PANDAS and PANS: An Inflammatory Hypothesis for a Childhood Neuropsychiatric Disorder

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Case

Nancy is a 9-year-old female referred to pediatric neuroimmunology clinic with a sudden onset of obsessive-compulsive disorder (OCD). Approximately 4 weeks prior to her presentation there, Nancy had been diagnosed with streptococcal pharyngitis by her pediatrician via a throat culture. The pediatrician prescribed a 10-day course of amoxicillin, with resultant resolution of her pharyngitis symptoms. On the day after the 10-day course was completed, Nancy's mother noticed that she began acting a little more anxious than usual. Nancy was not historically an anxious child, but her mother noted she seemed more "on edge." The following day, Nancy began washing her hands repeatedly, avoiding touching things, and showering multiple times per day. She began experiencing emotional meltdowns and separation anxiety from her mother and began to pull her hair out when frustrated, which she had never previously done.

Within the next week, Nancy began to wet the bed at night, though she had been accident-free since she was toilet-trained at age 2.5 years, and she would complain frequently of needing to urinate despite having just voided. Nightly, she would become emotionally dysregulated at the smallest provocation; these episodes would involve screaming, crying, and tearing out her hair and would often last up to 3 h. As Nancy's symptoms worsened, she would have difficulty keeping her symptoms "in check" while she was at school. Her teacher began to notice that she had trouble completing assignments and tolerating when her schoolwork was not perfect. Her teacher also reported to Nancy's parents that Nancy was refusing to write in class,

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and when she did, it appeared to be closer to scribbles than her usual, neat penmanship.

Her pediatrician prescribed an additional 10-day course of amoxicillin for concerns over reinfection with Group A *Streptococcus* (GAS), recommended she begin seeing a therapist for cognitive behavioral therapy, and referred her to a urologist due to the frequent enuresis. A urology work-up was unable to identify a reason for her urinary urgency, and the urologist referred her for a psychological consultation, suggesting that Nancy's symptoms may be attributed to pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Nancy was subsequently referred to a Pediatric Neuropsychiatry and Immunology Clinic which specialized in the evaluation and management of this condition.

Presentation and Relevant History

Upon evaluation, Nancy's symptoms were consistent with pediatric-onset obsessive-compulsive disorder (OCD) and were notable for a rapid progression in severity over the course of a few days. Nancy had no history of previous psychiatric or behavioral difficulties and no prior psychiatric treatment or hospitalizations. Her medical history was significant only for five GAS infections over the past 5 years, including the one that is relevant to her current presentation. Her first documented GAS infection, around 5 years of age, resulted in scarlet fever, but her parents denied any behavioral changes concurrent with that infection. Based on parent reports, pregnancy, delivery, and early childhood were unremarkable. Developmental milestones were met within normal limits. Family medical history was unremarkable for psychiatric conditions, including OCD, tic disorders, and attention deficit hyperactivity disorder.

Nancy's OCD severity was evaluated using the Children's Yale-Brown Obsessive-Compulsive Disorder Scale (CYBOCS); Nancy scored a 24 (out of a possible 40 points), which indicated moderate OCD severity. She described recurrent obsessions related to a fear that she would get sick due to a contaminant in the environment and that objects touched by other people were subsequently "contaminated" and may make her ill. Nancy also exhibited several compulsions that became functionally limiting for her and her family. She would lick her hands as a means to "clean" them. She frequently checked the bottom of her shoes to be sure she had not stepped in any "contaminants," such as dog poop.

Nancy had lab work conducted which showed elevated reactivity against Group A streptococcal proteins (antistreptolysin O titer = 946 (normal range 0–640) and anti-DNAseB titer = 2110 (normal range 0–375)). Her ESR and C-reactive protein results were within normal limits, and her antinuclear antibody was nonreactive. A test of her immunoglobulin levels for IgA, IgG, and IgM was within normal limits and showed no evidence for immune deficiency. Nancy had no focal neurological findings on exam, and did not exhibit any tics or adventitious movements; an MRI was deemed unwarranted at the time. To further evaluate Nancy's fine motor difficulties, she was administered with Grooved Pegboard and Beery-Buktenica

Developmental Test of Visual-Motor Integration (VMI). Although her basic fine motor skills were average on the pegboard, her visual motor skills fell in the 18th percentile, which when compared to her history of intact fine motor skills suggested a disruption of her visual-motor processing.

