The Burden of Caring for a Child or Adolescent With Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): An Observational Longitudinal Study

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ABSTRACT

Objective: To describe the longitudinal association between disease severity, time established in clinical treatment, and caregiver burden in a community-based patient population diagnosed with pediatric acute-onset neuropsychiatric syndrome (PANS).

Methods: The study included an observational longitudinal cohort design, with Caregiver Burden Inventories (CBIs) collected between April 2013 and November 2016 at the Stanford PANS multidisciplinary clinic. Inclusion criteria for this study were as follows: pediatric patients meeting strict PANS/pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) diagnostic criteria (n = 187), having a caregiver fill out at least 1 complete CBI during a disease flare (n = 114); and having family who lives locally (n = 97). For longitudinal analyses, only patients whose caregiver had filled out 2 or more CBIs (n = 94 with 892 CBIs) were included. In the study sample, most primary caregivers were mothers (69 [71.1%] of 97), the majority of PANS patients were male (58 [59.8%] of 97), and mean age at PANS onset was 8.8 years.

Results: In a patient's first flare tracked by the clinic, 50% of caregivers exceeded the caregiver burden score threshold used to determine respite need in care receiver adult populations. Longitudinally, flares, compared with quiescence, predicted increases in mean CBI score (6.6 points; 95% CI, 5.1 to 8.0). Each year established in clinic predicted decreased CBI score (−3.5 points per year; 95% CI, −2.3 to −4.6). Also, shorter time between PANS onset and entry into the multidisciplinary clinic predicted greater improvement in mean CBI score over time (0.7 points per year squared; 95% CI, 0.1 to 1.3). Time between PANS onset and treatment with antibiotics or immunomodulation did not moderate the relationship between CBI score and time in clinic.

Conclusions: PANS caregivers suffer high caregiver burden. Neuropsychiatric disease severity predicts increased caregiver burden. Caregiver burden tends to decrease over time in a group of patients undergoing clinical treatment at a specialty PANS clinic. This decrease could be independent of clinical treatment.

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Pediatric acute-onset neuropsychiatric syndrome (PANS) is characterized by the abrupt onset of obsessive-compulsive disorder (OCD) and/or food restriction with at least 2 other equally debilitating neuropsychiatric symptoms.[1] A specific category of PANS, defined by a preceding infection with group A *Streptococcus*, is known as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).[2] Both PANS and PANDAS typically follow a relapsing/remitting course in which patients experience acute flares between periods of relative or complete remission.[3–6] Flares are defined as abrupt deteriorations of neuropsychiatric symptoms and may be preceded by exposure to pathogens.[7,8] In some chronic/static cases, symptoms do not remit.

Caregivers spend considerable time assisting patients with activities of daily life. Furthermore, the course of disease can be unpredictable, which can create anxiety. Many patients exhibit symptoms of rage, aggression, and unpredictable behavior such as threatening their parents or attempting to jump out of moving vehicles. Finally, the disease is recently described, so schools often do not understand what these children need, putting additional burden on the caregiver. These factors may lead to high caregiver burden in PANS.[9] No study has evaluated caregiver burden longitudinally in this population. This study responds to a *JAMA* review article on caregiver burden[10] in which the authors called for more longitudinal studies of caregiver burden. Since that article was published, caregiver burden trends have been evaluated in Alzheimer's disease, dementia, and cancer.[11–15] In pediatrics, longitudinal studies of caregiver burden have focused on cancer, asthma, and brain-related conditions.[16–21]

This work is a longitudinal study of caregiver burden in a community-based

Clinical Points

- Caregiver burden is a key issue in treatment of pediatric acute-onset neuropsychiatric syndrome (PANS), but the longitudinal course of burden is unclear.
- Parents of patients with PANS have high burden, but the burden can lessen over time. Clinicians should consider the whole family when caring for a child or adolescent with PANS.

PANS population. Our a priori research aims were to (1) describe how caregiver burden changes over time during clinical treatment, (2) report the association between disease severity and caregiver burden, and (3) evaluate whether a shorter duration of time between disease onset and clinical treatment predicts a more rapid decrease in caregiver burden.

