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Five Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome of Differing Etiologies

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Abstract

Background: Pediatric acute-onset neuropsychiatric syndrome (PANS) is diagnosed by the abrupt onset of new obsessive compulsive disorder (OCD) or food-restricting symptoms, and at least two of a variety of other neuropsychiatric symptoms. Detailed clinical presentation of youth with this condition has not yet been provided in the literature.
Methods: We review the clinical charts of five youth meeting criteria for PANS in our PANS Clinic. These five patients were selected for differing underlying causes thought to be driving an inflammatory response that appeared to impact psychiatric symptoms.
Results: Five youth with varying potential etiologies impacting neuropsychiatric symptoms were identified. These youth were from 8 to 18 years old at the onset of their PANS illness, and had bacterial, autoimmune, and unknown etiologies. Treatment directed at presumed etiologies ranged from antibiotics to intravenous gamma globulin (IVIG) to other immunomodulatory regimens, and appeared to improve the psychiatric illness.
Conclusions: Youth with PANS may present in differing ways, with psychiatric and physical symptoms overlapping with inflammatory or infectious diseases, pain syndromes, and other psychiatric diagnoses. Patients' psychiatric symptoms may respond to treatments targeting the underlying cause of physical illness. Faced with a pediatric patient demonstrating the abrupt onset or exacerbation of psychiatric and physical symptoms, clinicians should consider PANS in their differential diagnosis.

Introduction

As its name implies, the diagnosis of pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection syndrome (PANDAS) requires documentation of a temporal association between the sudden onset or exacerbation of neuropsychiatric symptoms and a preceding infection with group A streptococci (GAS). This requirement for association with GAS created diagnostic difficulties for clinicians (Gabbay et al. 2008). It has been recognized that other pathogens may also contribute to acute neuropsychiatric disorders in youth, including herpes simplex virus, influenza A virus, varicella zoster virus, human immunodeficiency virus, *Mycoplasma pneumoniae*, *Borrelia burgdorferi*, and the common cold (Ercan et al. 2008; Morer et al. 2008; Chambert-Loir et al. 2009; Rhee and Cameron, 2012). Although originally described as ''pediatric infection-triggered neuropsychiatric disorders'' (PITANDs) (Allen et al. 1995), etiologic agents could not always be identified. Therefore, the diagnostic category was broadened to include all acute-onset neuropsychiatric cases and was named ''pediatric acute-onset neuropsychiatric syndrome'' (PANS) (Swedo et al. 2012).

Diagnosing PANS requires documentation of an abrupt onset of obsessive compulsive disorder (OCD) or food restriction, and at least two of the following associated symptoms: 1) Anxiety; 2) emotional lability and/or depression; 3) irritability, aggression and/or severely oppositional behaviors; 4) behavioral (developmental) regression; 5) deterioration in school performance; 6) sensory or motor abnormalities; and 7) somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency.

In the fall of 2012, we started the first interdisciplinary clinic at Stanford Children's Health, designed to evaluate and treat youth who meet criteria for PANS. Many of these youth have been extremely ill, with destructive rage outbursts, extreme compulsions (licking shoes, barking), motor and vocal tics (whooping, wringing hands), school dysfunction (caused by attention-deficit/hyperactivity disorder [ADHD] symptoms, memory impairment, and cognitive regression) and serial psychiatric hospitalizations.

In an effort to begin to describe the spectrum of presentations and clinical courses of these patients, and to describe some etiologies that have not been reported, we present five cases of youth who met criteria for PANS, who have been seen in our clinic.

Cases

Case 1 (PANS and probable inflammatory brain disease/autoimmune encephalitis)

A 13-year-old female with mild cognitive and learning disabilities (but good school performance, as she achieved As and Bs in a private/academically challenging school), no premorbid

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psychiatric history, and good social functioning, was prescribed minocycline by her pediatrician for facial acne. Within 1 week of starting the antibiotic, she developed extreme anxiety. Minocycline was, therefore, discontinued, and the anxiety symptoms fully resolved within 3 days. One month later she developed abrupt (overnight) onset of severe obsessions regarding her braces, and eating restrictions. She could not feed herself, swallow, or chew, and food would fall out of her mouth if her mother fed her. For example, it took 1.5 hours for her mother to coax her into drinking one can of Ensure (237 mL), and she subsequently had an 11 pound weight loss over the 1st week of illness. She also had severe insomnia (not sleeping for 4 consecutive days), nearly absent communication (both talking and writing) except to discuss her braces, constant wiping of her face with her right hand, and inconsolable crying and screaming, and she was unable to engage in daily life activities including bathing and other personal hygiene activities. All of these symptoms developed overnight, and were at their maximum intensity within 24 hours of illness onset. Her illness stayed at this intensity with continued behavioral regression, cognitive deterioration, anxiety, perseverations, repetitive self-soothing, delayed or absent verbal responses, persistent insomnia, poor hygiene, poor oral intake with ongoing weight loss, and jaw tremor. Her behavioral issues became unmanageable because of her constant and obsessive hitting of her parents, crying and screaming, running into the streets, hiding, and trying to jump out of moving cars. Three weeks into the course of this illness she developed urinary incontinence, and extreme persistent urinary frequency of unknown cause, ultimately requiring her to wear diapers.

