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Use of Intravenous Immunoglobulin in the Treatment of Twelve Youths with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections

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Abstract

This is a case series describing 12 youths treated with intravenous immunoglobulin (IVIG) for pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS). Although it is a clinically based series, the case reports provide new information about the short-term benefits of IVIG therapy, and are the first descriptions of long-term outcome for PANDAS patients.

Introduction

Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) has been conceptualized as a *forme fruste* of Sydenham chorea (SC), the neurologic variant of rheumatic fever (Swedo et al. 2012). Both disorders are postulated to result from cross-reactive autoantibodies produced in response to molecular mimicry of Group A streptococcal (GAS) bacteria (Kiessling et al. 1993; Swedo et al. 1994; Garvey et al. 1998; Swedo et al. 1998). The proposed disease mechanism suggests that PANDAS and SC should respond to immunomodulatory therapies, such as oral steroids, intravenous immunoglobulin (IVIG), and therapeutic plasmapheresis. For SC, two controlled trials and a small case series document the efficacy of IVIG in reducing symptom severity and shortening the duration of illness (Garvey et al. 2005; van Immerzeel et al. 2010; Walker et al. 2012). Data for PANDAS are limited to a single randomized-entry controlled trial that compared IVIG against plasmapheresis and placebo (sham IVIG); at 1 month, neuropsychiatric symptom severity was reduced by 45% in the IVIG group, by 58% in the plasmapheresis group, and by 0% in the placebo group (Perlmutter et al. 1999). These treatment gains were maintained at 1 year follow-up evaluations, and appear to be related to the autoimmunity of PANDAS, as subsequent reports noted a lack of benefit for plasmapheresis for the treatment of non-PANDAS obsessive-compulsive disorder (OCD) (Nicolson et al. 2000). Similarly, IVIG administration was found to be without benefit for non-PANDAS tic disorders (Hoekstra et al. 2004).

To date, there have been no reports of the long-term outcome of PANDAS patients treated with IVIG. To address this issue, case files from a large clinical practice specializing in the treatment of PANDAS were reviewed by the treating physician (M.K.), and 12 patients with illustrative case histories were selected for this report. In addition to providing new information about the course of illness in PANDAS, these cases represent the first experience with 1.5 g/kg IVIG (divided into two daily doses of 750 mg/kg). The dosage was calculated from historical pediatric plasma exchange formulas that found that the optimum ratio of exogenous-to-endogenous IgG was 2:1, which translates to 1.496 g/kg of IVIG product (Graham 1963; Stoop et al. 1969.)

Cases

Patient A

Patient A was a 7.5-year-old girl who had had an overnight onset of OCD symptoms 1 year previously. The symptoms began ~2 weeks after she had completed treatment with azithromycin for a GAS-positive pharyngitis. Her initial OCD symptoms included intrusive thoughts, contamination fears (urine, saliva), repetitive compulsive behaviors (running in circles in response to thoughts, the need to remember what foods she ate looked like, and avoidance of foods she feared she would not remember), and reassurance seeking. Ancillary symptoms included tics, separation anxiety, irritability, emotional lability, difficulty concentrating, sensitivity to light, and enuresis. Over the course of the next year, she had a relapsing-remitting symptom course, with exacerbations reportedly occurring after illnesses treated with multiple courses of antibiotics (including azithromycin, amoxicillin, and amoxicillin-clavulanate). She had also undergone a tonsillectomy. Trials of sertraline and fluvoxamine were felt not to be

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helpful, but she had a ''fair to good'' response to a 6 month course of cognitive-behavior therapy (exposure and response prevention).

Shortly after experiencing severe, abrupt symptom exacerbation, the patient presented for initial evaluation. Her OCD symptoms were severe and disabling, occupying 9–11 hours a day. Symptoms improved during a 5 day steroid burst, but worsened following cessation of therapy. She was then treated with IVIG. Partial remission of symptoms occurred about 2 weeks following infusion, and a complete remission was achieved by 1 month post-IVIG. Follow-up evaluations at 3 and 6 months revealed continued improvement. Antibiotic prophylaxis was continued for 18 months. Nine months later (27 months after initial IVIG therapy), she experienced a minor symptom flare (symmetry concerns and counting compulsions) following an upper respiratory illness. A course of antibiotics was felt to be somewhat helpful, with symptoms resolving over the course of 1 month, and amoxicillin-clavulanate was continued as prophylaxis against GAS infections. Despite this, 3 months later, the patient developed a febrile illness with facial rash, chest and joint pain, and adventitious movements of her fingers. Several weeks later, she had another symptom recurrence with obsessional fears of dying and worries about harm to self/others, as well as separation anxiety and pupillary changes. Treatment with IVIG was repeated (38 months after initial infusion) with good results. Follow-up telephone contact 4 years later revealed that the symptom remission had continued, and that the patient was doing ''very well.''