METHODS

Setting

The Stanford PANS Clinic is a multidisciplinary clinic serving Bay Area families affected by PANS and PANDAS. The clinic has treated 272 patients since opening in 2012. Treatment is coordinated between practitioners of various disciplines (psychiatry; psychology; primary care; rheumatology; immunology; ear, nose, and throat; and neurology) and includes access to a psychotherapist and an education specialist.

Data Sources

Longitudinal data on treatment duration and disease severity were collected and stored in REDCap electronic data capture tools hosted at Stanford University.[22] Our main predictor variable was time established in clinic (time-in-clinic), defined as the time (in years) between current clinic visit and first clinic visit. Our main disease severity variables were flare status (disease flare versus quiescence) and global impairment score. Flare status was determined by clinical assessments combined with patient questionnaires and parental report.[5] Global impairment score is a caregiver reported variable, obtained as part of a questionnaire completed prior to each clinic visit. We have validated the global impairment score in our patient population.[23]

For our secondary hypothesis, we were interested in the duration of time between disease onset and treatment. We defined treatment in 3 different ways: (1) first appointment at the Stanford PANS Clinic, (2) first antibiotic therapy, and (3) first immunomodulatory therapy (corticosteroids, intravenous immunoglobulin, or solumedrol).

Our main outcome variable was score on the CBI, which is among the questionnaires completed prior to each clinic visit. The CBI, initially described in 1989, was first used in gerontology to assess caregiver burden in patients with Alzheimer's disease.[24] We recently validated the CBI in a PANS population, which found a similar factor structure to geriatric populations; furthermore, we found the CBI does not perform differently in older children or adolescents compared with younger children.[9] The CBI divides caregiver burden into 5 categories: time dependency, emotional health, physical health, social relationships, and development (adult personal growth). Caregivers indicate their agreement with 24 statements, each corresponding to 1 of the 5 categories. Scores range from 0 to 96. Higher score indicates higher burden. A score of 36 is used as a threshold for respite need in adult populations.[25] Presumably, the respite cutoff for pediatric populations would be higher; however, no valid and reliable CBI threshold for respite need exists in a pediatric population.

Stanford's human subjects institutional review board approved this research. Parents provided informed consent, and competent patients provided assent.

Inclusion/Exclusion Criteria

Between April 2013 and November 2016, 1,263 CBIs were completed for 182 patients. For this study, we included patients of the Stanford PANS clinic who met strict PANS/PANDAS criteria (n = 187) and whose parents had filled out at least 1 complete CBI during a disease flare (n = 114). We then excluded patients who lived > 90 miles from clinic (n = 17) in order to study a local cohort. Our final cross-sectional analysis included 97 patients. For the longitudinal analysis, we excluded 3 patients who had only 1 CBI filled out, leaving us with 94 patients and 892 CBIs. To perform exploratory cross-sectional analyses, we used the first CBI filled out during a patient's flare (n = 97). Then, for our main longitudinal analyses, we included all CBIs filled out by caregivers of these patients, excluding 3 patients who had only 1 CBI. We also excluded CBIs that were missing > 30% of items (5 CBIs), resulting in 94 patients and 892 CBIs.

We also recruited 42 control subjects for this study. Our inclusion criteria were children and adolescents (aged 4–18 years) with no history of mental illness. Our selection method was advertising in the local community and through families of patients with PANS. The exclusion criterion was any evidence of preceding mental illness as assessed in a screening questionnaire.

Missing Data

Missing responses were found in 79 (8.9%) of 892 CBIs. The query most often left unanswered was item 3 of the social relationships section (21 [2.4%] of 892 responses): "I've had problems with my marriage (or other significant relationship)." Missing responses were imputed using the sample mean for a given item.

Additionally, the global impairment score was missing in 48 (5.4%) of 892 observations. We imputed values using a variation on mean imputation. If the missing data were from visits in which the patient was flaring, we used the patient's mean global impairment score during a flare; if during remission, we used the mean global impairment score during remission. After imputation, 10 (1.1%) of 892 observations were still missing global impairment score because flare status could not be determined (typically because some symptoms had resolved but the patient had not completely remitted). These observations were excluded from models

that included either global impairment score or flare status as predictors.

