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Treatment Barriers in PANS/PANDAS: Observations from Eleven Healthcare Provider Families

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Abstract

Introduction: Pediatric acute-onset neuropsychiatric syndrome (PANS) and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) are severe but highly treatable post-infectious inflammatory brain conditions. Despite published diagnostic and treatment guidelines for this condition, there are long delays in obtaining appropriate care. The reasons for these delays are poorly understood. We sought to identify healthcare system barriers to timely treatment by examining cases of PANDAS/PANS occurring in children of healthcare professionals.

Method: We recruited families via email request through the PANDAS Physicians Network. Participating parents completed a structured questionnaire and provided a written case description.

Results: Eleven families completed data collection, representing a broad spectrum of disease (child disease onset age 4-15, 7 males/4 females, mild to severe). Parents included 11 physicians, two mental health professionals, 2 nurses, and a PharmD. Nine cases (82%) had “very delayed” diagnosis and treatment (>4 weeks after onset). The most commonly encountered causes for treatment delay were clinician lack of awareness (82%), clinician skepticism (82%), overdependence on diagnostic testing (91%), and out-of-pocket expenses >\$100 US (82%). Other common challenges included difficulties finding a provider to spearhead care (64%), psychological misdiagnosis (55%), and children’s suppression of behaviors during assessments (55%).

Conclusions: We found numerous barriers to treatment of PANDAS/PANS among children of healthcare providers. Our findings suggest that even among the medically sophisticated, PANDAS/PANS diagnosis and treatment remains challenging. Improvement in PANDAS/PANS education of clinicians who may encounter children with this disorder is one key step towards addressing our identified barriers.

Background

Pediatric acute-onset neuropsychiatric disorder associated with streptococcal infections (PANDAS) and pediatric acute neuropsychiatric syndrome (PANS) are debilitating post-infectious inflammatory conditions of the brain. Animal and in vitro models suggest repeated streptococcal infections (PANDAS) or other infections (PANS) in susceptible children lead to autoimmune attack on the basal ganglia (Thamotharampillai et al., 2016; Hoffman et al., 2004; Yaddanapudi et al., 2010; Frick et al., 2018). As delineated in diagnostic guidelines (Chang et al., 2013), resultant behavioral changes include acute onset incapacitating obsessive-compulsive disorder (OCD), restricted food intake, severe anxiety, behavioral regression, urinary disturbances, and sleep disturbances. Emotional lability, oppositional behavior, sensory avoidance, and aggression occur. Motor tics, handwriting deterioration, and school difficulties are common. Most children exhibit multiple symptoms simultaneously in a rapid decline over days to weeks, with initial onset often described as “overnight.” Normally functioning children suddenly cannot attend school, maintain basic hygiene, play, or even leave the home (Calaprice, Tona, Parker-Athill, & Murphy, 2017; Tona, Bhattacharjya, & Calaprice, 2017). Some suffer from suicidal ideation or completed suicides.

Despite published treatment guidelines that recommend specific therapies such as non-steroidal anti-inflammatory agents, antibiotics, psychiatric, and behavioral interventions (Thienemann et al., 2017, Frankovich et al., 2017; Cooperstock, Swedo, Pasternak, & Murphy, 2017), parents uniformly report significant difficulties establishing a timely diagnosis and finding skilled providers. Treatment can be delayed for years (6), with undefined long-term consequences. Yet most children who find appropriate

treatment improve readily; one trial of intravenous immunoglobulin (IVIg) showed 88% complete/near complete remission after 3.3 years follow-up (Leon et al., 2018).

Therefore, treatment delays must be viewed as causing unnecessary suffering.

This article illustrates healthcare system challenges of PANS/PANDAS in a unique patient population—the children of physicians and other medical professionals. These “insider” parents would be expected to have less difficulty navigating to appropriate care. Therefore, challenges depicted in these “best case scenarios” highlight areas for improvement in our healthcare system for children with PANDAS/PANS.

Methods

An email request on the PANDAS Physicians Network listserv sought physicians with children diagnosed with PANS/PANDAS to complete a structured questionnaire and written description of their cases (Table 1). A small number of non-physician parents (mental health professionals and nurse practitioners) expressed interest and were included. All diagnoses were confirmed and managed by non-family clinicians.

