for evaluation and intervention (Chang et al., 2015; Cooperstock et al., 2017; Frankovich et al., 2017; Swedo et al., 2017; Thienemann et al., 2017). A multipronged treatment strategy includes immunomodulatory therapies, management of infections, and behavioral interventions to address what is now understood to be immune-mediated basal ganglia inflammation (Cutforth et al., 2016; Dileepan et al., 2016; Wayne et al., 2023; Xu et al., 2021).

The duration, severity, and frequency of PANS exacerbations vary widely across patients. The illness is most often relapsing–remitting, although chronic static and progressive courses also occur (Gromark et al., 2022). In our survey sample of 698 cases reporting on disease courses over an average of approximately 4 years, 19% had experienced PANS symptoms every day since onset, whereas 19% had been asymptomatic >75% of days (Calaprice et al., 2017). Similarly, although most PANS patients suffer significant emotional distress plus at least some difficulty performing age-typical activities including eating, grooming, bowel and bladder management, handwriting, academics, extracurricular activities, community and family social participation, and free play, others experience mild courses involving relatively little disruption to daily life (Tona et al., 2017).

For other mental health conditions, particularly those impacting children (Christiana et al., 2000; Iza et al., 2013; Wang et al., 2005), some variability in disease course appears to relate to access to care, which has been defined as ''the opportunity to reach and obtain appropriate health-care services in situations of perceived need for care'' (Levesque et al., 2013). In Levesque's framework, ''access'' includes first the perception of a health care need and then opportunities to seek, reach, and utilize health care services to fulfill the need. During each step, ''supply-side'' and ''demand-side'' dimensions of accessibility conjointly determine whether a patient receives adequate care. As examples, ''supply-side'' barriers may include pediatricians' perceptions of inadequate reimbursement, inadequate training, and lack of time, as well as insufficient confidence to treat mental conditions (Horwitz et al., 2007). ''Demand-side'' barriers may include perceived stigma and lack of knowledge about services (Gulliver et al., 2012).

In our survey of 698 PANS cases, access-to-care barriers appeared to impede diagnosis and treatment for many; subjects experienced, on average, a 2-year lag between symptom onset and diagnosis (Calaprice et al., 2018; Calaprice et al., 2017). Existing research strongly suggests that early treatment of PANS with nonsteroidal anti-inflammatory drugs and oral corticosteroids significantly shortens flare duration (Brown et al., 2017a; Brown et al., 2017b). It is important to establish whether unimpeded access to treatment improves longer term outcomes as well.

This article seeks to examine relationships between access to care and PANS course in the same cohort of participants reported on by Calaprice et al. (2018, 2017). Specifically, we sought to test two hypotheses. First, that unimpeded access to knowledgeable practitioners who are willing and able to diagnose and treat PANS is associated with increased *% of symptom-free days* over PANS course, and second, that financially unimpeded access to PANS treatment is associated with increased *% of symptom-free* days over PANS course.

Methods

Data capture

A 146-question, retrospective online survey gathered data from caregivers of children diagnosed with PANS or PANDAS, and from adult PANDAS/PANS subjects, regarding medical and family history, symptomatology, medical and nonmedical interventions, and outcomes. Instrument development and recruitment are detailed in Calaprice et al. (2017). The study was approved by the Social and Behavioral Sciences Institutional Review Board at the University at Buffalo. Participants were recruited from PANS- and obsessive compulsive disorder (OCD)-related organizational websites, emails, conferences, and radio shows, as well as via posters sent to PANS-treating providers. Respondents certified that they were at least 18 years old and either the parents or legal guardians of children who had been diagnosed by a physician with PANS/PANDAS or had themselves been diagnosed, and then clicked ''I agree to participate'' to continue to the survey instrument.

Although no documentation was required from the medical record to confirm the presence of key PANS criteria, the following definition was offered as part of the survey introduction, before the electronic 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 in the study by Swedo et al. (2012), and descriptions can be found at http://intramural.nimh.nih.gov/pdn/PANDAS-to-PANS2012.pdf We consider PANS to include PANDAS, which is Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus, and PITAND, which is pediatric infection-triggered autoimmune neuropsychiatric disorder. Therefore, when we use the term ''PANS,'' we mean PANS, PANDAS, and/or PITAND.*

Data analysis

Of the 753 surveys submitted, 55 were considered, based on predefined logic checks, to contain illogical or incomplete information that rendered the data unreliable (e.g., postpubertal status described in very young subjects, history inconsistent with diagnosis); any instance of unreliable information excluded that patient record from the data analysis, leaving 698 records in the dataset. For this article, the outcome variable *% days symptom-free* (numeric categories selected by respondents) was used as the measure of symptom 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 categorical choices offered were as follows: (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.