Statistical Analysis

We used a *t* test to compare CBI scores from patients with PANS with CBI scores from healthy controls, who were children and adolescents with no existing neuropsychiatric symptoms recruited from the community surrounding Stanford. Although these individuals were not explicitly matched with our patients with PANS, there was no difference between the 2 groups in terms of age or sex. We also regressed age on CBI total score for the healthy controls to evaluate the association between age and caregiver burden.

In exploratory cross-sectional analyses, we selected 11 disease severity or demographic variables that we predicted a priori would correlate with caregiver burden (see Table 2). (We later added in 2 additional variables—age at first CBI and years between PANS onset and first CBI.) In these analyses, we made caregiver burden into a binary variable (score ≥ 36 versus score < 36) because this score is often used as a cutoff for respite in adult populations.[25] We selected variables significant at the $P < .2$ level in a univariate test for consideration in an adjusted model.

To evaluate the longitudinal association between disease severity and caregiver burden, we constructed a mixed model with repeated measures. In our first model, our predictor was flare status (disease flare versus quiescence) as a measure of disease severity. We used flare status as our primary measure of disease severity because this status is characteristic of the relapsing/remitting course of PANS/PANDAS.[3–6] The model included a random effect for intercept and fixed effects for subject and time-in-clinic. We did not include a quadratic time term because the residuals of this model were not predicted by time-in-clinic. We also ran a sensitivity analysis using visit number as a measure of time rather than years since first clinic visit. Our correlation structure was variance components (chosen because of comparatively smaller AIC). We then ran a similar model, substituting global impairment score for flare status as the measure of disease severity. We used global impairment score as a measure of disease severity because it is a score that assesses patient function, has anchors, and is independently associated with caregiver burden (see Table 2). Given that we had prior knowledge that global impairment score correlated with caregiver burden, this analysis should be interpreted as exploratory. We then ran a third model including an interaction term between global impairment score and time-in-clinic to test the hypothesis that the relationship between global impairment score and caregiver burden changes over time in clinic.

To account for the fact that some families remain established in clinic long-term while others leave after a few visits, we ran a post hoc model that stratified our main analysis by a "dropout" variable indicating whether a patient had been established in clinic beyond a cutoff point. Our primary cutoff point was 1 year. This cutoff is arbitrary, chosen because approximately

Table 1. Characteristics of 97 Patients and Their Caregivers Evaluated in a Multidisciplinary PANS Clinic as Well as 42 Healthy Controls Included in a Preliminary Cross-Sectional Analysis of Caregiver Burden[a]

Variable	Patients With PANS (n = 97)	Healthy Controls (n = 42)
Male, n (%)	58 (59.8)	20 (47.6)
Age at PANS onset, mean (SD), y[b]	8.8 (3.7)	…
Age at clinic/study entry, mean (SD), y[c]	11.0 (4.0)	11.6 (3.3)
Non-Hispanic white, n/total n (%)[d]	66/81 (81.5)	25/42 (59.5)
Disease course		
Single episode	5 (5.2)	…
Relapsing/remitting	66 (68.0)	…
Chronic/static or progressive[e]	26 (26.8)	…
Symptoms at flare with caregiver burden data		
OCD	87 (89.6)	2 (4.8)
Anxiety	87 (89.6)	10 (24)
Mood dysregulation	79 (81.4)	1 (2.4)
Motor abnormalities	66 68.0)	…
Irritability/oppositionality/aggression	66 (68.0)	1 (2.4)
Sleep disturbance	66 (68.0)	5 (12)
Eating restriction	52 (53.6)	1 (2.4)
Behavioral regression	53 (54.6)	2 (4.8)
Rage	36 (37.1)	…
Urinary issues	32 (33.0)	2 (4.8)
Pain	56 (57.7)	3 (7.1)
Global impairment score (0–100), mean (SD)[f]	46.8 (25.0)	0.2 (0.8)
Parent CBI total score (0–96), mean (SD)[f]	36.0 (19.9)	8.1 (7.5)
Meets respite care criteria[g]	48 (49.5)	0 (0)
Caregiver who filled out questionnaire		
Mother	69 (71.1)	41 (97.6)
Father	7 (7.2)	1 (2.4)
Both parents	13 (13.4)	0 (0)
Missing	8 (8.3)	0 (0)
Caregiver currently married/in domestic partnership, n/total n (%)[h]	67/77 (87.0)	…
Annual household income < $150,000, n/total n (%)[h]	19/64 (29.7)	…
Caregiver education, n/total n (%)[h]		
Mother figure college graduate or higher	60/71 (84.5)	…
Father figure college graduate or higher	54/70 (77.1)	…
Caregiver highest occupation, n/total n (%)[h]		
Mother figure business manager or higher	43/82 (52.4)	…
Father figure business manager or higher	56/80 (70.0)	…