Data was tabulated and confirmed with parent-authors. Families could withdraw from participation at any time. Cases were assigned letters for privacy and identifying information such as location and dates of treatments was removed; no other information was altered. Barriers were defined as factors resulting in >1 week treatment delay or any out-of-pocket expense over \$100.

Approval for this observational study was obtained by [*blinded for review*].

Patient and Public Involvement

As noted above, parents of patients were solicited to provide patient narratives and review summaries of their child's case for accuracy.

Results

Fourteen families responded, representing fifteen cases. Three families representing three cases did not participate to completion. One cited overwhelming post-traumatic anxiety whenever writing was attempted. A second became too busy training therapists to treat PANS/PANDAS and managing her son's flares. A third did not cite a reason. The families not completing the process included 1 MD, 1 dentist, 1 PhD, and 1 nurse practitioner.

Twenty-two remaining parents included 11 MDs (1 neonatologist, 1 pediatric intensivist, 1 general pediatrician, 1 infectious disease physician, 3 adult intensivists, 3 family practitioners, 1 internist), 2 mental health professionals, 1 NP, 1 critical care nurse, and 1 pharmacist. Seven had academic appointments. Ten families were from the United States and one was from Sweden.

Eleven families had a total of 12 affected children (Table 2), ranging from toddlerhood to 15.3 years at onset (mean 8.6 years). The family with 2 affected children, both female, provided detailed information for only their older child. The final cohort included 7 males and 4 females. Onset was mostly abrupt, over 1-3 days. In two cases, onset was over approximately 2 weeks. In the three youngest cases, all 4 years old at onset, acuity was less clear.

Despite their high level of medical training, only 6 of 11 parent duos had heard of PANS/PANDAS prior to their child's diagnosis. Nevertheless, most cases (64%) were first suspected by parents themselves. Median time to diagnosis was 8 months (2

weeks-6 years, Table 3). Severity ranged from mild to life threatening, including 5 with suicidal ideation (2 suicide attempts), 5 medical hospitalizations, and 4 psychiatric hospitalizations. As of the time of this writing, all 11 children are described as “doing well,” with at most mild residual symptoms and follow-up ranging from 1 to 7 years (mean 3.4 years).

All families encountered barriers to timely diagnosis and treatment (Table 4). Nine children (82%) were undiagnosed and untreated for > 4 weeks, “very delayed care” as per treatment guidelines (9). Provider-related issues were the most common barriers, with lack of awareness of PANS/PANDAS and skepticism affecting 9 families each (82%). In a majority, providers were unsure what testing was needed (8 cases, 73%) or unsure how to interpret tests (7, 64%). Even after diagnosis, providers were hesitant to prescribe (5, 45%), frequently relying on non-local specialists to spearhead management. In 6 cases (55%), this lack of local specialists delayed treatment, although antibiotics, non-steroidal antiinflammatories, prednisone, and selective serotonin reuptake inhibitors are within the armamentarium of any primary care or emergency physician. Misdiagnosis, occurring in 7 cases (64%), usually pointed at a psychological cause. PANS patients may suppress behaviors outside the home, such as during a physician’s assessment. This occurred in 6 patients (55%). While pediatricians often benefit from knowing a family over many years, specialists lack this advantage. In 4 patients (36%), the lack of a long-term relationship with a provider delayed treatment. In the absence of a trusting parent-provider relationship, the specter of poor parenting or even abuse may loom, delaying medical diagnosis (3 patients, 27%).

Out-of-pocket expenses were the norm even in this well-insured cohort, which accrued out-of-pocket costs of \$4000 to \$200,000. 82% of families paid for care over

\$100 at some time. Cognitive behavioral therapy, a cornerstone of PANS treatment, was often not covered by insurance. A majority tried alternative therapies, which were rarely reimbursed. Five families (45%) experienced insurance denials of prescribed care.