Patient B

Patient B was an 11-year-old boy who developed new-onset choreiform movements, as well as motor and phonic tics (including cough and whole body ''shudder'') following a febrile illness that was treated with amoxicillin-clavulanate. A magnetic resonance imaging (MRI) scan of the brain, performed 1 month after symptom onset, showed decreased T2 signal in the basal ganglia. Tic severity was sufficient to warrant intervention, and $\sim$4 months after symptom onset the patient was treated with a 5 day steroid burst (1 mg/kg/day prednisone, orally) followed by IVIG 1.5 mg/kg infusion. The interventions were reported to be beneficial, with complete resolution of his symptoms. One year later, the patient experienced an exacerbation of tics and received a second IVIG infusion. Recovery was again reported to be complete.

Patient C

Patient C was a 9-year-old girl who was first diagnosed with PANDAS at 6 years of age. At that time, she was treated with a 14 day course of amoxicillin-clavulanate, with nearly complete remission of symptoms. One month prior to evaluation in Hinsdale, the patient had a fainting episode at school and was evaluated at a local emergency department, where she was diagnosed with vasovagal syncope. The episode revealed that she had been experiencing a variety of behavioral symptoms, including obsessional fears, generalized and separation anxiety, insomnia, and urinary frequency with at least two episodes of nocturnal enuresis. She also complained of nonspecific abdominal discomfort and a related fear of ''throwing up'' after meals, which led to significantly restricted eating and a weight loss of 2–3 kg (7% of body weight) over the course of 1 month. Following treatment with steroids and IVIG, the patient experienced a rapid resolution of her symptoms, with complete remission by 4 weeks. She received azithromycin prophylaxis (250 mg twice weekly) for 1 year, and at a 4 year follow-up evaluation, she continued to be symptom free.

Patient D

Patient D was a 9.5-year-old boy who had sudden onset of contamination fears at 7 years of age following a documented GAS infection. Over the ensuing 18 months, he developed a variety of neuropsychiatric symptoms, including tics, agoraphobia, irritability, aggression, and sensitivity to sounds. The diagnosis of PANDAS was made, and a therapeutic course of cefdinir had some beneficial effects. However, the patient subsequently developed a fear of choking and chronic abdominal pain, and the resultant food refusal led to a 4.5 kg (20%) weight loss, hospitalization, and tube feedings. These symptoms persisted for $\sim$1 year prior to his evaluation and treatment at Hinsdale. A 5 day course of oral prednisone (1 mg/kg/day) had modest benefits. He was then treated with IVIG, which produced noticeable symptom improvements starting 2 weeks after infusion. He was maintained on prophylactic antibiotics for 1 year. Seven years later, a follow-up evaluation by telephone revealed that he continued to be in full remission.

Patient E

Patient E presented for evaluation at Hinsdale at 8 years of age, but his mother had first suspected that he had PANDAS when he was 3, when he had an abrupt onset of OCD symptoms that reportedly appeared as sequelae of a GAS infection and resolved following steroid treatment. Family history was notable for tics in the patient's father and older brother. By 8 years of age, the patient had diagnoses of separation anxiety disorder, OCD, tic disorder, depression, and periodic limb movement disorder of sleep, with evidence of possible epileptiform activity that had been noted on overnight electroencephalogram (EEG) when he was 5 years of age. Trials of sertraline, mirtazapine, and escitalopram were somewhat helpful, but symptoms persisted. At the time of evaluation in Hinsdale, the patient's symptoms included intrusive thoughts and contamination obsessions; symmetry, checking, and repeating/reassurance-seeking compulsions; separation anxiety; temper tantrums and aggression; depression; school refusal; tics; and a decline in fine motor skills. Treatment with IVIG yielded an immediate response, with remission of his OCD symptoms and marked reduction in the frequency of tics. Four months later, his mother developed a GAS infection, and despite prophylactic antibiotics, the patient was noted to have increased school-related worries and ''stuck'' behaviors. The dosage of amoxicillin-clavulanate was increased, and 4 weeks later, the OCD symptoms had resolved, but motor and phonic tics remained. The patient's OCD symptoms returned again 3 months later, and were once again improved by therapeutic doses of antibiotics. Long-term follow-up information is not available for this patient.

