

A Link Between Perianal Strep and Pediatric Autoimmune Neuropsychiatric Disorder Associated With Streptococcal Infection (PANDAS)

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Perianal streptococcal dermatitis is an infection caused by group A streptococcus (GAS). Children with a pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) phenotype may have tics or obsessive compulsive symptoms secondary to a systemic immune activation by GAS infecting perianal areas. In this retrospective case series, the authors describe three children with symptoms consistent with PANDAS and a confirmed perianal streptococcal dermatitis as the likely infectious trigger. Concomitant perianal dermatitis and new-onset obsessive-compulsive symptoms and/or tics are strong indications for perianal culture and rapid antigen detection test in young children.

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Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) is a clinical phenotype gaining more interest and research in the pediatric community. It is a syndrome consisting of new onset of neuropsychiatric symptoms that are linked to a group A streptococcal infection (GAS). The criteria for making this diagnosis is as follows: presence of obsessive-compulsive disorder (OCD) and/or a tic disorder, pediatric onset of symptoms (age 3 years to puberty), episodic course of symptom severity, association with group A streptococcal infection association with neurological abnormalities (motoric hyperactivity, or adventitious movements, such as choreiform movements).¹ This clinical presentation has been associated with other infectious agents such as influenza A, *Mycoplasma pneumoniae*, which causes ‘walking pneumonia,’ and *Borrelia burgdorferi*, which causes Lyme disease.² Most children with PANDAS are prepubertal with an average age of onset of 7 years old. Children with PANDAS will develop a dramatic onset of new psychiatric symptoms noticed by their parents as rages, mood fluctuations, anxiety, hyperactivity, and

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oppositional behaviors that can quickly develop over 24–72 hours that begin during or soon after having a GAS infection or exposure to someone with GAS.¹ Children will also become more distractible and begin to have trouble in school with learning. Handwriting often worsens and becomes large and messy. The child may also begin to have frequent urination and nocturnal enuresis along with nightmares. In addition, children frequently develop new onset tics. This dramatic change in functioning has a significant impact on the child's social life, academic performance, and family interactions.³

GAS is the cause of 15% to 36% of pharyngitis among children in the United States and approximately 20% of children, are asymptomatic carriers of GAS.⁴ Younger children, such as 6 months to 10 years old,⁵ may manifest GAS infections as a perianal streptococcal dermatitis (PSD).^{5,6} Perianal streptococcal dermatitis tends to be more frequent in males than females and diagnosis can be confirmed by a perianal swab with culture or rapid streptococcal test of the perianal area.

This article describes three children who sought attention for obsessive compulsive (OC) symptoms or tics that were subsequently found to have confirmed and/or suspected perianal dermatitis that was temporally associated with the onset of their neuropsychiatric symptoms.

CASE REPORTS

Case # 1:

A 5-year-old boy with a diagnosis of attention deficit hyperactivity disorder (ADHD), speech and language delays, as well as gross and fine motor delays presented to his pediatrician with a frequent motor tic that consisted of a head shake and an infrequent vocal tic of throat clearing following a GAS infection confirmed by positive pharyngeal rapid antigen detection test (RADT). He was treated with 10-day course of amoxicillin. Parents report that his head tic decreased in frequency approximately 7 days following initiation of antibiotic treatment and reported complete resolution within 14 days.

At the follow-up visit, he was noted to have perianal itching and a rectal rapid antigen detection test was positive for GAS. His mother noted that during this time the head shaking began again. Following a 10-day course of clindamycin, the head shaking stopped and repeat rectal RADT was negative. Soon after his head tic

began again and patient was again noted to have a positive rectal rapid antigen test and was treated again with clindamycin. Father was also treated for GAS concomitantly after complaining of a sore throat and perianal itching at the same time.

Case #2:

A 6-year-old boy presents to the clinic with ADHD, tics and OC symptoms that began at age 3. At evaluation his OC symptoms consisted of excessive hand washing to remove germs, refusal to engage in activities that involved getting dirty such as using markers, finger paint or glitter, refusal to step on tiles or rugs, new sensory issues, and compulsions to do things in groups of two. He began to have tics around this same time that consisted of eye blinking that lasted 3 to 4 months and then remitted. He also had 3-week period of pulling out his eyelashes.