The patient was seen by a psychiatrist and diagnosed with bipolar disorder. The family psychiatric history was significant for bipolar disorder (maternal aunt) and an unknown mood disorder (maternal grandmother). Over the ensuing 6 months, the patient was admitted to inpatient psychiatric hospitals on six occasions and was treated with medications from nearly every psychotropic medication class, with little beneficial effect, and significant adverse effects, including sedation, drooling, and Parkinsonian movements. Benzodiazepines caused severely disinhibited behavior (sexualized gestures, cognitive impairment, and developmental regression). Divalproex, quetiapine, and aripiprazole were titrated to full dosages but were not helpful. Benztropine at 1 mg twice daily caused sedation, but did not improve extrapyramidal symptoms. Lithium was initiated, and propranolol was given for a presumed lithium-induced tremor. This regimen had some benefit in stabilizing the patient's mood, but other psychiatric symptoms continued. Other psychotropic trials included antidepressants (trazodone, escitalopram, venlafaxine, bupropion) and benzodiazepines (lorazepam, clonazepam). Multiple medications were used to help with sleep, with poor efficacy.

Because her condition was refractory to these psychiatric medications, she was referred for electroconvulsive therapy. At this point (1 year after her initial presentation) the patient was evaluated for a second opinion by a psychiatrist in the Stanford Pediatric Bipolar Disorders Program, who immediately suspected an inflammatory etiology based on the sudden-onset nature of her illness, unusual course of the mania, significant OCD symptoms, poor response to psychotropics, encephalopathic features, persistent tremor, and choreiform movements of her fingers (piano playing finger movements). She was, therefore, referred to the pediatric neurology and rheumatology departments and was evaluated for inflammatory encephalitis and systemic autoimmune diseases.

Based on brain imaging and serological and cerebrospinal fluid analysis, the following diagnoses were excluded: Limbic encephalitis (negative voltage gated ion channel antibodies, negative *N*-methyl-D-aspartate [NMDA]-receptor antibodies, negative paraneoplastic panel per Mayo Clinic), Hashimoto's encephalitis (negative thyroid antibodies), lupus cerebritis (negative lupus specific antibodies), and Sjogren's disease (negative anti-Ro and anti-La antibodies). Given her chorea, she was worked up for antiphospholipid antibodies and found to have normal values for lupus anticoagulant, dilute Russell's viper venom time, anticardiolipin antibodies, and β 2-glycoprotein I.

Primary and secondary central nervous system small vessel vasculitis was ruled out with a normal brain MRI, including perfusion studies, negative antibodies previously mentioned, and negative antineutrophil antibodies. Ongoing infectious encephalitis was thought to be unlikely given the patient's course. She also had negative infection screens (negative evaluations for *Bartonella* species, *Erhlichia chaffeensis*, *Babesia microti*, *Leishmania*, Lyme disease, West Nile virus, herpes simplex virus 1 and 2, Epstein–Barr virus [EBV], syphilis, and enterovirus). Metabolic/genetic evaluation was also negative for detectable abnormalities, and included normal results for lactate, pyruvate, ammonia, fatty acid profile, acylcarnitine profiles, serum/urine/cerebral spinal fluid (CSF) amino acid profiles, mucopolysaccharide and oligopolysaccharide profiles, cytogenetic fluorescence *in situ* hybridization (FISH), Fragile X, array comparative genomic hybridization, and mercury. The CSF study analysis was normal, including cell counts, glucose, protein, and immunoglobulin (Ig)G index. CSF studies also indicated negative IgG bands and the negative infectious and metabolic workup mentioned previously.

However, the patient was found to have an elevated antinuclear antibody (ANA) titer (1:320), positive antihistone antibodies, and low complement (C4) findings, which are nonspecific, but are known to be associated with lupus. Minocycline-induced lupus cerebritis was considered, but the short interval between minocycline and symptom development is atypical for this condition. The patient was later found to have antineuronal antibodies targeting dopamine 1 receptors, dopamine 2 receptors, lysoganglioside, and tubulin, which were detected under a research protocol by Dr. Madeleine Cunningham. Preliminary research on these antibodies suggests a link to the clinical syndromes of Sydenham's chorea and PANDAS (Kirvan et al. 2003, 2006, 2007). Both these disorders are thought to be caused by inflammation involving the striatum (i.e., basal ganglia) (Dale and Brilot 2012; Kumar et al. 2014).