Patient F

Patient F was a 16-year-old boy who had been initially diagnosed with PANDAS at 9 years of age when he suddenly developed irrational fears, intrusive thoughts, and insomnia. He was treated with two consecutive 14 day courses of amoxicillin-clavulanate and became asymptomatic within 1 month. One brief relapse was noted later that year, but it resolved without intervention. At 16 years of age, the patient experienced a sudden, abrupt onset of severe and debilitating tics, including marked movements of the upper torso, arms, head, and neck. He was taken to the emergency department, where he was treated with diazepam; a brain MRI and EEG were reportedly normal. General anxiety and increased irritability were apparent at this time as well, but there were multiple

psychosocial stressors. The patient had not been ill, but his roommate had recently had an upper respiratory illness. Treatment with amoxicillin-clavulanate produced only minimal improvements, but a 5 day course of steroids resulted in complete, albeit temporary, remission of the tics. The patient was then treated with IVIG, and a ''rocky'' postinfusion course was noted, with increased tic severity for the ensuing 2 weeks. The anxiety and tics continued to wax and wane in severity over the next 6 months, with periods of symptom improvement reported to occur in association with both increased dosages of antibiotics and school holidays (e.g., summer vacation, winter break). By 12 month follow-up, the patient was completely asymptomatic, and these treatment gains were sustained for at least 6 months longer, when he was evaluated for the final time.

Patient G

Patient G was a 9-year-old boy who presented with a sudden onset of debilitating separation anxiety, aggression, emotional lability, urinary frequency, insomnia, and dysgraphia. Most significantly, he developed compulsive, recurrent vomiting of all foods and liquids, including water, leading to a 7 kg weight loss. He was diagnosed with postinfectious gastroparesis, and fed exclusively via nasojejunal tube. His past medical history was positive for an episode of separation anxiety, tics, and OCD symptoms following a brief illness at 7 years of age. He responded to a 5 day steroid burst, with temporary symptomatic improvements. He had an immediate and dramatic improvement following IVIG therapy, resuming normal oral food intake, and his nasojejunal tube was removed. Although there was a significant improvement in most of his symptoms over the ensuing months, residual vomiting after meals (without weight loss) continued to interfere with his return to normal life. Eleven months following the initial IVIG treatment, he received another course of IVIG, this time resulting in complete remission of all symptoms. He remains asymptomatic 3 years later.

Patient H

Patient H was a 15-year-old boy with a history of reactive airway disease and a 3 year history of ''tic-like'' behaviors, including throat clearing and cough. The tics prompted consideration of a PANDAS diagnosis, but acuity of the symptom onset and evidence of preceding GAS infection were not documented. Subsequently, the PANDAS diagnosis became more evident when the patient had a sudden worsening of his tics, including the onset of coprolalia, and acute onset of intrusive thoughts and compulsive praying, as well as separation anxiety, temper tantrums, difficulty concentrating, and hyperactivity. The patient received two courses of IVIG, separated by 4 months. Five weeks after the second infusion, the patient's tics had remitted, but his OCD symptoms had worsened and were now associated with weight loss. It is unclear what eventually led to symptom remission, as interim history is not available, but a follow-up phone call 16 months after the second IVIG infusion revealed that the patient was ''almost 100% well.''