Responses of ''patient was too young'' and ''don't remember'' (g and h) were excluded, leaving 646 records available for analysis. Categories b and c were combined, resulting in the five symptom-persistence categories. Ordinal logistic regression models were used for categorical dependent variables and multivariate analysis

of variance for continuous variables. There was a significant relationship between age and *% days symptom-free* (likelihood ratio [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* and thus were not included as factors. To provide the most conservative estimates of statistical significance, Bonferroni corrections for multiple tests (multiple possible answers to the same question) were applied, as indicated in the table footnotes and text. The JMP® statistical program was used to perform data analyses. Sample sizes varied across questions because some respondents failed to answer some questions, some questions were not relevant for all respondents, and answers of ''don't recall'' were removed from the analyses.

Results

Demographic and disease-onset characteristics

Of the 646 surveys included in the present analyses, 631 (94.9%) were completed by mothers, 24 (3.7%) by fathers, 4 (0.6%) by other caregivers, and 5 (0.8%) by adult subjects themselves (Table 1). Approximately 92% of the subjects resided in the United States; 44 states and Washington, DC were represented. The median subject age was 11 years (mean 11.7), and the median length of PANS illness was 3 years (mean 4.1). Sixty-six percent were male. Eighty-eight percent had sudden-onset illness.

Persistence of symptoms ranged widely: 19.1% had no symptom-free days; 28.5% were symptom-free 1%–25% of days; 16.5% were symptom-free 26%–50% of days; 28.5% were symptom-free 51%–74% of days; and 18.8% were symptom-free 75%–99% of days. There was no significant relationship between *% days symptom-free* and whether onset was foudroyant or gradual.

Individuals suffering the most persistent illness (no symptom-free days) had a median 1-year lag between the onset of symptoms and treatment (mean 2.6), whereas the two categories that enjoyed more than 50% symptom-free days had been treated more promptly (median 0 year, mean 1.0–1.2; Table 1; $F = 4.43$, $p = 0.002$). There was a highly significant association between *% days symptom-free* and whether antibiotic treatment of the first episode had successfully resolved PANS symptoms (L-R $\chi^2 = 23.27$, $p = 0.0001$).

Percent days symptom-free by access to medical expertise

There were highly significant relationships between *% days symptom-free* and variables reflecting access to medical expertise (Table 2). Fifty-two percent of subjects with 75%–99% days symptom-free, but only 22% of those in the two symptom-persistence categories with <25% days symptom-free, reported no issues accessing expertise (L-R $\chi^2 = 22.47$, $p < 0.0001$, for comparison across all symptom-persistence categories).

Table 1. Percent Days Symptom-Free by Age, Illness Duration, and Characteristics of Disease Onset

	No days symptom-free	*1%–25% Days symptom-free*	*26%–50% Days symptom-free*	*51%–75% Days symptom-free*	*>75% Days symptom-free*	*Statistic*	p
Age at time of survey (years)							
Mean (*N*)	13.0 (122)	11.6 (182)	11.1 (105)	10.9 (110)	12.0 (120)	$F = 4.08$	0.003
Median	12.5	11	11	10	12		
Duration of illness (years)							
Mean (*N*)	4.4 (116)	3.8 (168)	4.2 (103)	3.9 (105)	4.2 (116)	$F = 0.56$	0.68
Median	3	3	3	3	4		
Characteristic of onset, % (N)						L-R $\chi^2 = 9.6$	0.29
Gradual	11 (14)	7 (12)	9 (9)	9 (10)	5 (6)		
Sudden worsening, but in context of existing issues	27 (33)	30 (50)	20 (21)	25 (28)	20 (23)		
Sudden (ramp up over ≤3 days)	61 (75)	63 (105)	71 (73)	65 (72)	75 (87)		
Lag between onset of symptoms and first treatment (years)							
Mean (N)	2.6 (125)	1.9 (183)	2.3 (106)	1.0 (111)	1.2 (121)	$F = 4.43$	0.002
Median	1	1	1	0	0		
Was the initial, inciting infection treated with antibiotics? % Yes (N)	86 (67)	93 (100)	93 (65)	87 (62)	93 (74)	0.63	0.43
If Yes, did the infection resolve on those antibiotics **% Yes (N)**	56 (31)	68 (50)	63 (30)	74 (39)	69 (42)	L-R $\chi^2 = 1.78$	0.18
Did the PANS symptoms resolve on the initial course of antibiotics[a] **% Yes (N)**	18% (10)	19% (17)	44% (26)	36% (20)	46% (31)	L-R $\chi^2 = 23.27$	0.0001