Discussion

Because PANS/PANDAS uproots normal families abruptly and completely (Demchick et al., 2019), it is imperative that children receive prompt, appropriate care, based on treatment guidelines (Thienemann et al., 2017, Frankovich et al., 2017; Cooperstock, Swedo, Pasternak, & Murphy, 2017). Our study aimed to identify healthcare system barriers to timely care in a privileged cohort of medical families. These families should be skilled at navigating the medical system, and if obstacles are encountered, they should be able to detail them accurately. Even for our cohort of medical “insiders,” barriers to timely treatment abounded. The most common were provider-related (lack of awareness, skepticism, uncertainty about testing, and lack of a provider to lead care) and financial. Psychiatric misdiagnosis was common; children were often diagnosed with anxiety, eating disorders, or obsessive compulsive disorder.

Poor provider understanding of PANS/PANDAS remains common. Even aware clinicians may have heard that this diagnosis is “controversial,” despite the growing body of evidence showing clear biologic mechanisms for disease (Thamotharampillai et al., 2016; Hoffman et al, 2004; Yaddanapudi et al., 2010; Frick et al., 2018; Cutforth, DeMille, Agalliu, & Agalliu, 2016; Wald, 2019). They may not understand that the diagnosis is a clinical one, with no specific test required. Instead, testing only serves to suggest a trigger, identify underlying immune dysfunction, or exclude other diagnoses. Because there are not enough specialty PANS clinics, waiting lists are months or years

long. Often, these children are too ill to travel to a PANS clinic. As such, educating front line community physicians remains critical.

Community clinicians' role includes providing first line treatment promptly and aggressively while seeking specialty support. If IVIG is needed, they may need to battle for insurance authorization. Some insurance companies expressly prohibit payment for IVIg (United Healthcare policy for immune globulin, 2019), despite its inclusion in published standard-of-care treatment guidelines (Thienemann et al., 2017, Frankovich et al., 2017; Cooperstock, Swedo, Pasternak, & Murphy, 2017). Appeals to regulatory agencies may be required. It should be noted that insurance obstacles in the US are beginning to fall; multiple states have legislation mandating payment for PANS/PANDAS treatments, such as Illinois' Charlie's Law and seven other U.S. states.(Pandasnetwork.org, 2021) Further research supporting treatment pathways will reduce insurance difficulties. For our one European family, obtaining authorization for specialty evaluation and immune treatment continues to be extremely difficult, so even the existence of a national healthcare system fails to guarantee timely and appropriate care.

Most parents in our series concur with one mother's statement, "This is the worst thing I have ever lived through." Indeed, the Caregiver Burden Inventory (CBI) in one PANS/PANDAS clinic exceeded that for caregivers of Alzheimer's patients (Frankovich et al., 2019). All families except for Case F reported extreme emotional, financial, and social impacts. Parents voiced feelings of inadequacy and guilt, wondering if they made a parenting error. They worried about unrecognized physical or sexual abuse. Parents feared greatly for their child's future. Marriages were strained; siblings feared for their own safety. Property damage was common. Great lengths were taken to avoid triggering tantrums, resulting in tense, fearful home atmospheres. Extended family and

close friends often did not understand the situation. Two parents feared losing custody of their child. Immense time was spent researching, calling to find help, and coordinating care. School and work were missed, often for extended periods; careers were permanently altered. Even after recovery, families retained post-traumatic fear of recurrences. As healthcare professionals, parents suffered guilt for not having diagnosed their child sooner or for permitting their child to experience traumatic psychiatric hospitalizations. Some felt abandoned by their colleagues and medical system. Many felt uncomfortable being, at times, the most knowledgeable doctors caring for their child.

Despite these difficulties, parents reported that working in healthcare afforded many advantages. Professional networks sometimes shortened time to diagnosis and treatment. Parents self-managed much care, reducing doctor visits. They capably coordinated complex multi-specialty care involving a mean of 6.5 different specialties, most commonly psychiatry, psychology, infectious diseases, neurology, and emergency medicine, in addition to pediatrics. Parents were able to give a clear history, reducing diagnoses like “Munchausen” or “conversion disorder.” Medical training also allowed accurate interpretation of informational resources.

Overall, parents felt fortunate to work in healthcare. One wrote that the care their child received would be “unattainable for the typical, non-physician parent, and the child would likely go undiagnosed and untreated.” Another summed it up, “We would not have been viewed as seriously or treated as promptly if we weren’t physicians able to navigate the complex medical system.” It is reasonable to believe that the obstacles encountered by these eleven healthcare families would be as severe for non-medical families, if not worse, or accompanied by additional challenges.