Patient I

Patient I was a 7-year-old girl who experienced the sudden onset of multiple symptoms following an illness characterized by severe sore throat. (The patient had had recent GAS exposure, but a throat culture obtained during the illness was negative.) Her symptoms included intrusive thoughts and a variety of obsessional fears, including fear of being ''fat,'' as well as separation anxiety, temper tantrums, immature behavior and baby talk, motoric hyperactivity, inattention, aggressiveness, emotional lability, tics, mydriasis, nocturnal enuresis, and multiple somatic complaints including joint pain, chest pain, stomach pain, fatigue, and dizziness. A steroid burst was helpful for a brief time and was followed by IVIG infusion. Two weeks following IVIG infusion, the patient was reportedly ''80% back to normal,'' and by 6 weeks postinfusion she had returned to 95% of her baseline. A few weeks later, she developed a GAS infection, and several symptoms returned, including nocturnal enuresis. A second 5 day course of steroids secured remission, and she was noted to be ''100% well'' 5 months following initial IVIG treatment. Over the ensuing 18 months, she had a relapsing-remitting symptom course with exacerbations occurring in association with illnesses. (Relapses were not as severe as the initial episode.) She received a second IVIG infusion and had a complete remission of symptoms. Follow-up phone evaluation revealed that she was continuing to do well >12 months later.

Patient J

Patient J was a 12-year-old boy with a complex medical history that included asthma, celiac disease (diagnosed at 9 years of age because of significant growth failure), and eosinophilic esophagitis, requiring gastrostomy and insertion of a feeding tube. It is of note that his chief complaint at that time was ''fear of choking,'' not dysphagia, as might be expected. At 10 years of age, the patient developed severe OCD symptoms and debilitating generalized and separation anxiety, possibly related to a GAS pharyngeal infection that had occurred 6 weeks earlier (and was associated with elevated antistreptococcal DNAase B titers), or a periorbital cellulitis, which had occurred 1 month prior to symptom onset. Citalopram, sertraline, and finally risperidone were tried, without reported benefits. The patient had a ''positive'' response to the steroid burst, but no discernable improvements were noted for 11 weeks following IVIG administration. Then, he had a sudden and dramatic remission of all of his symptoms. His feeding tube was removed, and he returned to normal activities. Eight months later (and despite adherence to the prescribed regimen of prophylactic antibiotics), he had a recurrence of obsessions, compulsions, and generalized anxiety (without eating restrictions). He was treated with IVIG and experienced an almost immediate and lasting recovery. Follow-up evaluation 5.5 years later revealed that he continued to be asymptomatic and functioning optimally.

Patient K

Patient K was an 11-year-old boy, who had a sudden onset of OCD, anxiety, and tics at 6 years of age, following a GAS infection. He was treated with psychiatric medications and behavior therapy, with some benefits, but his therapist noted that symptom control worsened following GAS exposure/infection. At the time of his presentation to Hinsdale, his tics were severe and impairing to the point that they interrupted sleep and had caused injury (by his biting his tongue). The patient was receiving risperidone, fluvoxamine, buspirone, and atomoxetine for diagnoses of Tourette Syndrome, generalized anxiety disorder, OCD, and attention-deficit/hyperactivity disorder. A steroid burst resulted in transient improvements in his phonic tics. Both motor and phonic tics began to decrease in intensity and frequency ~ 5 days following IVIG administration. The tics continued to diminish over the next 2 weeks, and for the first time in several years, the patient was tic free for several days at a time. Medications were, therefore, discontinued. Tics returned ~ 1 month following IVIG, and risperidone was restarted, but at a lower dose. Six months following IVIG, the patient was noted to be

''tic free'' and he continued to do well on low-dose risperidone over the next 2 years. When the patient was 13.5 years of age, tics returned ''in full force'' after the patient was exposed to a sibling with GAS. He was treated with a 10 day course of azithromycin, and placed on prophylactic antibiotics, and his tics resolved over the course of a few weeks. At follow-up, 6 years following IVIG treatment, the patient was noted to be tic free and doing well. Of particular note was that he had received a number of immunizations without difficulty, delivered his high school commencement speech, and had been awarded a scholarship to attend college.