The working diagnosis of inflammatory brain disease, most likely striatal encephalitis (based on the acute and severe psychiatric presentation and choreiform movements of the patient's fingers) served as the basis for her treatment regimen. She first received 3 days of high dose methylprednisolone (1000 mg daily for 3 days) followed by a slow prednisone taper (60 mg p.o. twice daily for 4 weeks followed by 10% reduction every 3 days). The high dose steroid trial resulted in remarkable and sustained improvement, thus meeting criteria for ''steroid responsive encephalitis'' (Vernino et al. 2007). The patient returned to 90% of her baseline functioning, and psychotropic medications were streamlined. However, when attempts were made to wean the prednisone below 60 mg daily, the patient started to develop a recurrence of symptoms, most notably the return of insomnia and OCD symptoms such as washing, cleaning, and measuring herself repeatedly. She was re-hospitalized for a second steroid induction with methylprednisolone (1000 mg daily for 3 days), again with good results, and mycophenylate mofetil was added to her regimen in hopes that this would allow further tapering of prednisone.

During our second attempt to taper prednisone, now with mycophenylate added, there was a re-escalation of the patient's psychiatric symptoms at 15 mg/day, resulting in a second medical hospitalization that lasted 3 months. The re-escalation of symptoms was severe, and associated with a GAS exposure (from her sister), but the patient did not test positive for streptococcus herself. Monthly intravenous gamma globulin (IVIG) (2 g/kg) was added to her regimen for 3 consecutive months. When the pre-IVIG antineuronal antibody testing returned positive (i.e., Cunningham Research Panel), and given the connection of these particular antibodies to Sydenham's chorea/PANDAS, antibiotics to treat and prevent GAS were added to the patient's regimen.

Although she improved on her new regimen of IVIG and mycophenylate, she again failed our third attempt to taper the prednisone, which then resulted in a third prolonged hospitalization. During all three prolonged hospitalizations the patient required a 1:1 sitter for 24 hour supervision because of severe behavior deterioration and OCD symptoms with regard to drinking fluids (e.g., water intoxication caused by obsessive water drinking; the patient also drank nail polish remover and her own urine). Interestingly, with each flare up of her disease, the nature of her OCD symptoms changed.

During the third hospitalization, steroid escalation failed. Given the patient's critical state, she was treated with plasma exchange (PEX) (1.5 volume exchange for 3 consecutive days) followed by two infusions of rituximab (750 mg per infusion separated by 2 weeks). This regimen resulted in daily steady improvement and allowed for successful weaning of prednisone. The patient achieved 80% of her baseline functioning at month 3, and 100% of baseline at month 6 post- PEX/rituximab with no residual OCD, food restriction, anxiety, sleep issues, or other psychiatric symptoms. At this point we considered her as having ''quiescent disease on aggressive immunosuppressive therapy.''

The patient has had three disease flares after achieving ''quiescence.'' Each of these disease flares corresponded to our attempts to wean her off of immunosuppressive therapy. She had a minor disease flare up at month 6 following the initial rituximab/PEX, and coincident with waning effects of the rituximab and prednisone taper to low dose (7.5 mg daily), despite ongoing mycophenylate therapy. This flare up consisted of behavior regression, return of OCD, and polyuria, but her symptoms remitted 1 month after redosing with rituximab. She had a more severe flare (same symptoms as mentioned, but also including life-threatening impulsivity) at month 12 following initial rituximab/PEX, which also corresponded to waning rituximab (second round) effect and another attempt at decreasing her prednisone to low dose (7.5 mg/day). Her third disease flare up occurred after stopping mycophenylate mofetil, despite being adequately treated with rituximab. At this point, she appears to require combined rituximab/mycophenylate therapy, which is not unusual in inflammatory brain disease/autoimmune encephalitis.

The patient has now had 22 months of relative quiescent disease (90% of baseline), with only three disease flares, as mentioned, which corresponded to reduction in immunosuppression and responded to re-escalation of steroids, rituximab, and mycophenylate mofetil. Her new baseline is absent of OCD symptoms, impulsive behavior, anxiety, sleep dysfunction, tremors, and other movement abnormalities. Recent school testing indicates that her cognitive function is currently above her premorbid baseline. After 2 years of living in psychiatric institutions, our medical hospital, and a group home, all of which provided 1:1 care; she is now living a normal teenage life at home and has been successfully integrated back into public school. She remains on mycophenylate mofetil, rituximab, hydroxychloroquine, low dose prednisone, and GAS prophylaxis with cefadroxil. Lithium and all other psychotropic medications were tapered and discontinued early in the course of her immunotherapy, except for quetiapine used as needed during her three flare ups for sleep and mood control. She now functions well at school and home without any the use of psychotropics.