His medical history is significant for three episodes of recurrent rectal GAS beginning at age 3. With each perianal dermatitis, parents reported that he would develop odd compulsive behaviors and motor tics. Culture done at the age of 3 confirmed rectal GAS, and he was treated with a course of amoxicillin. At age 6, he had two recurrences of perianal dermatitis associated with obsessive compulsive symptoms and an eye blinking tic. The dermatitis was assumed to be GAS by the primary care physician because of his history, and he was treated empirically. During the last episode as described above, he presented with both pharyngeal and rectal GAS concomitantly clinically diagnosed by his primary care physician. He was not rectally cultured at this time but streptococcal antibodies were obtained. All episodes were treated with a 10-day course of amoxicillin and with each treatment his OC symptoms remitted and tics became very mild.

Case # 3:

A 6-year-old male presents to the clinic for an evaluation of new onset tics after a perianal streptococcal infection confirmed with a positive culture. His tics primarily involved eye movements. He was treated with a 14-day course of amoxicillin/clavulanate and his tics, which were primarily eye movements, became less pronounced within 4 weeks and eventually subsided after 6–8 weeks. Eight months later, motor tics returned of eyes and neck, as well as new onset vocal tics with hyperactivity and restlessness. These symptoms coincided with the development of perianal rash in one of his siblings and

TABLE 1. Characteristics of the Patients at the Time of Presentation

	Case 1	Case 2	Case 3
Age	5	6	6
Gender	M	M	M
Age of OCD/tics onset	5	3	5
Age of perianal dermatitis	5	3.6	5
Tics	Y	Y	Y
OC symptoms	N	Y	N
Neuropsychiatric symptom remission with antibiotics	Y	Y	Y
Anti-DNase B	NM	614	480
ASO	10.9	328	137
History of pharyngitis	N	Y	Y
Positive rectal RADT	Y	NM	NM
Perianal GAS confirmed by culture	N	Y	Y
PSD responded to systemic antibiotics	Y	Y	Y

ASO: anti-streptolysin O; GAS: group A streptococcus; NM: not measured; OC: obsessive compulsive; OCD: obsessive-compulsive disorder; PSD: perianal streptococcal dermatitis; RADT: rapid antigen detection test.

Upper limit normal (ULN) ASO 5-year-old child: 160 Todd units/mL; 6-year-old child: 240 Todd units/mL; ULN Anti-DNase B 5-year-old child: 320 Todd units/mL; 6-year-old child: 480 Todd units.¹⁷

a self-limiting truncal rash in the patient and his sibling. A pharyngeal culture was done but lost by the laboratory. Penicillin prophylaxis was begun by his pediatrician, and tics remained, though became milder.

For a description of the cases, see Table 1.

DISCUSSION

This article describes three children who sought attention for OC symptoms and/or tics and with a suspected PANDAS-like presentation that were subsequently found to have perianal dermatitis temporally associated with their symptoms. Perianal dermatitis is a relatively common condition in children, which is frequently referred to as diaper rash and often also involves the vulva and penis.⁵ The differential diagnoses include irritant dermatitis, candidiasis, seborrheic dermatitis, atopic dermatitis, psoriasis, allergic contact dermatitis, pinworm infection, inflammatory bowel disease, histiocytosis, sexual abuse, and perianal streptococcal dermatitis. Males are usually affected more than females and diagnosis is confirmed by perianal swab with culture. It is sometimes referred out to dermatologists or colorectal surgeons as it often perpetuates for weeks to months without resolution, not being recognized accurately by the child's primary care physician. In a recent study of 124 patients with anorectal complaints, 16% were diagnosed with PSD, making streptococcus the most

common infectious agent found, with the mean duration of symptoms lasting 6.6 months.⁵

Various case series associate pharyngeal streptococcal infections with perianal dermatitis via the oral to anal route by scratching.⁷ Roos et al.⁷ have postulated that pharyngeal bacterial colonization with alpha hemolytic streptococci interferes with colonization by GAS but perianal areas do not share the same microbial flora thereby allowing selective colonization of the perianal area over the pharynx.⁸