[a]Excludes subjects for whom antibiotics were still being taken for the inciting infection.
L-R, likelihood ratio; PANS, pediatric acute-onset neuropsychiatric syndrome.

Table 2. Percent Days Symptom-Free by Access to Medical Expertise

	No days symptom-free (N = 120)	*1%–25% Days symptom-free (N = 171)*	*26%–50% Days symptom-free (N = 96)*	*51%–75% Days symptom-free (N = 105)*	*>75% Days symptom-free (N = 111)*	*Estimate and 95% CI*	*L-R χ^2*	p
Access to expertise has not been an issue for this patient	22% (26)	22% (38)	25% (24)	30% (32)	52% (58)	0.39 (0.23 to 0.56)	22.47	<0.0001[a]
To what extent has the patient's treatment for PANS been impacted by access to medical expertise? (Select all that apply) % (N)								
Insufficient access to medical expertise impacted the process of diagnosis	46% (55)	46% (78)	39% (37)	43% (45)	28% (31)	–0.18 (–0.33 to –0.04)	6.16	0.01
Insufficient access to medical expertise has impacted treatment decisions	38% (45)	40% (68)	34% (33)	43% (45)	17% (19)	–0.20 (–0.35 to –0.05)	6.88	0.009[b]
Insufficient access to medical expertise has prevented timely access to treatment	49% (59)	50% (85)	46% (44)	46% (48)	26% (29)	–0.22 (–0.37 to –0.08)	9.02	0.003[b]
Insufficient access to medical expertise has prevented the patient from any access to required treatment	22% (26)	12% (20)	13% (12)	10% (11)	5% (6)	–0.36 (–0.58 to –0.14)	10.33	0.001[c]
How many doctors did the patient see for signs and symptoms of PANS before PANS was diagnosed?							36.55	<0.0001[a]
One	13% (33)	18% (33)	25% (26)	21% (23)	34% (40)			
Two to three	32% (40)	40% (72)	38% (39)	49% (54)	45% (54)			
Four to six	20% (25)	24% (43)	18% (18)	20% (22)	10% (12)			
More than six	35% (44)	18% (32)	19% (19)	10% (11)	11% (13)			
Physicians seen who did NOT diagnose PANS								
Pediatrician	70% (87)	74% (135)	70% (73)	71% (79)	58% (70)	–0.15 (–0.30 to 0)	3.76	0.05
Family physician/GP	42% (52)	25% (45)	22% (23)	18% (20)	18% (21)	–0.36 (–0.52 to –0.19)	17.66	<0.0001[d]
Neurologist	56% (70)	40% (74)	46% (48)	40% (44)	25% (30)	–0.30 (–0.45 to –0.16)	17.80	<0.0001[d]
Psychiatrist	54% (68)	43% (79)	36% (38)	24% (27)	29% (35)	–0.34 (–0.50 to –0.19)	19.27	<0.0001[d]
Naturopath	9% (11)	11% (20)	5% (5)	3% (3)	4% (5)	–0.32 (–0.59 to –0.05)	5.49	0.01
Infectious disease specialist	22% (28)	16% (29)	18% (19)	19% (21)	9% (11)	–0.19 (–0.38 to –0.01)	4.13	0.04
ER doctor	31% (39)	22% (41)	21% (22)	19% (21)	14% (17)	–0.25 (–0.42 to –0.08)	8.24	0.004[b]
Immunologist/allergist	30% (38)	25% (45)	22% (23)	19% (21)	17% (20)	–0.23 (–0.39 to –0.06)	7.36	0.007
Rheumatologist	8% (10)	8% (15)	7% (7)	11% (12)	7% (8)	0 (–0.25 to 0.25)	0	0.99
PANS specialist	10% (12)	8% (15)	8% (8)	5% (6)	9% (11)	–0.07 (–0.32 to 0.19)	0.25	0.62

[a]Bonferroni-correction not needed, $p < 0.0001$.
[b]Bonferroni-corrected $p < 0.05$.
[c]Bonferroni-corrected $p < 0.01$.
[d]Bonferroni-corrected $p < 0.001$.
CI, confidence interval; ER, emergency room; GP, general practitioner; PANS, pediatric acute-onset neuropsychiatric syndrome.