While writing up this case, and having more understanding that the patient's antibody profile and symptom presentation were similar to reports of Sydenham's chorea and PANDAS, we went back and questioned the family about prior episodes of chorea and OCD. The family reported that in the fourth grade, the patient had had abrupt-onset OCD (regarding frequent need to urinate) which self-resolved after 4 days. Simultaneously, her best friend, who was also in her school class, went through a similar illness of abrupt onset OCD that lasted 3 months. We cannot definitively say that GAS was the trigger for our patient's earlier episode or her more fulminant presentation described here. Also, we do not know why the first episode of OCD was mild and self-limited whereas the second episode was severe and requires ongoing immunosuppression to control symptoms. Given her response to and dependence on immunotherapy, her case more closely matches striatal/basal ganglia encephalitis.

Case 2 (PANDAS)

An 11-year-old boy, with a history of dyslexia and learning disability, presented to our clinic with sudden-onset separation anxiety and rage 2 weeks after a febrile illness with pharyngitis (no throat culture was obtained). Four weeks after the onset of the separation anxiety, he suddenly developed OCD symptoms, motor tics, and vocal tics. OCD symptoms included tapping hallway walls, checking rituals, counting rituals, contamination fears, repeating words, asking the same question repeatedly, and a need for symmetry and exactness. His tics included blinking, shoulder and neck movements, and complex vocal tics in which he would repeat ''Ga ga ga.'' The following month he developed a mood disorder characterized by depressed mood, anhedonia, insomnia, and irritability that was punctuated by violent anger explosions. Additionally, this illness was accompanied by new-onset physical symptoms, including nocturia and severe joint pain requiring crutches. His joint pain primarily involved his feet, knees, and elbows, lasted 3–7 days at a time, and coincided with escalations in anxiety and rage.

Six weeks after the presentation of psychiatric symptoms, the patient's pediatrician ordered antistreptolysin O (ASO) and antideoxyribonuclease B titers (anti-DNase B) which were 368 and 666 Todd units/mL, respectively. As both of these were elevated (Kaplan et al. 1998), suggesting recent GAS infection, his pediatrician suspected PANDAS, and put him on azithromycin for 5 days, which resulted in temporary improvement in his OCD; for example, his checking routine prior to bed that had previously lasted 2 hours took only 2 minutes. His anxiety, motor tics, and vocal tics completely resolved. However, impulsivity and impaired concentration continued, causing difficulties in school and academic functioning.

Approximately 5 days following discontinuation of the antibiotics, the patient's OCD, anxiety, tics, and irritability recurred. Administration of azithromycin (250 mg daily) for 4 weeks resulted in rapid and sustained improvement of the patient's anxiety, tics, OCD, and irritability. The psychiatric and physical symptoms recurred when azithromycin was discontinued after 10 days;

therefore, the pediatrician restarted the azithromycin and added amoxicillin/clavulanate 500 mg twice daily.

Over the next year, the patient had falling ASO and anti-DNase B titers, but had ongoing flare ups in psychiatric symptoms, tics, nocturia, and joint pains that seemed to correlate with viral illnesses. He was referred to a pediatric immunologist at our institution who prescribed IVIG, 2 g/kg. This infusion occurred 14 months after the patient's initial presentation, and was associated with subjective improvement. However, 2 weeks after his IVIG infusion, he developed an upper respiratory infection and had an acute worsening of his neuropsychiatric symptoms that eventually self-resolved.

The patient was first evaluated in our PANS clinic 22 months after the onset of his initial psychiatric/medical illness. At that time, he had a pattern of waxing and waning neuropsychiatric symptoms (oppositional behavior, irritability, depressed mood, checking behaviors, motor tics) and physical symptoms (joint pains, heel pain, neck pain, and nocturia). His symptoms seemed to worsen after viral illnesses, but he would improve 2–3 weeks later. He had a more severe exacerbation that corresponded to an increase in his ASO and anti-DNase B titers. Multiple attempts were made to discontinue the antibiotics, but his symptoms would recur 1–2 weeks after the antibiotic was discontinued, according to the family. Approximately 2.5 years after onset, his antibiotics were discontinued, and he remained largely symptom free, with good functioning. He also benefited from weekly cognitive behavior therapy (CBT) aimed at addressing his anxiety and mood disorders. The family refused prophylactic antibiotics.

