

# Selective Serotonin Reuptake Inhibitor-Induced Behavioral Activation in the PANDAS Subtype

Tanya K. Murphy, MD, Eric A. Storch, PhD, and Melissa S. Strawser, BA

## ABSTRACT

*Although selective serotonin reuptake inhibitors (SSRI) are an effective and commonly used treatment for pediatric obsessive-compulsive disorder (OCD), their use has come under close scrutiny following reports of adverse reactions. The authors of this case report believe that children with the OCD subtype, pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS), may have increased vulnerability. The following report provides initial data on behavioral activation following SSRI use in 38 children with OCD of the PANDAS subtype. The authors use a particular case to highlight this issue and discuss treatment implications.*

## INTRODUCTION

Selective serotonin reuptake inhibitors (SSRI) are an effective and commonly used treatment for pediatric obsessive-compulsive disorder (OCD). Yet, the use of these medications has come under close scrutiny following reports of behavioral activation following treatment initiation. Among the pediatric OCD trials, SSRI use has been associated with higher activation rates (12.3% to 13.0%) relative to placebo (2.0% to 3.2%).<sup>1,2</sup>

Whether this activation rate is related to pharmacokinetic differences<sup>3</sup> or pharmacodynamic differences<sup>4</sup> is still in the early phases of exploration. Phenotypic differences

## FOCUS POINTS

- Pediatric autoimmune neuropsychiatric disorders associated with streptococcus is a subtype of obsessive-compulsive disorder and tics associated with an infectious trigger.
- Children with this subtype may be prone to selective serotonin reuptake inhibitor (SSRI)-induced behavioral toxicity.
- Successful treatment may involve lower-than-typical SSRI doses and cognitive-behavioral therapy.

such as age, comorbid diagnoses, and, perhaps, immune status, may play a role as well.

In a subgroup of patients with pediatric OCD, evidence is accumulating that supports an association between symptom onset and/or exacerbation and streptococcal infection.<sup>5,6</sup> Termed pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS), the diagnostic criteria include the presence of OCD and/or a tic disorder; pediatric onset of symptoms (3 years of age to puberty); episodic or sawtooth course of symptom severity; an association of symptom onset and/or  $\geq 2$  exacerbations with group A streptococcal (GAS) infection as evidenced by positive throat cultures for strep or history of scarlet fever; and evidence of concurrent neurologic abnormalities (motoric hyperactivity or adventitious movements, such as choreiform movements). While the validity of PANDAS is still questioned by some,<sup>7</sup> it is evident that there is at least a subgroup of children who are particu-

Dr. Murphy is associate professor and chief of the Division of Child and Adolescent Psychiatry in the Department of Psychiatry, Dr. Storch is assistant professor in the Departments of Psychiatry and Pediatrics, and Ms. Strawser is research assistant in the Department of Psychiatry at the University of Florida in Gainesville.

Disclosure: Dr. Murphy receives research support from Bristol-Myers Squibb, the National Institutes of Health, and the National Institute of Mental Health. Dr. Storch receives research support from the Association for Glycogen Storage Disease, the Barth Syndrome Foundation, the Florida Department of Health, Genentech, the Human Growth Foundation, the National Institutes of Health, and the Obsessive-Compulsive Foundation. Ms. Strawser reports no affiliation with or financial interest in any organization that may pose a conflict of interest.

Please direct all correspondence to: Tanya K. Murphy, MD, Associate Professor and Chief, Division of Child and Adolescent Psychiatry, Department of Psychiatry, University of Florida, JHMHC 100256, Gainesville, FL 32610; Tel: 352-392-3681; Fax: 352-392-2579; E-mail: tmurphy@psychiatry.ufl.edu.

larly prone to symptom flare up with infectious triggers. These exacerbations are possibly due to immune system activation as evidenced by prolonged streptococcal antibody elevations.<sup>6</sup> Potential mechanisms by which autoantibodies could cause clinical manifestations in PANDAS include direct stimulation or blockade of receptors in the basal ganglia, with recent research supporting antibody-mediated neuronal cell signaling in the pathogenesis of Sydenham's chorea.<sup>8,9</sup> Another possibility is via cytokine modulation. GAS is a potent inducer of interferon gamma (IFN- $\gamma$ ) and most pro-inflammatory cytokines.<sup>10</sup> Interesting but not fully explored parallels are that SSRIs have been found to exert anti-inflammatory effects through suppression of IFN- $\gamma$ .<sup>11</sup> GAS infections have been reported to also lead to tryptophan degradation, which may influence serotonin function.<sup>12</sup> Further research is needed to more clearly delineate these neuroimmune interactions. Until then, observations by the authors of this case report suggest that children meeting the diagnostic criteria for PANDAS may have increased vulnerability to behavioral activation following SSRI initiation.

During the course of a prospective study on infection-triggered OCD, the authors of this case report evaluated and followed 38 children (mean age=10.4 years; 92% Caucasian) with a past history of SSRI treatment that also met the criteria for PANDAS with the exception that they were only required to have  $\geq 1$  GAS associations (onset or exacerbations). Fourteen of these children reported symptoms in the behavioral activation spectrum that remitted once the SSRI was discontinued. The most common symptoms reported were hyperactivity (n=5), mania (n=4), disinhibition/silly behavior (n=2), worsening OCD/compulsive behavior (n=5), aggressiveness/irritability/agitation (n=6), and suicidality/self harm (n=2). Many of these patients reported similar symptoms of activation on more than one SSRI. The case below typifies the history of one such child with an ultimate successful treatment with SSRI therapy.