[a]Values are shown as n (%) unless otherwise noted.
[b]Determined by chart review before first visit in PANS clinic.
[c]Age at first visit in PANS clinic.
[d]Some patients were missing data on self-reported race/ethnicity.
[e]Chronic-static or progressive course refers to PANS/PANDAS cases with steady or worsening neuropsychiatric symptoms. In these cases, patients do not return to their pre-onset baseline functioning.
[f]Global impairment and CBI scores come from the first CBI during a flare.
[g]Cutoff for respite care is a CBI score ≥ 36.
[h]These data come from a one-time demographic survey, which had a response rate of 79 of 97. Some responses were filled in using information from the medical record. The denominators are the number of patients for whom we have data.
Abbreviations: CBI = Caregiver Burden Inventory, OCD = obsessive-compulsive disorder, PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, PANS = pediatric acute-onset neuropsychiatric syndrome.
Symbol: … = not applicable or data not available.

Table 2. Cross-Sectional Association Between Caregiver Burden and Disease and Demographic Variables in Patients Diagnosed With Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) Who Enrolled in a Multidisciplinary Clinic[a]

Characteristic	CBI Score < 36[b]	CBI Score ≥ 36[b]	*P* Value[c]
Male	26/49 (53.1)	32/48 (66.7)	.17
Age at PANS onset, mean (SD), y	9.1 (3.4)	8.4 (4.0)	.36
Age at first CBI, mean (SD), y	10.8 (3.8)	11.4 (4.3)	.53
Years between PANS onset and first CBI, mean (SD)[d]	1.7 (2.0)	2.9 (2.9)	.07
White	29/33 (87.9)	37/39 (94.9)	.28
Mother has college degree or higher	24/32 (75.0)	36/39 (92.3)	.05
Chronic or progressive disease	11/49 (22.5)	15/48 (31.3)	.32
OCD score (0–15), mean (SD)	6.0 (3.9)	8.1 (4.5)	.02
Aggression/rage	25/45 (55.6)	33/44 (75.0)	.05
Sleep disturbance	31/47 (66.0)	36/45 (80.0)	.13
Eating restriction	25/48 (52.1)	26/40 (65.0)	.22
Pain	30/49 (61.2)	26/48 (54.2)	.48
Patient global impairment score, mean (SD)	38.6 (20.3)	54.8 (26.7)	.001

[a]Values shown as n/total n (%) unless otherwise noted.
[b]A cutoff value of 36 suggests a higher need for respite care and other services. There are no studies evaluating the cutoff score that indicates respite care need in caregivers of pediatric patients.
[c]All variables with $P < .2$ in the univariate analyses were placed in a logistic regression modeling qualification for respite care. In this adjusted analysis, only global impairment score correlated with respite need at the $P = .05$ level.
[d]Skewed variable. *P* value comes from a Wilcoxon rank sum test.
Abbreviations: CBI = Caregiver Burden Inventory, OCD = obsessive-compulsive disorder, PANS = pediatric acute-onset neuropsychiatric syndrome.