Case 3 (PANS and mycoplasma)

A 10-year-old girl presented to our clinic for evaluation of sudden-onset behavioral changes, compulsions, and involuntary movements. Three months prior to these behavior changes, her parents reported that she had had an illness consisting of episodic low-grade fever, unproductive cough, and sore throat, causing her to miss school. After the third episode, she had an episode of prolonged sleep (from 2:30 p.m. to 4:30 a.m.), after which she awoke disoriented to time. Over the next few hours, she was extremely irritable and had tantrums, throwing furniture off the balcony and racing around the house punching and kicking. She stated that she could not control her legs. She huddled in her bed, thinking her parents intended to kill her. Her parents described her as looking like a trapped animal, scanning her room and repeating, ''Don't kill me,'' over and over. On the drive to a medical clinic, she attempted to jump out of the moving car.

A consulting neurologist considered the diagnosis of PANDAS because of the acute nature of the onset of compulsions, and she drew blood and initiated treatment with azithromycin 500 mg daily. Over the next 5 days, the patient's agitation decreased significantly, but she continued to complain about uncomfortable leg movements, and experienced a labile mood and passive suicidal ideation. Her ASO and anti-DNase B titers were found to be within the expected range for her age.

Three weeks after initiation of azithromycin, her mood and leg movements improved substantially, but anxiety persisted. A week later, she stated that she vaguely remembered her previous weeks as if they had been a bad dream. At that time, with an apparent improvement coincident with azithromycin therapy; no evidence of GAS infection; and premorbid unproductive cough, fever, and sore throat history consistent with *M. pneumoniae*; serum antibody titers were checked. *M. pneumoniae* IgM level was high (2321 U/mL, reference > 950 positive) as was *M. pneumoniae* IgG (> 5.00 immune status ratio [ISR], reference > 1.10 positive). Five weeks after the acute onset of symptoms, azithromycin was decreased to 250 mg per day.

The patient continued to improve, and returned to normal function and development. Azithromycin was discontinued at 8 weeks, which coincided with escalation of behavior and mood symptoms. Azithromycin was restarted with coincident improvement in symptoms, and the patient remained asymptomatic on the antibiotic for the ensuing 12 weeks. She has remained asymptomatic without antibiotics.

Case 4 (PANS and chronic sinusitis)

This female patient presented at 13 years of age with a chief complaint of OCD and rage episodes that had been ongoing for 2 years. OCD symptoms were only partially responsive to cognitive behavioral therapy, sertraline, and risperidone. OCD symptoms suddenly began at 11 years of age, 2 months after her aunt died of breast cancer. The patient felt that many things, including her family, were contaminated by grease, so she avoided contact with greasy food, her family, and their belongings. She saved wrappers and paper towels. She became physically aggressive, hitting and kicking if her (OCD) demands were not met. During these episodes, she would flip from being aggressive and angry to feeling remorseful and sad.

A community psychiatrist diagnosed OCD, the onset of which was attributed to stress caused by the loss of her aunt. Treatment with CBT began when she was 11 years of age, which was slightly helpful. Seven months after exposure therapy began, her teachers reported that she appeared distracted in class and met criteria for ADHD, except for age of onset. She was highly sensitive to sound, which was a new symptom for her. Her mood became labile, shifting within the week from manic euphoria, with rapid speech, increased activity and increased irritability, to depression, with crying spells and decreased appetite, sleep, and motivation. The addition of risperidone improved mood symptoms. Concomitantly, she had a 9 day upper respiratory illness that coincided with the descent of a ''black cloud of depressed mood'' and further escalation of rage. Divalproex was added to her medication regimen, again with moderate improvement in her mood symptoms.

Over the following months, her OCD and rage worsened, and when she was 13 years of age, a new psychiatrist suspected PANS. Her evaluation elicited a history of worsening of penmanship with escalations in OCD, which is consistent with the PANDAS phenotype (Snider and Swedo 2004). Workup (ASO, anti-DNase B, and throat culture) was negative. However, the window of opportunity to detect GAS most likely had passed.

Medical history was significant for parental report of ongoing chronic sinus infections and a deviated septum. In addition to her psychiatric medication, the patient had routinely taken loratadine (to treat nasal allergies) and had many courses of antibiotics. Because of concern for ongoing sinusitis as an infectious source for PANS, the psychiatrist gave her amoxicillin, which coincided with a marked improvement in her symptoms.

Following a 3 week course of amoxicillin, the patient's sinus and psychiatric symptoms remained remarkably improved. Three months later, she experienced another acute sinus infection that was associated with worsening of her mood, and she was treated with cefdinir for 2 weeks. Sinus and emotional symptoms improved and the patient remained stable for 6 months.