Nancy was determined to meet criteria for PANDAS. A referral was made for cognitive behavioral therapy in their local area. Nancy was also initiated on a 2-week course of a nonsteroidal anti-inflammatory drug (NSAID) using naproxen sodium, dosed at 10 mg/kg BID. A follow-up appointment to discuss additional management of her symptoms, including psychotropic medications, was scheduled for 6 weeks following this initial appointment.

Disease Course

At her 6-week follow-up appointment, Nancy stated her OCD symptoms had improved considerably. She had completed her course of naproxen without significant side effects and did not experience a worsening of her symptoms following discontinuation. She had also begun seeing a cognitive behavioral therapist for weekly sessions, and she reported that she felt more in control of her symptoms now that she was learning strategies to "fight" them. Her parents also endorsed feeling more confident knowing how to coach Nancy through times that she expressed OCD, separation anxiety, or increased irritability, thanks to strategies they learned as well. Her CYBOCS score was reduced to an 18, which indicated borderline/mild OCD severity. At her next follow-up appointment, 12 weeks following her initial evaluation, she and her family reported continued symptom improvement. The OCD obsessions were mostly transient, and she was no longer experiencing compulsions except on rare occasions when she felt stressed. Her CYBOCS had at that point decreased to 12, indicating subclinical OCD severity. It was determined that Nancy would continue in behavioral therapy for the additional 8 weeks. No further medical therapy was deemed necessary.

Discussion

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS) refer to the acute and dramatic onset of a constellation of neuropsychiatric symptoms in children, defined primarily by obsessive-compulsive and tic symptoms, and may further include symptoms of inattention, hyperactivity, food restriction, and separation anxiety [1, 2]. The diagnostic criteria for PANDAS detail a sudden onset of these symptoms following an antecedent Group A streptococcal (GAS) infection and require that these be the first time a child has displayed significant obsessive-compulsive or tic symptoms in their life. Further requirements for the diagnosis are a prepubertal age of onset, episodic exacerbation or remittance of symptoms in conjunction with further GAS infections, and neurological abnormalities, which

include motoric hyperactivity and adventitious movements, particularly of the hands and fingers. This diagnostic category was later broadened to include infectious triggers other than GAS and to include acute avoidance of food intake as an additional diagnostic criterion. This diagnosis has been termed pediatric acute-onset neuropsychiatric syndrome (PANS), and it should be noted that PANDAS and PANS are mutually exclusive diagnoses, with PANDAS being the appropriate diagnosis if the infection preceding symptom onset was a Group A streptococcal infection.

The PANDAS diagnosis was introduced by Dr. Susan Swedo at the National Institute of Mental Health in the 1990s and was the product of investigations into OCD symptoms in children with Sydenham chorea (SC). SC is a neuropsychiatric disorder characterized by involuntary, hyperkinetic movements and is recognized as the major neurological manifestation of acute rheumatic fever (ARF), a constellation of inflammatory conditions which occur following GAS infection.

While the pathogenesis of SC remains unknown, multiple neuroimaging studies suggest inflammatory involvement of the basal ganglia may underlie the varied neuropsychiatric symptoms of the disorder. The involvement of the basal ganglia in SC may explain why patients with SC also frequently display new-onset obsessive-compulsive symptoms, as the basal ganglia have been frequently implicated in the pathogenesis of OCD [2]. In studying the association between SC and OCD, Dr. Swedo and colleagues described a group of children who failed to meet criteria for SC, though displayed new-onset OCD symptoms following a GAS infection. The PANDAS diagnosis was subsequently proposed as a variant of SC, with the hypothesis that both disorders share a similar post-infectious, inflammatory etiology.

A cohort of PANDAS patients was described for the first time in 1998 [3]. Based upon age of onset, comorbid diagnoses, and phenomenology of obsessive-compulsive symptoms (i.e., contamination obsessions, ordering/arranging obsessions), the cohort of PANDAS patients described does not appear to differ considerably from the typical symptoms of pediatric-onset obsessive-compulsive disorder (OCD). However, the dramatic onset of these symptoms, periods of significant symptom exacerbation and remission, and association with recent streptococcal infections have been shown in cohort studies to differentiate between these two populations.