Perianal cultures have proven that pharyngeal strains of GAS may travel to and colonize other susceptible areas of the anatomy.^{8,9} For diagnosis, a swab of the red affected area is usually sufficient to determine the bacteria responsible for the infection. A RADT has been proven to be an adequate method to quickly verify GAS as the infectious agent with an accuracy of about 93% although, for a definitive diagnosis a culture is recommended.¹⁰ Tests for streptococcal antibodies have proven to be unreliable in identifying GAS as the cause of perianal dermatitis^{11,12}; therefore, these serological tests are not recommended to prove presence of GAS in this scenario.¹³

Antibiotic treatment courses as outlined in our case series were quite short compared with what the literature suggests. This may have played a role in the recurrence of the infections with each patient. Therapy in patients with PSD tends to require more time than the pharyngeal counterpart and a duration of therapy, from 14 to 21 days, seems to be necessary.^{5,6,14} Jongen et al. note that 10-day treatments are insufficient for eradication of the bacteria, and such a limited course of treatment will most likely result in infection recurrence.⁵ Treatment with topical antibiotics and antifungal lotions do not provide the adequate permeability in the tissue to eliminate the infection.¹⁴

For children that are frequently infected with GAS pharyngitis and have recurrent PANDAS presentations, it is strongly recommended that the family members also be cultured to assess if they are GAS carriers. To avoid person-to-person spread and recurrence of perianal GAS dermatitis, Herbst et al. recommend swabbing the perianal and pharyngeal areas of not only the patient but, also asymptomatic siblings, parents and other family members living in the household.¹⁰ Treating the colonized asymptomatic family members would help avoid reinfection in the patient and a recurrence of symptoms. Treatment should include monitoring with post-treatment perianal and throat swabs as well as urine analysis to rule out post-streptococcal glomerulonephritis.

Case 1 demonstrates the complexity of a child with comorbid diagnoses but this should not limit a clinician to suspecting a PANDAS presentation if neuropsychiatric symptoms can be associated with a distinct, temporal association with GAS. The outcome or course of PANDAS illness of typical or less psychiatrically comorbid PANDAS cases is not known which makes it even more difficult to manage the complexity of symptoms and predict outcome without evidence based treatment protocols. Epidemiologically, all of our cases were males, which support the higher incidence of PSD in male population but also the higher frequency of tics and PANDAS in males. It should be noted that in our clinic, we had several reports of females with vulvar dermatitis with new onset OCD symptoms but did not have GAS confirmation and were not included in this series. The recurrence of tics in case 3 occurred when his brother had a perianal rash, which exemplifies the need to inquire about family members infections when gathering history. This subject still had mild tics despite being treated with a prophylactic dose of penicillin that coincides with our clinical experience that low dose beta-lactams are often not sufficient to show remission in neuropsychiatric symptoms and supports the literature that longer treatment courses of antibiotics may be required to eradicate PSD.

Although it is argued that streptococcal antibodies are not useful in perianal GAS diagnosis, it should be noted that elevated GAS titers are also not sufficient data to classify a child as having PANDAS because of multiple factors that can alter levels such as hyperlipidemia, treatment with antibiotics, or an individual's innate immune functioning.¹⁵ In addition, titers can remain elevated for longer periods of time because of reinfection, frequent exposure, or abnormal immune responses thus following

GAS titers provides only limited information. Paired titers at symptom onset and 4–6 weeks later provides the most useful information.^{16,17}

We would like to propose the notion that perianal streptococcal infections should be considered as another means in which GAS may activate the immune system leading to the subsequent development of PANDAS. Although the relationship between pharyngeal streptococci and PANDAS has been investigated and reported in the literature, the link between perianal GAS infection and PANDAS has not been studied to date. Our case series has limitations because of the small number of patients and because some cases have with pre-existing neuropsychiatric symptoms and retrospectively collected information. Despite these limitations, it is hoped that clinicians begin to investigate associations between PSD as a possible infectious trigger in the clinical workup for new onset OCD and tics, especially in young children. We propose that pediatricians begin to inquire about and examine for perianal dermatitis when seeing children with a PANDAS-like presentation who are not found to have streptococcal pharyngitis or another obvious infectious trigger. Prompting the family to talk about an issue that would normally not be mentioned at a neuropsychiatric consult may reduce the time and resources spent on unnecessary examinations and procedures. Early detection and appropriate antibiotic treatment may lead to a reduction in neuropsychiatric symptoms.^{15,18} In conclusion, further research is needed to examine the relationship of perianal streptococcal infections with pediatric neuropsychiatric presentations.

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