Having been diagnosed at first presentation was associated with a less persistent course: for example, 34% of subjects with the least persistent symptoms, but only 13% of those with the most, were diagnosed by the first doctor seen for PANS symptoms, while conversely, 35% of subjects with the most persistent symptoms, but only 11% of those with the most intermittent, had seen more than six doctors before diagnosis (L-R $\chi^2 = 36.55$, $p < 0.0001$, for comparison across all categories). Subjects with less persistent symptoms were significantly more likely to have been diagnostically ''captured'' by ''first-line'' providers including general practitioners (L-R $\chi^2 = 17.66$, $p < 0.0001$, Bonferroni-corrected $p < 0.001$) and emergency room (ER) physicians (L-R $\chi^2 = 8.24$, $p = 0.004$, Bonferroni-corrected $p < 0.05$), as well as by neurologists (L-R $\chi^2 = 17.80$, $p < 0.0001$, Bonferroni-corrected $p < 0.001$) and psychiatrists (L-R $\chi^2 = 19.27$, $p < 0.0001$, Bonferroni-corrected $p < 0.001$).

Importantly, access to *treatment* was more strongly associated with symptom-free days than was access to diagnosis. For example, 49% of subjects with the most persistent symptoms, compared with 26% of those with the least, reported that insufficient access to medical expertise had prevented *timely* access to treatment (L-R $\chi^2 = 9.02$, $p = 0.003$, Bonferroni-corrected $p < 0.05$, for comparison across all categories); and 22% of subjects with the most persistent symptoms, compared with 5% of those with the least, reported that insufficient access to medical expertise had prevented *any* access to treatment (L-R $\chi^2 = 10.33$, $p = 0.001$, Bonferroni-corrected $p < 0.01$, for comparison across all categories).

Percent days symptom-free by financial access to care

Financial access to care was also strongly associated with % *days symptom-free* (Table 3). For example, diagnosis and treatment decisions had been unencumbered by financial constraints for 72% of subjects with the least persistent symptoms, compared to 42% of those with the most (L-R $\chi^2 = 27.83$, $p < 0.0001$, for overall comparison across categories). Financial constraints had prevented timely access to treatment for only 5% of subjects with the least symptom persistence, compared to 24%–27% of those with the most (L-R $\chi^2 = 16.76$ $p < 0.0001$, Bonferroni-corrected $p < 0.001$, for overall comparison across categories).

Percent days symptom-free by status of IVIG

As described in the companion article (Calaprice-Whitty et al., 2023), there were no significant differences across symptom persistence categories in whether or how subjects had been treated with intravenous immunoglobulin (IVIG). However, there were significant differences in why subjects had stopped IVIG treatment: for example, 90% of subjects with the least symptom persistence, versus 23% of those with the most, had discontinued IVIG only when it was deemed no longer necessary; in contrast, 5% of subjects with the least symptom persistence, versus 30% of those with the most, had discontinued for financial reasons or lack of a prescribing provider (L-R $\chi^2 = 32.25$, $p < 0.0001$) (Table 4).

Among the subset who found IVIG ''very effective'' or ''effective at first but lost effect over time,'' 11 of 50 (22%) subjects in the 2 most symptom-persistent categories (25% or fewer days symptom-free) had stopped treatment for financial reasons and an additional 6 of 50 (12%) subjects stopped because they no longer had a practitioner who would prescribe, whereas only 1 of 45 (2%) subjects who spent most (>50%) days symptom-free discontinued for financial reasons and 1 of 45 (2%) for lack of access to a prescription (data not in tables).