The introduction of PANDAS and PANS as unique diagnostic entities apart from pediatric OCD and tic disorders has been, and continues to be, controversial. The primary objection to this classification has been the assumption that, in PANDAS/PANS patients, the symptoms arise from an inflammatory or autoimmune etiology as opposed to the genetic or environmental factors which are hypothesized to typically underlie OCD or tic symptoms. This controversy has been compounded by a lack of available biomarkers for identifying PANDAS/PANS patients, a relatively low prevalence of OCD in the pediatric population (1–2%), and the association of OCD and tic symptoms with a nearly ubiquitous infection in school-age children (i.e., "strep throat").

Relevant Neuroanatomy and Pathophysiology

Multiple lines of evidence suggest dysfunction in cortical-striatal circuitry contributes to both OCD and tic disorder symptoms. Accordingly, the hypothesized mechanism in both PANDAS and SC involves an inflammatory response directed at these neural networks. Evidence for this hypothesis has been provided from an MRI study which displayed volumetric increases in the basal ganglia nuclei of PANDAS subjects compared to controls, as well as a positron emission tomography (PET) study which found increased activation of microglia, the resident immune cell in the brain, in PANDAS subjects compared to those with Tourette's syndrome [2].

Additional support for autoimmunity in PANDAS comes from the identification of reactivity of serum and CSF to postmortem human caudate and putamen samples [2]. Recently, this finding has been extended through experiments which infused serum from PANDAS subjects into the striatum of mice; serum from PANDAS subjects, compared to healthy controls, was found to bind selectively to the cholinergic acetyltransferase (ChAT)-expressing neurons of the striatum [4]. This binding was found to decrease in correlation with symptomatic reductions in OCD severity following intravenous immunoglobulin (IVIG) treatment in the PANDAS subjects [4].

Additional research is necessary to investigate these potential autoimmune antibodies in PANDAS subjects; furthermore, it should be noted that these antibodies have only been investigated in patients with PANDAS, while no autoimmune antibodies have been identified in patients with PANS. However, if future investigations demonstrate that these antibodies are reliably identifiable in patients with PANDAS/PANS and are pathogenically relevant to PANDAS/PANS symptomatology, it would provide evidence that PANDAS/PANS may more accurately be classified as an acute, post-infectious basal ganglia encephalitis.

Treatment Strategies

Few randomized, controlled treatment trials have been conducted in children with PANDAS, which limits a clinician's ability to make empirically informed treatment decisions for this population. As such, a number of consensus guidelines for treatment of PANDAS/PANS have been published by a consortium of academic investigators and clinicians, and these guidelines cover the use of psychotropic or behavioral interventions, antimicrobial therapies, and immunomodulatory therapies. These three approaches are complementary and can be pursued concurrently [5].

Symptomatic treatments for OCD and behavioral symptoms include psychoeducation, psychotropic medications, and cognitive behavioral therapies. The consensus recommendations are to begin as soon as possible following diagnosis given the delay between treatment initiation and expected benefit (e.g., 8–12 weeks for psychotropic medications including upward taper; 12–16 weeks for cognitive behavioral therapy). Psychotropic medications are often indicated based on the presenting

symptoms. For example, selective serotonin reuptake inhibitors (SSRIs) remain the first-line pharmacological intervention for OCD symptoms, while alpha-2 adrenergic agonists (clonidine and guanfacine) are the initial pharmacological intervention for tic symptoms. If comorbid attention deficit hyperactivity disorder (ADHD) symptoms are present, stimulants, atomoxetine, and alpha-2 adrenergic agonists, guanfacine and clonidine, may be indicated. Inpatient psychiatric hospitalization may be required for children with symptoms of self-injury, suicidality, or severe aggression. Hospitalization may also be required for children presenting with symptoms of severely restricted food or fluid intake that result in inadequate nutrition and hydration.

Behavioral interventions are also frequently indicated in the treatment of PANDAS-/PANS-related symptoms. Cognitive behavioral therapy (CBT) with exposure and response prevention (CBT/ERP) is the first-line choice for OCD and anxiety symptoms and has been found to be effective in treating OCD symptoms in PANDAS patients. Behavioral interventions may also include implementation of an Individualized Education Plan (IEP) or 504 Plan to provide school accommodations and services to support the child's specific needs and address the impacts of symptoms in the academic setting. For example, students with handwriting deterioration may benefit from the use of a computer for note taking, those with urinary frequency may be allowed to leave the class when needed, and a student with frequent absences related to the disorder may be excused from missed work, to name a few [6].