In summary, PANS/PANDAS usually presents in a dramatic, very characteristic fashion. Diagnosis is generally straightforward using published guidelines. In the face of diagnostic uncertainty, many suspected cases could be confirmed by response to treatment, which can be dramatic, “clinching” the diagnosis and sparing suffering. Initial treatments, such as antibiotics, NSAIDS, and oral steroids, exist in the toolkits of primary care and emergency physicians but are rarely prescribed in a timely manner. Treated children frequently recover to baseline/near baseline (Leon et al., 2018; Calaprice, Tona, & Murphy, 2018), while delayed treatment may result in worse outcomes, as the disease mechanism is proposed to be brain inflammation. For this reason, we urge providers to err towards prompt, aggressive, and empiric treatment for the possibility of inflammatory brain disease, while alternative conditions (including psychiatric) are simultaneously ruled out.

There are clear limitations to extrapolating this data to the population at large. The healthcare families who volunteered their case histories may have experienced an unusual number of care barriers, making them more motivated to participate. However the authors feel it is most likely that the general population would fare no better, given the extreme complexity of this syndrome and the low level of understanding that is common in the medical community. As a retrospective analysis, our study is subject to recall bias, although we found the healthcare professional parents reporting to have precise records and recollections, particularly with regard to timing of symptoms, diagnosis, and treatment. The quality of reporting was sufficient to identify common healthcare system barriers faced by PANS/PANDAS families and thus targets for improvement.

We conclude that clinicians faced with a new presentation of PANS/PANDAS have an obligation to recognize this “can’t miss” diagnosis, as well as an opportunity to

make a life-changing positive impact through prompt treatment. Published guidelines have brought timely treatment within the realm of standard of care. Increasing healthcare providers' awareness, legislative mandates, and insurance coverage for treatments remain central in the effort to combat PANS/PANDAS.

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Table 1. Information collected

Presentation and diagnosis

- Acuity of onset
- Symptoms
- Time to diagnosis and diagnosing clinician
- Specialists involved in care
- Any relevant work up
- Hospitalizations
- Disease pattern (single episode, relapsing remitting, chronic/static, progressive)
- Past medical and family histories

Treatments attempted, including psychological therapies, alternative therapies, and special diets

- Time from treatment to response
- Management of relapses
- Barriers to timely diagnosis and treatment

Family impact- financial and non-financial

- School absences
- Impact on siblings and family, including parental work
- Out-of-pocket expenses and covered medical expenses
- Residual emotional and behavioral effects

Table 2. Patient characteristics

Case	age at onset	sex	onset acuity	trigger	type	OC	restricted food intake	anxiety	emotional lability	irritability, aggression, or oppositional behavior	behavioral regression	school difficulties (ADHD, cognitive, memory)	sensory or motor abnormalities	somatic signs or symptoms (sleep, urinary)	suicidal ideation or attempt	additional clinical features	parent specialty (ies)	academic appointment / professional fellowships
A	11	F	sudden	GAS pharyngitis	PANDAS	x		x	x	x	x		x			stiffness and joint pains, exhaustion, weight loss without food restriction, amnesic episodes	family practice, integrative medicine	Pennsylvania Medical Society
B	9	M	sudden	GAS PCR +	PANDAS	x		x	x	x			x	x	SI	headaches, 10% weight loss, shaking movements in head and arms, urinary incontinence and urgency	neonatology, PharmD	NA
C	8	F	sudden	GAS	PANDAS	x	x	x	x	x	x	x	x	x		fear of vomiting, 12# weight loss, gagging on food	cardiac APN	NA
D	8	M	sudden	gastroenteritis	PANS	x	x	x	x	x	x	x	x	x	SI	bed wetting, fear of vomiting	pediatrics, family practice	Assistant professor, FAAP
E	8	M	Acute / subacute	unclear	PANS	x	x	x	x	x	x	x	x	x	SI/SA	throat clearing tic, urinary frequency, headaches, flight episodes, persistent poor stamina and joint pains during recovery	academic PhD psychology	Assistant professor
F	4	M	unclear	impetigo	PANDAS	x					x		x			inhalation tic	academic family medicine	Associate professor
G	12	F	sudden	tonsillitis	PANS	x	x	x	x	x	x	x	x	x	SI	flight episodes, piano playing tremor hands and feet, dilated pupils, handwriting deterioration, difficulty walking direct paths, episode of Capgras delusion	intensive care/ emergency medicine/ general practice, anesthesia - intensive care	NA
H	12	F	sudden	flu/PNA	PANS	x	x	x	x	x		x	x	x	SA	eye blinking tic, repetition of nonsensical phrases, extreme startle reflex, flapping hand movements, up to 20 catatonic episodes per day	both parents academic pulmonary /intensive care	Assistant professor, Associate professor
I	15	M	subacute	Pharyngitis, GAS exposure	PANS	x	x	x	x		x	x	x	x		multiple motor and phonic tics, inability to walk direct paths, 12% weight loss, spitting, handwriting deterioration, extreme fatigue during recovery	academic ID, internal medicine	Professor, FIDSA, Associate professor, FACP
J	4	M	gradual	Lyme?	PANS	x	x (brief)	x	x	x			x	x		motor and verbal tics, sleep difficulties, ADHD symptoms	psychotherapy LMFT, cardiothoracic ICU RN	AAMFT, AACN