Table 3. Percent Days Symptom-Free by Financial Access to Care

	No days symptom-free (N = 122)	*1%–25% Days symptom-free (N = 168)*	*25%–50% Days symptom-free (N = 100)*	*51%–75% Days symptom-free (N = 104)*	*>75% Days symptom-free (N = 111)*	*Estimate (95% CI)*	*L-R χ^2*	p
Financial/coverage concerns have played no role in the diagnostic process or treatment decisions for this patient	42% (51)	32% (54)	45% (45)	55% (57)	72% (80)	0.40 (0.25 to 0.55)	27.83	<0.0001[a]
Financial/coverage concerns … (select all that apply) % (N)								
… impacted the process of diagnosis	9% (11)	16% (27)	12% (12)	10% (10)	3% (3)	−0.22 (−0.44 to 0)	3.83	0.05
… have impacted treatment decisions but not prevented access to treatment	30% (37)	37% (62)	33% (33)	31% (32)	23% (26)	−0.10 (−0.25 to 0.06)	1.54	0.21
… have prevented the patient from timely access to required treatment	24% (29)	27% (45)	20% (20)	16% (17)	5% (5)	−0.37 (−0.55 to −0.19)	16.76	<0.0001[b]
… have prevented the patient from any access to required treatment	12% (15)	11% (18)	6% (6)	4% (4)	2% (2)	−0.47 (−0.74 to −0.20)	11.49	0.0007[c]

[a]Bonferroni-correction not needed, $p < 0.0001$.
[b]Bonferroni-corrected $p < 0.0001$.
[c]Bonferroni-corrected $p < 0.01$.
CI, confidence interval.

Table 4. Percent Days Symptom-Free by Status of IVIG Treatment

	No days symptom-free (N=43)	*1%–25% Days symptom-free (N=51)*	*25%–50% Days symptom-free (N=26)*	*51%–75% Days symptom-free (N=31)*	*>75% Days symptom-free (N=21)*	*L-R* χ^2	p
Current status of IVIG treatment (all subjects treated with IVIG) % (N)						32.25	<0.0001[a]
Stopped for financial reasons	21% (9)	18% (9)	4% (1)	6% (2)	5% (1)		
Stopped because healthcare practioner would not prescribe	9% (4)	14% (7)	27% (7)	3% (1)	0		
Stopped because of side effects	9% (4)	4% (2)	4% (1)	3% (1)	0		
Stopped because no longer perceived a need	23% (10)	24% (12)	13% (6)	61% (19)	90% (19)		
Stopped because ineffective	5% (2)	10% (5)	8% (2)	0	0		
Ongoing >6 months	21% (9)	18% (9)	27% (7)	16% (5)	5% (1)		
Ongoing <6 months	12% (5)	14% (7)	8% (2)	10% (3)	0		

[a]Bonferroni-correction not needed, $p < 0.0001$.
IVIG, intravenous immunoglobulin.

Discussion

PANS is classically described as a relapsing and remitting illness with heterogeneous symptoms, severity, and functional impacts (Brown et al., 2017a; Brown et al., 2017b; Calaprice et al., 2017; Gromark et al., 2022; Frankovich et al., 2018). The present study looks at clinical course with a novel measure, *% days symptom-free*. This measure is important because it reflects the proportion of time that a child, and often his/her family, can participate in life activities normally. We examined correlations between this measure of symptom persistence and access-to-care variables, with the goal of identifying opportunities for intervention to shift patients toward less persistent disease.

At every health care access step examined, we found robust relationships between long-term persistence of PANS symptoms and patients' access-to-care histories. Patients receiving timely diagnosis and adequate treatment from the first presentation enjoyed significantly more symptom-free days over the disease course than those who required visits with multiple doctors. The most favorable course was associated with diagnostic ''capture'' by front-line practitioners such as family practitioners and ER doctors, underscoring the potential importance of recognition and action at first point of contact. Our observations suggest that front-line physicians should not wait for behavioral health or other specialist providers to weigh in before treating, as access to mental health care, particularly for youth, is in crisis, with many U.S. patients waiting months to see specialists (Overhage et al., 2023; The White House, 2021).

Subjects whose PANS symptoms resolved with antibiotics for their inciting infection fared better over time than those who did not, suggesting that initial treatment should be not only expeditious but also aimed at resolving *both* the inciting infection and PANS symptoms. That many subjects did not achieve either of these endpoints with initial antibiotics suggests that more intensive dosing and/or duration than is typically prescribed may be required, possibly related to the high level of immunodeficiency reported in this population (25%) compared with the general population prevalence of 0.08% (Boyle and Buckley, 2007). In addition, evaluation for undiagnosed immunodeficiency, as recommended by Chang et al. (2015), seems reasonable since children with immunodeficiency may require more intensive management to achieve therapeutic targets.