She had an acute exacerbation of psychiatric symptoms in the winter of that year, with an abrupt return of mood lability, aggression, OCD, and hypersensitivity to sounds and smells, but without changes in urinary frequency, handwriting, or tics. She developed severe irritability and aggression, leading her to kick and dent the dishwasher, cut off pieces of her skin, cut on her wrists, and threaten to jump from a moving car. Later, she did not remember these violent outbursts. Over that winter and spring, her OCD, mood issues, and aggression were so severe she was admitted to a specialized residential OCD unit for adolescents, and received cognitive behavior therapy for 2 months. She achieved remission of OCD and mood symptoms.

Over the following 2 years, when she was 14–16 years of age, she experienced many exacerbations of psychiatric symptoms coincident with acute sinusitis symptoms and responsive to antibiotic treatment. She was seen by her otolaryngologist, who observed the severely deviated septum, hypertrophied turbinates, and enlarged maxillary sinus cyst seen on CT scan (obtained 4 years earlier) and on recent MRI. He recommended sinus surgery, but the family declined. Eleven months later, at age 17, the patient developed another sinus infection associated with irritability, mood lability, poor concentration, worsening OCD, and frequent urination. Treatment with azithromycin and ibuprofen was initiated. Laboratory results, including ANA, ASO, Anti-DNase B titers, erythrocyte sedimentation rate (ESR), complete blood count (CBC), EBV, Coxsackie A, and *M. pneumoniae* IgM titers were all negative.

Because of the persistence of debilitating psychiatric symptoms for 2 months, the patient opted to go through with sinus cyst removal and turbinate resection and reduction. Immediately following the surgery, she experienced an almost complete remission of her psychiatric symptoms, including her OCD and mood symptoms. She reported that, ''They pulled the OCD right out of me when they pulled out the cyst!'' She was maintained on cefdinir postoperatively. Overall, she improved in her school and family function. She continues on sertraline and risperidone. In the 12 months since the sinus surgery, the she has had several exacerbations, each of which was associated with GAS pharyngitis, and which resolved with antibiotic treatment. Interestingly, on these occasions, the family contacted the psychiatrist with concerns about worsening OCD, without searching for preceding or concomitant infection. We are in the process of conducting streptococcus screening for family members and other close contacts with the goal of identifying and eradicating close contacts who may be reinfecting her. If this approach does not improve the issue with recurrent streptococcus, then we will recommend prophylactic antibiotics.

Case 5 (PANS following PANDAS, immunodeficiency, spondyloarthropathy, and gluten sensitivity)

A 25-year-old man with a 7 year history of OCD, anxiety, musculoskeletal pain, and abdominal complaints was evaluated for continuing symptoms. His past medical history was notable for two early episodes of PANDAS. At age 5 years, a few days after a febrile illness, he had a sudden onset of irrational fears, separation anxiety, OCD symptoms and polyuria. The symptoms self-resolved in ~2 months. At age 8, he had another febrile illness followed by a sudden onset of OCD, intense fears of the night, highly ritualized bedtime routine, anger episodes, and depressed mood. The symptoms slowly remitted with the exception of mild anxiety. At age 18, while taking citalopram, he had another symptom exacerbation characterized by return of OCD and escalation in anxiety. Anti-DNase B titers were elevated, but ASO titer was normal. Testing for Lyme and mycoplasma were negative.

He was placed on azithromycin for 10 days, with a working diagnosis of PANDAS. His OCD and anxiety symptoms improved initially, then re-escalated after the antibiotic was stopped. Therefore, he was restarted on azithromycin and his escitalopram dose was increased. Although this helped initially, his symptoms eventually re-escalated to the point that he could not attend school.

At 18 years of age, he also developed chronic back pain, knee pain, heel pain, pain on the bottoms of his feet, and vague abdominal symptoms that included tenderness, discomfort, and bloating. In addition, his past medical history was significant for motor tics, migraines, frequent ear infections, and frequent GAS pharyngitis. His family history was notable for acute rheumatic fever (maternal grandmother) and celiac disease (paternal grandfather).

An immunology evaluation found him to have high IgE and low IgG levels, and poor response to pneumococcal vaccine, suggesting mild immunodeficiency. Therefore, he underwent a trial of IVIG (2 g/kg), which was complicated by a hemolytic reaction, but resulted in marked improvement in his OCD and anxiety symptoms. Unfortunately, he contracted GAS pharyngitis 6 weeks later and had re-escalation of his psychiatric symptoms. He requested repeat IVIG treatment, which was denied because of the risk of another hemolytic reaction and the lack of sustained improvement with the initial IVIG treatment.