## CASE REPORT

A 9-year-old Caucasian male presented with a 7-week history of OCD exacerbation with the complication of mood and suicidality. The patient had an onset of OCD in a dramatic fashion that occurred approximately 24 hours before developing a fever and a sore throat. The next morning, he was seen in the pediatrician's office and cultured positive for GAS. The standard 7-day course of antibiotics did not result in improvement of his neuropsychiatric symptoms. Three weeks after OCD onset, he was started on sertraline 25 mg/day. However, mood instability, especially suicidality, began a few days later and prompted a cross taper to fluvoxamine 25 mg/day, with

no adverse effects while on both. Upon discontinuing sertraline, suicidality returned and the community child psychiatrist abruptly discontinued medication 3 days prior to evaluation by the authors of this case report. One day prior to evaluation, the patient vomited all day. His OCD symptoms consisted of obsessions about germs and compulsive praying. His developmental history revealed that his motor skills developed normally with the exception of mild fine motor skill deficits; he could read at an early age and tested in the gifted range. While in preschool, he had an episode of tracing tiles and remained with subclinical OCD symptoms until this exacerbation. Family history was remarkable only for a maternal uncle with bipolar symptoms.

Upon referral to the authors of this case report, the patient was diagnosed with OCD, attention-deficit/hyperactivity disorder (ADHD)-combined type, and major depressive disorder. He was started on fluoxetine 5 mg/day for treatment of mood and OCD, and within 5 days of treatment became suicidal, threatening to jump from a moving car. Fluoxetine was discontinued but restarted shortly after at a dose of 2 mg/day, which he tolerated with no further activation symptoms or threats to self or others. Although his mood gradually improved, OCD remained clinically significant after 3 months on this regimen, and the dose was increased to 4 mg/day. He responded well following this increase (no adverse effects and OCD improved). Guanfacine was added 1 year later to treat ADHD. However, it is unclear if the improvement was due to a medication response or due to a natural remission of the OCD component of his PANDAS. He was followed for 2 years, and at the point of study exit only the ADHD symptoms remained clinically meaningful.

## CONCLUSION

This case serves to highlight two treatment considerations. First, children with OCD of the PANDAS subtype may be at elevated risk for behavioral activation following SSRI initiation. Second, even with a background of SSRI activation, OCD can be successfully treated with low doses of SSRIs. Therefore, conservative dosing and close monitoring for behavioral activation may be necessary in this population. The high rate of comorbid symptoms and the possibility of central nervous system sensitivity to immune and pharmacologic challenges put these children at a higher risk for adverse effects. Cognitive-behavioral therapy, which has strong empirical support in non-PANDAS OCD<sup>13</sup> and preliminary evidence in the PANDAS subtype,<sup>14</sup> may be an alternative treatment approach. Future research should examine predictors of response in children with OCD, both with and without the PANDAS subtype. *PP*

## REFERENCES

1. March JS, Biederman J, Wolkow R, et al. Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. *JAMA*. 1998;280(20):1752-1756.
2. Riddle MA, Reeve EA, Yaryura-Tobias JA, et al. Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40(2):222-229.
3. Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. *Pharmacogenomics*. 2002;3(2):229-243.
4. Perlis RH, Mischoulon D, Smoller JW, et al. Serotonin transporter polymorphisms and adverse effects with fluoxetine treatment. *Biol Psychiatry*. 2003;54(9):879-883.
5. Swedo SE. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). *Mol Psychiatry*. 2002;7(suppl 2):S24-S25.
6. Murphy TK, Sajid M, Soto O, et al. Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcus in children with obsessive-compulsive disorder and tics. *Biol Psychiatry*. 2004;55(1):61-68.
7. Kurlan R, Kaplan EL. The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) etiology for tics and obsessive-compulsive symptoms: hypothesis or entity? Practical considerations for the clinician. *Pediatrics*. 2004;113(4):883-886.
8. Kirvan CA, Swedo SE, Heuser JS, Cunningham MW. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. *Nat Med*. 2003;9(7):914-920.
9. Kirvan CA, Swedo SE, Heuser JS, Cunningham MW. Antibody-Mediated Neuronal Cell Signaling Links Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS) with Sydenham's Chorea. *J Neuroimmunol*. In press.
10. Miettinen M, Matikainen S, Vuopio-Varkila J, et al. Lactobacilli and streptococci induce interleukin-12 (IL-12), IL-18, and gamma interferon production in human peripheral blood mononuclear cells. *Infect Immun*. 1998;66(12):6058-6062.
11. Kubera M, Lin AH, Kenis G, Bosmans E, van Bockstaele D, Maes M. Anti-inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. *J Clin Psychopharmacol*. 2001;21(2):199-206.
12. Murr C, Gerlach D, Widner B, Dierich MP, Fuchs D. Neopterin production and tryptophan degradation in humans infected by *Streptococcus pyogenes*. *Med Microbiol Immunol (Berl)*. 2001;189(3):161-163.
13. Pediatric OCD Treatment Study (POTS) Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. *JAMA*. 2004;292(16):1969-1976.
14. Storch EA, Gerdes AC, Adkins JW, Geffken GR, Star J, Murphy T. Behavioral treatment of a child with PANDAS. *J Am Acad Child Adolesc Psychiatry*. 2004;43(5):510-511.