Table 3. The Longitudinal Association Between Disease Severity and Caregiver Burden in a Community-Based Multidisciplinary PANS Clinic

Predictor	Unadjusted Effect Estimate (95% CI)[a]	Effect Estimate, Model 1 (95% CI)[b]	Effect Estimate, Model 2 (95% CI)[c]	Effect Estimate, Model 3 (95% CI)[d]
Intercept		29.1 (25.0 to 33.3)	23.8 (19.9 to 27.7)	24.2 (20.1 to 28.3)
Years in clinic[e]	−3.8 (−2.6 to −5.1)	−3.5 (−2.3 to −4.6)	−2.1 (−0.9 to −3.3)	−2.3 (−4.3 to −0.3)
Flare status[f] (yes/no)	7.1 (5.6 to 8.6)	6.6 (5.1 to 8.0)		
Global impairment score[g] (0–100)	0.3 (0.2 to 0.3)		0.3 (0.2 to 0.3)	0.2 (0.2 to 0.3)

[a]Intercept effect estimate is the estimated CBI total score when all predictors have a value of zero. Predictor effect estimates are interpreted as the change in caregiver burden total score associated with a 1-unit increase in the predictor. Unadjusted models were run separately for each predictor.
[b]Model 1 outcome is CBI total score and predictors are time-in-clinic (years) and flare status (yes/no).
[c]Model 2 outcome is CBI total score and predictors are time-in-clinic (years) and global impairment score (0–100).
[d]Model 3 is the same as model 2 except it includes a nonsignificant interaction term between global impairment and years in clinic (estimate for interaction = 0.005; 95% CI, −0.04 to 0.05).
[e]Years in clinic is defined as the amount of time, in years, that patient has been established in the Stanford PANS clinic. For example, a visit that is 182 days after a patient's first visit would have a time-in-clinic of 182 days/365.25 days/1 year = 0.498 year.
[f]Flare status is defined by whether a patient is in a flare at the time of the appointment. It is a time-changing variable.
[g]Global impairment score is a caregiver-reported measure of disease severity. Caregivers report this variable before every clinic visit.
Abbreviations: CBI = Caregiver Burden Inventory, PANS = pediatric acute-onset neuropsychiatric syndrome.

half of patients remain in clinic for longer than a year. We also performed sensitivity analyses using cutoff points of 0.5 and 1.5 years. The goal of this analysis was to understand whether families who do not establish with clinic long term have a more rapid decrease in caregiver burden than families who remain engaged with clinic.

To evaluate the hypothesis that a shorter lag time between symptom onset and treatment predicted a more rapid decrease in caregiver burden, we used the same repeated-measures mixed model as described previously in this section. Our predictors were time between symptom onset and clinical treatment at the PANS clinic, disease flare status, time-in-clinic, and an interaction term between treatment delay and time-in-clinic. We performed the same analysis twice more with different treatment delay predictors: delay to antibiotics and delay to immunomodulatory therapy. The interaction term indicates whether patients with a shorter time to treatment have a trend in caregiver burden different from that of patients with a longer time to treatment. These analyses were hypothesis-generating, not designed to test the efficacy of treatments for PANS.

SAS University (Cary, North Carolina) was used for all analyses.

RESULTS

The typical patient was a non-Hispanic white male with a relapsing/remitting course of PANS or PANDAS (Table 1). The typical caregiver was a mother with a college degree or higher. CBI scores were high; in 48 (49%) of 97 respondents, CBI scores during the first flare were at least 36—a value that has been used to signify increased need for respite care[25,26] (Table 1). Only 2 families reported hiring respite care. The mean (SD) CBI score in healthy controls was 8.1 (7.5). The estimated difference between CBI scores in patients with PANS during first flare and CBI scores in healthy controls

Table 4. Exploratory Analysis Comparing Caregiver Burden Trend in PANS Patients Who Received Care From a Multidisciplinary Clinic for a Short Period of Time Versus Patients Who Remained Established in the Clinic for a Longer Period of Time