An additional consideration in the treatment of PANDAS/PANS involves antimicrobial therapy. The consensus guidelines suggest that all patients being evaluated for PANDAS/PANS receive a throat swab for evaluation of Group A streptococcal pharyngitis. The use of streptococcal serologies (i.e., antistreptolysin O and anti-DNAseB) for the diagnosis of PANDAS/PANS at a single time point (i.e., initial evaluation) is discouraged, though serial evaluations of streptococcal serologies displaying increasing titers may be indicative of a streptococcal infection in lieu of a throat swab and may aid in the diagnosis of PANDAS. Treatment of streptococcal pharyngitis typically involves oral, or alternatively intramuscular, penicillin, though may include cephalosporin or macrolide antibiotics for those with penicillin allergies. Azithromycin should be used cautiously given the emergence of macrolide-resistant streptococcal strains, and the potential for QT prolongation when used in combination with psychotropic medications which also prolong the QT interval, such as SSRIs and antipsychotics [7].

As stated in the consensus guidelines, there is currently insufficient evidence to support long-term use of antibiotics for prophylaxis against streptococcal infections in children with PANDAS/PANS. However, this practice is frequently employed clinically in children with PANDAS/PANS who display recurrent streptococcal infections or individuals with immunoglobulin deficiencies. Further research is warranted to determine the risks and benefits of prophylactic antibiotic children with PANDAS/PANS.

Bacterial infections other than Group A *Streptococcus* are an additional factor for consideration in the use of antimicrobial therapy. Case reports of childhood infections with *Mycoplasma pneumoniae* suggest that infections with this agent are

associated with the development of obsessive-compulsive symptoms, restless leg syndrome, and, rarely, necrotic lesions of the basal ganglia. Similar to serologies for Group A *Streptococcus*, serologies for *M. pneumoniae* may frequently return false-positive results, particularly when using single time point serologies of IgG and IgM titers against *M. pneumoniae.* Confirmatory testing using indirect immunofluorescence assays or PCR testing is recommended for evaluation of acute *M. pneumoniae* infection, and treatment with azithromycin or a tetracycline is warranted following confirmation, or a high degree of suspicion, of infection. Additional bacterial triggers of PANS in children, including Lyme disease or *Borrelia burgdorferi* infections, have not been reported in the scientific literature [7].

Finally, based upon the hypothesis that PANDAS and PANS are due to an inflammatory or autoimmune reaction, immune-modulating therapies have been employed in both research trials and clinical management in children with PANDAS. The first of these trials employed therapeutic plasma exchange (PEX), intravenous immunoglobulin (IVIG), and a "sham-IVIG" control group [8]. Results from this trial displayed a 58% and 70% decrease in OCD symptom severity from baseline to a 1-month follow-up in the IVIG and PEX groups, respectively, with no significant change in the "sham-IVIG" group [8]. A second clinical trial in PANDAS patients, employing IVIG versus a placebo infusion with a blinded, randomized design, failed to show a significant difference in the reduction of OCD symptom severity between baseline ratings and a 6-week follow-up evaluation [9]. The discrepant results from these two trials have cast doubt on the efficacy of IVIG in the treatment of PANDAS symptoms, though further research is needed to explain the discordant findings between these two trials.

A number of additional immunomodulatory therapies for the treatment of PANDAS/PANS symptoms have been reported in open-label case reports and included in the consensus treatment guidelines for the treatment of PANDAS/PANS [10]. The use of nonsteroidal anti-inflammatory (NSAID) therapies (commonly naproxen sodium, dosed at 10 mg/kg BID, maximum 500 mg per dose) in PANDAS/PANS patients has been shown to both decrease neuropsychiatric symptoms acutely in PANDAS/PANS patients and shorten the duration of symptom exacerbations following infections, though this intervention has yet to be investigated in a randomized clinical trial. Duration of these therapies is recommended to be approximately 6 weeks, with careful monitoring of symptoms of GI distress and NSAID-associated bruising or bleeding symptoms; longer-term therapy has been used in selected cases along with monitoring of liver function tests, CBC, BUN/creatinine, and urinalysis.