K	4	M	gradual	unclear	PANS	x										preschool onset social difficulties and motor tics, low muscle tone, and poor handwriting, urinary frequency, difficulty swallowing saliva, responsiveness to steroids, extremely elevated Cunningham panel	academic pediatric critical care	Assistant professor, FAAP, FSCCM
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Table 2 Abbreviations:

GAS = group A streptococcus, PCR = polymerase chain reaction, PNA = pneumonia

Acuity categories: sudden onset \leq 3 days, subacute \leq 1 month, gradual $>$ 1 month

APN = advanced practice nurse, PharmD = doctor of pharmacy LMFT = licensed marriage and family therapist,

RN = registered nurse

FAAP - American Academy of Pediatrics, FIDSA - Infectious Diseases Society of America, FACP - American College of Physicians, AAMFT - American Association for Marriage and Family Therapy, FSCCM - Society of Critical Care Medicine

Table 3. Management

Cas e	antibiotics	NSAIDS	steroids	IVIg (# of infusions if available)	plasmapheresis	rituximab	CBT/ psychotherapy	psychotropic medication	other treatments attempted	most effective treatment(s)	hospitalizations (type-medical or psychiatric and #)	months to diagnosis	duration of follow up	# of specialties involved in care
A	cephalexin followed by PCN prophylaxis	ibuprofen	no	no	no	no	CBT, guided imagery, counseling, breathing techniques, behavioral modification	no	GF/DF diet, fish oil, turmeric, iron, vitamin D	cephalexin and penicillin prophylaxis	none	8	2 yrs	8
B	amoxicillin, PCN prophylaxis	ibuprofen	no	no	no	no	CBT	sertraline		ibuprofen and penicillin prophylaxis	medical (1)	0.5	2 yrs	6
C	amoxicillin clavulanate, clindamycin	ibuprofen	no	no	no	no	counseling	amitriptyline	famotidine, tonsillectomy, vaccination delay	amoxicillin clavulanate	none	26	4 yrs	4
D	azithromycin, amoxicillin clavulanic acid	ibuprofen, naproxen	yes	no	no	no	CBT	citalopram, sertraline, clonazepam, fluoxetine		azithromycin	none	3	5 yrs	6
E	cefdinir, amoxicillin clavulanate	naproxen, ibuprofen	yes	yes (3)	no	no	CBT, ERP, mindfulness, others	citalopram, fluvoxamine, sertraline, aripiprazole, risperidal, quetiapine	melatonin, cetirazine, nasal steroids, cannabidiol oil, avoidance of dairy, gluten, sugar, soy, corn, nuts	IVIg; to a much lesser extent: amoxicillin clavulanate, NSAIDS, prednisone	psychiatric (2)	18	3 yrs	8
F	cephalexin	yes	no	no	no	no	no	no		antibiotics and NSAIDS	none	0.5	4 yrs	2
G	PCN, amoxicillin clavulanate	yes	no	no	no	no	CBT, Family Based Treatment, Compassion Focused Therapy	olanzapine, benzodiazepines, fluoxetine	frequent feeding, valerian, hops, melatonin, curcumin, hydroxyzine, promethazine,	penicillin, curcumin, amoxicillin clavulanate	psychiatric (1)	13	3 yrs	7
H	ceftriaxone, others, as well as prophylactic dosing	yes	yes	yes (multiple)	yes	yes	inpatient and outpatient therapies	benzodiazepine, atypical antipsychotics	beta blocker, dexmedetomidine, tonsillectomy, weekly methotrexate, subcutaneous tocilizumab, guaifenesin	combination immunomodulation with dexmedetomidine	medical (3), psychiatric (1, residential eating disorder unit)	3	2 yrs	10
I	azithromycin, cephalexin, amoxicillin clavulanate	naproxen	yes	yes (8)	no	no	CBT, ERP, and hypnosis	fluvoxamine, fluoxetine, clonazepam, mirtazapine	diphenhydramine, melatonin, curcumin, fish oil, vitamin D	IVIg, to a much lesser degree azithromycin	medical (1)	1.25	1 yr	10