	Left Clinic Before Cutoff Point		Stayed in Clinic After Cutoff Point		
Cutoff Point	n (%)	Time Effect, Estimate (95% CI)[a]	n (%)	Time Effect, Estimate (95% CI)[a]	*P* for Interaction[b]
1.0 year (n = 89)[c]	38 (43)	−9.2 (−3.6 to −14.8)	51 (57)	−3.4 (−2.1 to −4.6)	.01
0.5 year (n = 94)[c]	27 (29)	−22.3 (−9.2 to −35.4)	67 (71)	−3.5 (−2.2 to −4.7)	.005
1.5 years (n = 77)[c]	44 (57)	−3.4 (−0.3 to −6.5)	33 (43)	−3.7 (−2.4 to −5.1)	.7

[a]Time effect is the effect estimate for time established in clinic on caregiver burden. Therefore, a time effect of −9.2 indicates that the model predicts a 9.2-point decrease in Caregiver Burden Inventory score per year in clinic.
[b]Probability that the time effect is not the same in the 2 groups. [c]Patients whose first visit was within the cutoff point plus 1 month were excluded because it is unclear whether they will remain established beyond the cutoff point.
[c]Patients whose first visit was within the cutoff point plus 1 month were excluded because it is unclear whether they will remain established beyond the cutoff point.
Abbreviation: PANS = pediatric acute-onset neuropsychiatric syndrome.

Table 5. Results of Longitudinal Mixed Model[a] Evaluating the Effect of Longer Delay in Treatment on Trend of CBI Score Over Time in 94 Patients Diagnosed With PANS at a Community-Based Multidisciplinary PANS Clinic

	Effect Estimate (95% CI)			
Treatment Modality[b]	Intercept[c]	Time[d]	Delay[e]	Interaction[f]
Clinic	27.3 (22.0 to 32.5)	−5.5 (−3.6 to −7.4)	3.0 (1.3 to 4.6)	0.7 (0.1 to 1.3)
Antibiotics	29.8 (25.5 to 34.2)	−4.6 (−3.1 to −6.2)	3.5 (1.6 to 5.3)	0.5 (−0.1 to 1.1)
Immunomodulation	28.7 (23.1 to 34.3)	−4.9 (−2.9 to −6.8)	2.6 (0.9 to 4.3)	0.4 (−0.2 to 0.9)

[a]Outcome is CBI total score (0–96); predictors are a treatment delay variable (defined in footnote "e"), disease flare status, time established in clinic, and an interaction term between treatment delay and time established in clinic.
[b]The treatment modality variable refers to the duration of time between PANS onset and initiation of a given treatment. For example, when treatment modality is clinic, the model evaluates whether time between onset and first clinic appointment predicts CBI score.
[c]Intercept refers to the predicted CBI score at first clinic appointment for a patient, not in a flare, with 0 years in between onset and first clinic appointment.
[d]The time effect refers to the predicted decrease in CBI score associated with each additional year established in clinic.
[e]The delay effect estimate is the predicted increase in CBI score associated with each additional year's delay in the treatment modality.
[f]The interaction effect estimate is the predicted increase in the slope of CBI associated with each additional year's delay in the treatment modality.
Abbreviations: CBI = Caregiver Burden Inventory, PANS = pediatric acute-onset neuropsychiatric syndrome.

was 28.1 points (95% CI, 21.6 to 34.5). There were no significant differences between healthy controls and patients with PANS in terms of age or sex (data not shown).

In exploratory cross-sectional analyses, the only variable that correlated with CBI in the adjusted model was patient global impairment score (Table 2).

Our final longitudinal sample contained 94 patients whose caregivers had filled out 892 CBIs (range of CBIs per patient, 2–31; median = 8; IQR, 5–13). Patients excluded from this analysis were more likely to be male than patients who were included; no other differences were found between the groups. There was no association between age and CBI total scores in the healthy controls (coefficient = −0.32, *P* = .37).