He was referred for rheumatologic examination at age 25. He ranked his back pain as 4–6/10 on most days, with pain and stiffness worse in the morning and with prolonged sitting or standing. Movement made his pain better. Physical examination revealed tenderness over his temporomandibular joints, sternocostal joints, Achilles tendon insertion points, and sacroiliac joints. He had pain with internal rotation of hips and a limited Schober's test (limited forward bending flexibility). Laboratory testing revealed negative human leukocyte antigen (HLA) B27 but positive HLA B51. Because his presentation was consistent with inflammatory back pain, he was started on naproxen (500 mg twice daily) and given a referral to physical therapy for core strengthening.

At rheumatology follow-up, the patient reported overall improvement of axial skeletal pain and stiffness, but he had ongoing discomfort in his back requiring him to move every 60 seconds in order to keep his back comfortable. Additionally, he described ongoing distress from his neuropsychiatric symptoms including OCD, anxiety, insomnia, difficulties with concentration, racing thoughts, and mood instability. He again requested IVIG, which was again denied, because the benefit of IVIG did not outweigh the risk of a potentially life-threatening hemolytic reaction. Given his continued back pain, and concern for spondyloarthropathy, the rheumatologist initiated a trial of sulfasalazine and requested an MRI of the patient's back and sacroiliac joints.

When the patient was seen 4 months after starting sulfasalazine, his back pain and stiffness had mostly resolved and, therefore, the MRI was not pursued. He reported that his pain was 0–1/10 on most days, and it was the first time that he recalled that he did not have to be in constant movement to prevent back pain. He also had resolution of knee, hip, heel, and foot pain. Interestingly, his OCD and anxiety symptoms were also much improved and he stated that his psychiatric symptoms were now ''manageable.'' However, he had occasional ''flares'' of pain and stiffness associated with abdominal symptoms. In the interim, he had been treated by his primary care physician with clarithromycin for presumed sinusitis. It is not clear

which medication (sulfasalazine or clarithromycin) helped his neuropsychiatric symptoms, because both were given during the same time period.

Given the patient's abdominal symptoms, associated back pain, and OCD flares, his holistic medicine physician and rheumatologist suggested a limited trial of removing wheat/gluten, dairy, and soy from his diet. Four months later he reported that his back pain and neuropsychiatric symptoms had completely resolved, and that he had ''never felt so good in his life.'' He adhered to his gluten/dairy/soy-free diet with occasional slips. Interestingly, he reported that when he initially went on a gluten-free diet, he developed headaches, dizziness, sleep difficulties (severe nightmares and night sweats), mood instability, and agitation, but that these symptoms self-resolved over a 10 day period. After achieving his new baseline of no neuropsychiatric or musculoskeletal symptoms, accidental exposures to gluten or soy triggered deterioration in the following manner: 4–12 hours after the food exposure (especially gluten) he would develop abdominal pain and distention; 12–24 hours after exposure, back pain would ensue; 24–48 hours later headaches, worsening mood symptoms, OCD, and anxiety would ensue. This pattern was repeated at least eight times over the next 12 months. He self-discontinued the sulfasalazine and did well overall, but he noticed that while not taking the sulfasalazine, gluten and soy exposures resulted in more intense abdominal symptoms, back pain, and psychiatric symptoms as compared with when he was taking sulfasalazine.

Overall, his new baseline was improved, as he was pain free and had minimal psychiatric symptoms. Because multiple therapies were introduced (limited course of antibiotics for sinusitis, anti-rheumatic medication, dietary changes, and previous escalation of selective serotonin reuptake inhibitor [SSRI]) it is not clear which therapies were responsible for his recovery.

Discussion

The overlap of PANS and inflammatory disease processes (infection, autoimmune disease, and rheumatological disorders) in youth has not been previously described, and begs further investigation into the role of inflammation in the etiology of PANS. All of the youth described here meet the proposed criteria for PANS: acute onset within 24–48 hours of OCD symptoms, with at least two associated symptoms. Most youth had significant mood symptoms, in some cases meeting criteria for major depression or manic episodes. Motor tics, vocal tics, and cognitive impairment were also common. Physical symptoms and medical illnesses were observed (abdominal pain, musculoskeletal pain, and sinus pain) and in some cases led to medical interventions that appeared to improve both the physical and psychiatric symptoms. Despite the consistency of their psychiatric presentations, the youth had a variety of underlying inflammatory illnesses/triggers including autoimmune encephalitis (case 1), immunodeficiency (case 5), inflammatory back pain and food intolerance (case 5), GAS (cases 2 and 5 and possibly 1), mycoplasma (case 3), and sinusitis caused by an unknown pathogen (case 4).