Of note, some antibiotics, for example, macrolides and tetracyclines, may exert neuroprotective benefits through known anti-inflammatory/immune-modulating effects (Bahrami et al., 2012; Firth and Prathapan, 2020) and/or may alter the gut microbiome. An overabundance of Bacteroidetes species has been found in the gut microbiome of PANS children aged 4–8 years, and it has been proposed that streptococcal infections alter bowel flora to favor proinflammatory species, thus activating the immune response and the balance of metabolites important to brain function and the gut–brain axis (Quagliariello et al., 2018). Increasing evidence suggests a role for the microbiome in human inflammatory and central nervous system disorders, including anxiety, depression, schizophrenia, and autism (Clapp et al., 2017). Treating PANS with antimicrobials beyond the point of clear infection resolution may be a counterintuitive approach in the era of ''antibiotic stewardship,'' but as for any therapy, the risk–benefit ratio in the setting of brain inflammation should be weighed when determining dosage and duration.

As for any condition lacking payer-recognized treatments, access to care for PANS faces not only the aforementioned supply-side challenges but also the demand-side challenge of treatment affordability. Sadly, our analysis supports a strong relationship between financial and insurance challenges and persistent PANS symptoms. Subjects for whom financial considerations played little or no role in diagnosis or treatment decisions were significantly more likely to report mild, intermittent courses compared with those for whom financial limitations prevented or delayed clinically indicated care. In the specific case of IVIG treatment, subjects whose IVIG was discontinued for financial reasons fared worse than those who terminated IVIG treatment only when clinically indicated. Recent support for the benefit of repeated IVIG treatments comes from an open label trial of IVIG that followed 21 patients receiving IVIG infusions of 1 g/kg every 21 days for 6 months. In this trial, treatment was associated with significant improvement in PANS symptoms, but symptom reduction became significant only by the third infusion (Melamed et al., 2021). For most of these participants, symptom reduction was enduring, lasting 29–46 weeks after the final infusion. A previous analysis of our current data set also found repetitive treatment with IVIG to be associated with more favorable outcomes (Calaprice et al., 2018). However, many large insurers currently have policies prohibiting all coverage of IVIG for

PANDAS, despite its inclusion in standard treatment guidelines (Aetna, 2023; Anthem, 2023; United Healthcare, 2023), and very few families can afford repetitive IVIG cycles.

Taken together, differences in families' ability to pay cash for treatment are likely to explain some of the variation in symptom persistence in our population. However, alternative explanations are plausible. For example, the potentially greater caregiving demands of more persistent disease could have consequences on parental employment (and thus access to benefits) and earning ability and hence increase financial constraints. Caregiver burden among PANS parents is in fact very high, similar to that experienced by caregivers of Alzheimer's patients (Frankovich et al., 2018; O'Dor et al., 2022; Tona et al., 2023). Much of this burden stems from difficulty accessing PANS care (Dolce et al., 2022; Frankovich et al., 2018), potentially creating a vicious cycle whereby high caregiver burden leads to poor financial access to treatment, which in turn leads to poor outcomes and greater caregiver burden. Families with fewer financial resources or less comprehensive insurance may also have poorer baseline health or greater stress levels, conceivably driving greater symptom persistence.

This study has the weaknesses associated with community-based surveys; namely, that participants are self-selected, diagnoses are self-reported, and responses are subjected to potential confounding factors including recall bias. Aware of these limitations, we cast a broad net in our recruitment, publicizing the survey using the mailing list of PANDAS Network, the most visited website for PANDAS/PANS searches, as well as at specialist practices. We provided diagnostic criteria and required subjects to actively confirm diagnosis by a physician; and the fact that there was no benefit whatsoever offered to subjects, together with the time-consuming nature of survey, would be expected to minimize participation by subjects not meeting diagnostic criteria. We allowed ''don't know'' or ''don't recall'' responses to all questions, including the question about symptom persistence, to relieve any pressure to guess about poorly recalled variables. As noted earlier, 52 out of our original data set of 698 did not feel confident that they could answer this question about symptom persistence with accuracy and were excluded from the analysis.