Flares predicted a 6.6-point increase in total CBI score compared with quiescence (95% CI, 5.1 to 8.0). Each additional year since first clinic appointment predicted a 3.5-point decrease in CBI score (95% CI, −2.3 to −4.6) (Table 3). In our sensitivity analysis, we found each consecutive visit predicted a 0.4-point decrease in CBI score (95% CI, −0.3 to −0.5). After adjusting for global impairment, the effect was attenuated slightly (−0.3; 95% CI, −0.1 to −0.4). In another sensitivity analysis, we found no independent effect of an interaction term between global impairment score and years in clinic (data not shown). In our post hoc dropout analyses, longer time-in-clinic values predicted decreased CBI scores in both groups (those who left clinic before the cutoff time and those who remained established in clinic long term) (Table 4). When the cutoff point was 1.0 year, the group who remained established in clinic had a 3.4-point decrease in CBI score per year (95% CI, −2.1 to −4.6) while the group who left clinic before 1.0 years had a 9.2-point decrease in CBI score per year (95% CI, −3.6 to −14.8) (Table 5). The group who remained in clinic were more likely to have a chronic/static course of disease (40.5% vs 7.5%) (data not shown).

Finally, shorter time between symptom onset and clinical treatment predicted a more rapid decrease in CBI score over

the course of time in clinic (Table 5). Each 1-year delay in antibiotics and immunomodulatory therapy did not predict a more rapid decrease in caregiver burden over time (Table 5).

DISCUSSION

In our PANS population, the median CBI total score during a patient's first flare was 37, higher than the average found in a study of the CBI in Alzheimer's disease,[13] which found a mean (SD) CBI score of 29.7 (19.1) in caregivers of live-in patients with Alzheimer's disease after 6 months of clinical treatment. Our average is comparable to that in the validation study of the CBI in Rett syndrome, a debilitating developmental and neurologic disorder requiring almost total dependence on a caregiver throughout life.[27,28] It is difficult to directly compare our mean to the mean in the Rett syndrome study because the researchers in the latter modified the CBI, editing the language of some of the questions and adding in 2 positively worded questions. They did find the average score was less than 50% of the maximum score. (Our study's average score was 38% of the CBI's maximum score, indicating the 2 averages are at least comparable.) That PANS caregivers report comparable levels of burden speaks to the severity of stress that PANS places on the family unit. CBI score decreased over time while patients were receiving treatment from our specialty clinic.

One limitation of our study is that the CBI has never been formally validated as a longitudinal data collection tool. Also, both the CBI score and the global impairment score are caregiver-reported variables, which could introduce bias. Furthermore, our population was mostly non-Hispanic white individuals with high socioeconomic status who were able to establish with a specialty referral clinic, which may limit generalizability. Importantly, we did not compare our population to a population of patients with PANS who were not undergoing treatment, so any effect of time in clinic on caregiver burden could be explained by non–clinic-mediated time effects. To assess the hypothesis that clinic causes decreased caregiver burden over time, a study controlling for non–clinic-mediated time effects is necessary. The ideal study design, a randomized controlled trial, is not feasible due to the severity of this disease. A waiting-list–controlled trial could be a feasible way to evaluate the hypothesis that clinical treatment causes decreased caregiver burden in PANS. We could also compare the trajectories of CBI scores among cohorts who receive care from clinics that have different treatment approaches. Previous research, in both adult and pediatric care receiver populations, has found that disease severity is associated with higher caregiver burden.[26,29,30] Our study supports this finding, as both neuropsychiatric disease flares and global impairment scores predicted increased CBI scores over the course of a patient's time in clinic. Since both CBI and global impairment score are caregiver-reported variables, bias toward the association between these scores was very likely introduced. However, disease flare is a clinician-determined variable, which minimizes this bias.

Few studies have evaluated caregiver burden longitudinally.[10] We could find only 3 studies characterizing longitudinal caregiver burden trends in pediatric brain-related conditions (in attention-deficit/hyperactivity disorder [ADHD],[16] autism spectrum disorder [ASD],[21] and traumatic brain injury [TBI][18]). The ADHD and ASD studies found no change in caregiver burden over time.[16,21] On the other hand, the TBI study found that family burden decreased over time after initial injury, possibly because some families adapt to the child's long-term sequelae.[18] Caregiver burden decreased throughout a family's participation in our multidisciplinary PANS clinic, but we were not able to determine the specific cause of this correlation.