Patient L

Patient L was an 8-year-old boy who suddenly developed debilitating OCD symptoms (excessive showering and hand washing, refusal to eat certain foods after making unreasonable excuses) 2 weeks after a GAS infection. Over the next 6 months, his OCD symptoms worsened and he also developed a coughing tic, anxiety, and a number of ill-defined abdominal complaints that prompted a gastroenterological evaluation (with negative results) and that eventually led to the patient's complete refusal to eat. The patient lost nearly 25% of his body weight (declining from 22 kg to 17 kg) and was hospitalized numerous times for tube feedings and psychiatric interventions. Multiple selective serotonin reuptake inhibitors were tried, without appreciable benefit; a trial of lorazepam resulted in severe disinhibition; therefore, it was immediately discontinued. A consulting physician prescribed amoxicillin, which seemed to produce some minimal improvements, and the patient's weight eventually stabilized. The patient's response to a steroid burst was described as ''strongly positive,'' and response to IVIG treatment was described as ''remarkable.'' Immediately after completing the IVIG infusions, he was able to visit a restaurant (a previously unacceptable venue) and to eat a meal without difficulty. Although his other symptoms also improved over the next few months, his improvement was not complete, and all progress stalled $\sim$ 4 months later. The patient received a second course of IVIG to address the remaining anxiety and OCD symptoms, and he experienced a complete recovery within weeks of the infusion. Six years later, he remains completely well.

Discussion

These 12 cases provide new information about the clinical features and course of PANDAS, as well as describing a variety of patterns of response to IVIG administration. The case series is limited by its selective nature, retrospective approach, and dependence on subjective reports from patients and their parents. The lack of a placebo control for the IVIG treatment is an additional shortcoming, as PANDAS is an episodic disorder that is expected to have periodic symptom remissions. However, all patients had failed prior therapies, suggesting that the immunomodulatory effects of IVIG were responsible for the symptomatic improvements.

All patients had an abrupt onset or exacerbation of severe OCD and comorbid neuropsychiatric symptoms as sequelae of GAS infections or exposures; therefore meeting diagnostic criteria for PANDAS (Swedo et al. 1998, 2004). Patients also met criteria for pediatric acute-onset neuropsychiatric disorder (PANS) because of the acuity of OCD onset and presence of multiple comorbid symptoms. The duration of illness and number of recurrences varied among individuals, but all patients benefited from IVIG administration, even when the neuropsychiatric symptoms had been present for several years prior to treatment.

Unlike typical autoimmune disorders, in which multiple doses of IVIG are required, PANDAS may respond to a single course of treatment. The neuropsychiatric symptoms appear to result from a misdirected immune response (triggered by the molecular mimics of GAS epitopes); therefore, inactivation of the cross-reactive antibodies with a single course of IVIG could be sufficient to produce lasting symptom improvement (Perlmutter et al. 1999). However, it is worth noting that 2 of the 12 patients received a second course of IVIG because of an inadequate response to the initial course of treatment, and 5 patients received a second IVIG treatment for a recurrence of symptoms. Further, all patients had received a 5 day course of oral steroids, administered as 1 mg/kg/day prednisone, followed by a 2 week observation period. The purpose of the ''steroid burst'' was to determine if long-lasting improvements could be produced by steroids alone, thus obviating the need for IVIG. A persistent response to steroids is unlikely in patients with PANDAS, as they produce only transient benefits in patients with SC (Garvey et al. 2005), and a similar etiopathogenesis is postulated for both disorders. In this case series, none of the children had persistent improvements following prednisone therapy or after antibiotic treatment (Murphy et al. 2014); therefore, IVIG was administered at a dose of 1.5 gm/kg (in two divided doses.)

Conclusion

This case series demonstrates the benefits of IVIG therapy for youths with PANDAS/PANS, including those who had been symptomatic for several years prior to treatment. Although the generalizability of this retrospective report is limited, the selected cases represent the breadth of symptom presentations in PANDAS/PANS and provide additional evidence that IVIG may be useful in the management of children with moderate-severe symptoms.

Clinical Significance

IVIG was used as part of a multimodal therapeutic approach and demonstrated benefits for these 12 youths with moderate-severe symptoms of PANDAS/PANS. In addition to IVIG, patients received prophylactic antibiotics to prevent future infection-triggered symptom exacerbations. They also received standard psychiatric care, including use of anti-obsessional medications and cognitive-behavior therapy. For optimum symptom relief, it is necessary to utilize a combination of immunomodulatory therapy, antibiotic prophylaxis, and targeted symptom treatments, as described at the PANDAS Physicians Network (PPN) (www.pandasppn.org). The website [presents a systematic graduated approach to treatment of PANDAS/PANS based on the ''best practice'' standards of expert clinicians from across the United States. In addition to providing suggestions for recognition and diagnosis of PANDAS/PANS, it also offers guidance in the management of patients with varying levels of severity.

Disclosures

No competing financial interests exist.

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