J	amoxicillin clavulanate	ibuprofen	no	no	no	no	no	CBT and behavioral modification	no	GF/DF diet, herbal tincture and supplements, homeopathic remedies, sublingual immunotherapy	diet, complement ary therapies, ibuprofen, and later antibiotics	none	36	4 yrs	5
K	amoxicillin clavulanate, azithromycin , clindamycin	no	no	yes (7)	yes	yes	no		lisdexafeta mine, topiramate, guanfacine, methylphenid ate	multiple medications for tics, including experimental medications, occupational therapy, tonsillectomy	prednisone, amoxicillin clavulanate, rituximab	none	70	7 yrs	5

Table 3 Abbreviations:

CBT = cognitive behavioral therapy, PCN = penicillin, OCD = obsessive compulsive disorder, T+A = tonsillectomy and adenoidectomy, SSRI = selective serotonin reuptake inhibitor, IVIg = intravenous immunoglobulin, GF/DF = gluten free/dairy free, ERP = exposure and response prevention, NSAIDS = nonsteroidal antiinflammatory drugs, IVIg = intravenous immunoglobulin

Table 4. Barriers to care encountered at any time during course sufficient to impact timely diagnosis and treatment

Case	A	B	C	D	E	F	G	H	I	J	K	# with barrier (%)
Healthcare provider lack of awareness	x	x	x		x	x	x	x	x	x		9 (82)
Parental lack of awareness of PANS/PANDAS	x	x	x		x		x		x			6 (55)
Healthcare provider skepticism	x	x	x			x	x	x	x	x	x	9 (82)
Child did not display behaviors during clinical assessments	x	x					x	x	x	x		6 (55)
Providers hesitant to prescribe		x			x	x	x		x			5 (45)
Providers unsure of testing needed	x	x	x	x	x		x		x	x		8 (73)
Providers unsure regarding test interpretation	x				x	x	x	x	x	x		7 (64)
Providers lack long term relationship with family		x	x				x	x				4 (36)
Poor parenting suspected by providers							x	x	x			3 (27)
Needed specialty support not available locally	x			x	x	x	x	x				6 (55)
Difficulty finding a provider to lead care	x	x	x		x		x		x	x		7 (64)
Insurance denial of treatment		x			x				x	x	x	5 (45)
Need to self-pay portions of treatment > \$100	x		x	x	x	x	x		x	x	x	9 (82)
Misdiagnosis												
Neurological (Tourette syndrome, tic, seizure, etc)											x	1 (9)
Psychological (anxiety, OCD, eating disorder, psychosis, conversion disorder, etc.)	x		x		x		x	x	x	x		7 (64)
other (rheum, drugs, bad parenting/suspected abuse)							x					1 (9)
Number of barriers encountered	9	9	8	3	10	6	13	8	12	9	4	

Table 4 Legend

PANS = Pediatric acute neuropsychiatric syndrome

PANDAS = Pediatric acute-onset neuropsychiatric disorder associated with streptococcal infections

OCD = obsessive compulsive disorder

* behaviors suppressed in public

** including insufficient duration or strength of prescriptions

*** for example, "the throat culture is negative, so this cannot be PANS/PANDAS"

**** need to travel out of town to find knowledgeable help

***** providers waiting for another specialist to prescribe treatment