One possible explanation for our finding is that our families, like the TBI families, adapt to the child's symptoms over time. Another explanation is regression to the mean—the first clinic visit may occur at a time when burden is abnormally high; over time, burden may decrease regardless of clinical treatment. Also, caregiver burden may decrease as children age with PANS and are better able to manage their own care. If these explanations are correct, the CBI scores of a nontreated cohort of patients with PANS would be expected to also decrease over time. However, we do not have those data.

It is also possible that clinical treatment causes a decrease in caregiver burden, partly through decreasing disease severity and partly through a direct effect of clinical care (eg, compassionate listening, psychotherapy services, parent support groups hosted by our program, parent skills groups, and an education specialist who communicates with schools regarding the child's illness). Support groups and mindfulness-based stress reduction practices have been shown to modestly decrease caregiver burden in families of patients with chronic illnesses.[31,32]

Since we did not compare our cohort with a control group of untreated patients with PANS, we cannot conclude that one explanation is correct. However, given the mechanism of PANS, we find it unlikely that we would have seen the same relationship between time and global impairment in untreated patients with PANS. As a severe psychiatric illness, most likely involving neuroinflammation, the disease would be predicted to worsen over time if left untreated, similar to other neuroinflammatory conditions, especially in patients with multiple relapses. Since no study has examined the natural history of the disease, we cannot confirm this hypothesis. However, our finding that families who meet respite criteria have lived with the disease for longer than families who do not meet respite criteria (Table 2, $P = .07$) suggests that the disease does worsen over time naturally.

Our post hoc dropout analysis indicates that a subset of families who had rapidly decreasing caregiver burden were in our clinic only for a short period of time. The remainder of the families had a slower decline in caregiver burden and engaged in the clinic for a longer period. It is our clinical experience that when a child's illness resolves, the family

stops coming to our clinic, but when a child continues to be ill, the family continues with regular follow-up. Our analysis supports this clinical observation; however, there may be unmeasured variables influencing the association.

Families who came to clinic sooner following symptom onset had a more rapid decrease in caregiver burden than those who came to clinic later in the disease course. This finding supports the recommendation for rapid intervention after PANS onset.[33] While shorter time between symptom onset and first PANS clinic appointment predicted a greater decrease in CBI score, time to first antibiotic and time to first immunomodulatory therapy did not have the same effect; however, there was a trend toward improved CBI course with more rapid administration of these treatments. The interaction term between time-in-clinic and these 2 variables was not significant. Relevant to this finding, there were 10 patients who never received immune modulation; therefore, the power to detect an effect was lower than for the lag time to visit or lag time to antibiotics variables (all patients had a first visit, and all patients received antibiotics). However, if the effect of time to immune modulation is truly null, and given the association between neuropsychiatric symptom severity, caregiver burden, and time-in-clinic, two explanations exist: either (1) our strategy of using antibiotics and immunomodulatory therapies in this cohort was not sufficient, or (2) antibiotics and immunomodulatory therapy may improve the course of a subset of individuals or a subset of flares, but they do not improve the course for the cohort as a whole.

Future Directions

Advocacy work for caregivers of children with neuropsychiatric disease is warranted. Advocates can use data presented here to promote respite care for caregivers of patients with PANS.

CONCLUSIONS

Families of youth with PANS experience a significantly high caregiver burden, on par with or higher than that of families of patients with other debilitating neurologic and psychiatric disease. Caregiver burden improves over time among patients followed in our multidisciplinary clinic, but it is unclear what factors (including natural history of the disease) contribute to this improvement. Disease flares predict spikes in caregiver burden, and sooner entry into our multidisciplinary clinic setting predicts improved caregiver burden course, but more rapid treatment with antibiotics and immune modulation does not necessarily predict improved caregiver burden course in our clinic. Psychosocial stress and burden upon families of youth with PANS would appear to be an important consideration when treating youth with PANS and may be lessened by more rapid introduction to a clinic support system geared to the specific needs of these patients.

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