On the contrary, a major strength of our approach is that it achieves an otherwise impossibly large and broad sample for an uncommonly diagnosed disease. Our sample characteristics align with those of other study samples for PANS (e.g., gender and age distribution, time to diagnosis, range of acuity of onset, frequency of presenting symptoms, recurrence rates), suggesting our sample to be representative of the clinical population (Frankovich et al., 2015; Johnson et al., 2019; Lepri et al., 2019; Murphy et al., 2015). Although strict diagnostic criteria for PANS depict sudden onset, PANS clinics recognize a minority of cases with less abrupt onset that are clinically identical to acute-onset cases in all other respects, including treatment response, and render PANS diagnoses in these cases (Frankovich et al., 2015). Because we are aware from our colleagues that patients with gradual onset may indeed carry specialist-rendered PANS diagnoses, and because we found no significant relationship between *% days symptom-free* based on foudroyant versus more gradual onset, the small fraction of ''gradual onset'' subjects in our sample (11%) were included in the analysis. Notwithstanding the similarities between our sample and other cohorts, however, our population is almost certainly more heterogeneous—and more ''real world''—with respect to access to care than are most research cohorts, who generally receive care at specialty clinics, and we consider this representation essential to this study's research objectives.

Potential confounding factors specific to the present analyses exist. Most significantly, highly intermittent cases most closely fitting ''classic PANS'' may be easiest to correctly diagnose; in fact, nonspecialists may be willing to diagnose and treat *only* such cases without referral. Thus, a causal relationship may indeed exist between access to expertise and treatment that sets the disease on a more intermittent course, but plausibly, a more intermittent course may also be more confidently recognized by practitioners as PANS, with corresponding impacts on both treatment and perceptions of the expertise received. It is also conceivable that negative outcomes may cause some respondents to recall previous disease course more negatively. Although such biases may play some role in shaping a fraction of our results, they would not be expected to impact data that were established before the long-term disease course was known, for example, onset characteristics or types or numbers of practitioners seen before diagnosis.

Our data were collected nearly a decade ago. In the interim, with increased understanding of PANS and management guidelines published by PANS experts, barriers to care may now be attenuated. However, recent research confirms that access-to-care issues are far from resolved. In a 2022 study of 441 primary caregivers of PANS patients, families still reported visiting a median of 3, and a range of up to 80, clinicians before receiving a PANS diagnosis. The majority traveled more than 50 miles, and 15.6% traveled more than 500 miles, to receive care (O'Dor et al., 2022). Similarly, 72.6% of caregivers reported paying out of pocket for care that was not covered by insurance, with a median expense-to-date of $6000 and a range of $0–$1,000,000. In response to ongoing insurer denials of PANS treatments such as IVIG, 11 states have passed laws as of 2023 mandating insurers to pay for the treatment of PANS/PANDAS, and legislation is in process in a dozen others.

As reflected in our companion article, persistent PANS symptoms impact a child's ability to function at an even a basic level; hence, we must modify PANS management whenever possible to maximize the time a child spends symptom-free. Given that PANS is estimated to affect ~5% of children with OCD (Jaspers-Fayer et al., 2017), and 1%–4% of children are thought to have OCD (Keeley et al., 2007), it is likely that tens of thousands to more than one hundred thousand of the 82 million children in the United States alone (U.S. Census Bureau) are impacted by inadequate access to care that results in persistent symptoms, when a milder course may have been possible. Future research should explore the health economics of PANS to support optimal treatment strategies and best practices for insurance coverage.

Conclusions and Clinical Significance

The results of our analyses suggest that both supply-side and demand-side access-to-care issues, at every step of the health care journey, substantially contribute to persistence of symptoms in PANS. The following factors were significantly associated with a PANS child having few (or no) symptom-free days over the course of illness: longer time between onset and treatment; barriers to medical expertise that impacted decision-making and treatment; number of doctors seen before a PANS diagnosis was rendered; having the diagnosis missed by a family practitioner, emergency medicine doctor, neurologist, and/or psychiatrist; and financial/insurance barriers impacting diagnosis and treatment. Every effort should be made to improve access to skilled providers and timely treatment, and front-line practitioners should consider initiating guideline-based treatment without delay. Further research should identify appropriate goals for a treat-to-target strategy.

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Disclosures

The authors have no conflicts of interest to disclose.

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