Both oral and IV steroids have also been employed in the treatment of the neuropsychiatric symptoms of PANDAS/PANS. A publication detailing the use of steroids in a community-based clinic of PANDAS/PANS patients reported the duration of symptom exacerbations was significantly shorter when either short courses (5 days) or extended courses (up to 8 weeks) were used, compared to exacerbations which were not treated with steroid therapy [10]. The authors note that side effects were common in those treated with steroids (44%), the most notable being a transient increase in the severity of neuropsychiatric symptoms in the days following steroid initiation.

Additional research is warranted into treatment responses in children who meet criteria for PANDAS/PANS. The heterogeneous response to IVIG, preliminary findings of autoimmune antibodies in PANDAS patients, and reports of response to NSAIDs and steroids suggest neuropsychiatric symptoms in some patients with PANDAS/PANS may be related to autoimmune antibodies, while others with PANDAS/PANS may display symptoms due to inflammatory cytokines. Should future research lead to a diagnostic test for autoimmune antibodies in PANDAS/PANS similar to current tests for NMDA receptor autoimmune encephalitis, it may allow for empirically validated therapies for PANDAS/PANS in the near future.

Clinical Pearls

1. Patients with a sudden, severe onset of OCD or tic disorders warrant a medical work-up to rule out causes of acute infections, such as Group A streptococcal pharyngitis. Those with marked movement disorder symptoms warrant a work-up for Sydenham chorea, including an echocardiogram to rule out rheumatic carditis. Other causes for sudden neuropsychiatric changes, such as viral and autoimmune encephalitis, should be ruled out when appropriate prior to provision of a diagnosis of PANDAS/PANS. This may require brain imaging, lumbar puncture, serology, etc. in order to thoroughly evaluate other symptom etiologies.
2. Patients who meet criteria for PANDAS/PANS may show benefit from short courses of anti-inflammatory medications, though treatment with additional first-line therapies for OCD or tic disorders may be warranted and necessary.
3. Children with mild OCD can experience exacerbation of their underlying symptomatology in the setting of stressors, which include infections. As a result, careful screening for the existence of signs and symptoms of OCD, anxiety, and other compulsive disorders should be done.

Lessons Learned About Neuropsychiatry

The contribution of the immune system to the development of neuropsychiatric disorders continues to be of significant interest to the fields of psychiatry and neurology. For disorders in which autoimmune antibodies have been identified, such as anti-NMDA receptor encephalitis, little controversy exists regarding the link between pathological immune processes and neuropsychiatric symptoms. For putative disorders such as PANDAS/PANS, the evidence for immune involvement is suggestive, though remains incomplete. However, with continuing advances in neuroimaging modalities, antigen discovery techniques and careful analysis of clinical data, the continued controversy over the diagnosis of PANDAS/PANS may soon be put to rest (Tables 23.1 and 23.2).

Table 23.1 Diagnostic criteria for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

1. Sudden onset of OCD/tic symptoms and an episodic course of symptom severity
2. Presence of OCD or tic disorder
3. Prepubertal age of onset
4. Temporal association between onset of symptoms and a GAS infection
5. Associated neurological abnormalities (adventitious movements, marked motoric hyperactivity, handwriting deterioration)

Swedo SE, Leckman JF, Rose NR. From research subgroup to clinical syndrome: modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). Pediatr Therapeut. 2012;2:113

Table 23.2 Diagnostic criteria for pediatric acute-onset neuropsychiatric syndrome (PANS). In addition to onset correlated with an infection agent other than GAS and symptoms that cannot be better explained by a known medical or neurological disorder, patients must experience an abrupt and dramatic onset of OCD behaviors or severe eating restrictions, along with at least two accompanying symptoms

(a) Markedly increased level of anxiety, particularly new onset of separation anxiety
(b) Emotional lability and/or depression
(c) Irritability, aggression and/or severely oppositional behaviors
(d) Deterioration in school performance, including sudden difficulties with concentration or learning
(e) Developmental regression (“baby talk,” temper tantrums)
(f) Sensory or motor abnormalities, including handwriting deterioration, new onset of motor hyperactivity, adventitious movements, pronator drift, or truncal instability
(g) Somatic signs, including increased urinary frequency or increased urge to urinate, enuresis, or sleep disorder (e.g., insomnia, night terrors, refusal to sleep alone)

Swedo SE, Leckman JF, Rose NR. From research subgroup to clinical syndrome: modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). Pediatr Therapeut. 2012;2:113

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