We have had little precedent to guide treatment in our PANS clinic; therefore, we base our interventions on those useful for PANDAS, for which most youth receive antibiotics (Snider et al. 2005) and failing a satisfactory response, IVIG, or plasma exchange (Perlmutter et al. 1999). In the cases presented, treatments were aimed at controlling underlying infectious/inflammatory disease: Immunosuppression for autoimmune process (case 1); anti-inflammatory medication for rheumatic disease (case 5); IVIG for PANDAS (cases 2, 4, and 5), autoimmune encephalitis (case 1) and immunodeficiency (case 5); antibiotics to treat mycoplasma, sinusitis, and GAS (all cases); sinus surgery for recurrent sinusitis (case 4); and removal of offending foods in a case of spondyloarthropathy/irritable bowel (case 5). These treatments resulted in moderate to complete improvement, even in cases in which multiple psychotherapies had failed. Although relapses were common in the cases presented, the relapses appeared to correspond to withdrawal (weaning) of medical treatments (immunosuppression and/or antibiotics) or return/flare up of a medical illness (re-exposure to streptococcus, recurrence of sinusitis, re-exposure to a poorly tolerated food). Beneficial response to medical therapies suggests that the underlying etiology of these PANS cases is different from ''typical'' OCD, tic disorder, bipolar disorder, and depression. Currently, it is unknown if any ''typical'' childhood psychiatric illness would also respond to antibiotic, anti-inflammatory or immunomodulatory treatments. It is known that OCD that is not PANDAS-related does not improve with PEX (Nicolson et al. 2000).

The common underlying thread appears to be inflammation. For PANDAS and post-streptococcal striatal encephalitis (basal ganglia encephalitis) this may be caused by antineuronal antibodies (Kirvan et al. 2003, 2006 2007; Dale and Brilot, 2012; Dale et al., 2012; Cox et al. 2013), a mechanism that is supported by studies in rats exposed to GAS or IgG from GAS-exposed rats (Yaddanapudi et al. 2010; Lotan et al., 2014). But for non-GAS causes, the inflammation might or might not be caused by similar mechanisms. Exposure to other infectious agents, such as mycoplasma pneumoniae, might also lead to similar cross-reactive antibodies (Dale and Brilot 2012). Underlying causes could also include other autoinflammatory and autoimmune processes as is the case in lupus (Slattery et al. 2004) and other systemic autoimmune diseases, in which an infection or medication can trigger dysregulation of the adaptive and/or innate immune systems. Inflammation has increasingly been investigated and implicated in psychiatric illness, particularly depression and bipolar disorder (Goldstein et al., 2009; Berk et al., 2013;), although it is not clear if it is etiologic or if it occurs as a result of mood episodes. Therefore, whereas inflammation could be occurring in all these patients, the mechanisms of inflammation, and the reasons for neuropsychiatric symptoms, could be subtly to grossly different.

PANS is diagnosed using clinical course and symptoms that may stem from a variety of etiologies, acting through different disease mechanisms. Even within the presumed neuroinflammatory cases of PANS, it is likely that there are different immune dysregulations that affect subgroups of PANS patients. Such is the case with juvenile idiopathic arthritis (JIA), in which a broad clinical category involves many distinct clinical subtypes with heterogeneous mechanisms of dysfunction. The PANS phenomenon deserves further empirical study in order to determine etiologies and proper treatment algorithms.

Conclusion

Acute-onset neuropsychiatric symptoms in youth signal a serious risk for cognitive and psychosocial impairment. The heterogeneity of presentation and potentially serious sequelae of PANS require clinicians to be alert to the possibility of PANS when faced with youth who abruptly develop psychiatric and physical symptoms. When suspicious, psychiatrists need to work with pediatricians and physicians with expertise in other disciplines to diagnose and treat the underlying infectious and/or inflammatory diseases. In

our cases, psychiatrists, pediatricians, immunologists, rheumatologists, neurologists, otolaryngologists, and infectious disease specialists collaborated. Alertness to the possibility of PANS and cross-discipline coordination can lead to a positive treatment response in youth with the illnesses described as PANS.

Clinical Significance

This case series highlights the varied presentation of youth with PANS and how severe these cases can be. With proper diagnosis, medical workup, and management, youth with PANS can have significant improvement in their psychiatric symptoms and function. Long-term follow-up of these and other children with PANS needs to be conducted to understand their course and outcome. Even though we do not yet understand the mechanisms of how inflammation affects the brain in PANS, it is our experience, as illustrated here, that addressing the source of inflammation in patients with PANS (e.g., treating infections and rheumatologic conditions) is associated with improvement in neuropsychiatric symptoms overall.

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