Pediatric Autoimmune Neuropsychiatric Disorders Associated with *Streptococcus* in Identical Siblings

Adam B. Lewin, Ph.D., Eric A. Storch, Ph.D., and Tanya K. Murphy, M.D.

Abstract

Termed pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus* (PANDAS), these cases of childhood-onset obsessive compulsive disorder and tic disorders resemble the presentation of Sydenham chorea, in that they have an acute onset following a group A beta-hemolytic streptococcal infection (group A *Streptococcus*), with accompanying neurological signs, and an episodic or sawtooth course. Familial associations of this subgroup of patients remain understudied. This report provides phenotypic descriptions of three youth with PANDAS as well as their genetically identical siblings (in two cases of twins and one case of triplets). These cases highlight the potential for environmental influences for discordant presentations in genetically identical siblings. Despite identical genetics, presentations showed marked variation across siblings (from a full PANDAS presentation to asymptomatic). Further research into environmentally driven influences such as postinfectious molecular mimicry and epigenetic factors that may influence the manifestation of these pediatric neuropsychiatric disorders will promote our understanding of their prevention and treatment.

Familial preponderance of obsessive compulsive disorder (OCD) and tic disorder has been well documented (Pauls et al. 1991, 1995; Walkup et al. 1996; Grados et al. 2001; Nestadt et al. 2010) and evidence for a strong genetic contribution is mounting (Pauls 2008). Concordance rates of OCD is higher in monozygotic twins (80%–87%) compared with dizygotic twins (47%–50%) (Carey and Gottesman 1981). Twin studies also suggest a high concordance rate for tic disorders (Hyde et al. 1992; O’Rourke et al. 2009). In one study, 77% of monozygotic twins (compared with 23% of dizygotic twins) were concordant for tic disorders (Price et al. 1985). The rate of OCD in first-degree relatives of affected probands is 10%–11% versus 2% among relatives of non-OCD controls (Pauls et al. 1995; Nestadt et al. 2000; Hanna et al. 2005). Rates of OCD in parents of youth with OCD range from 17% to 20% (Lenane et al. 1990; Riddle et al. 1990). Rates of tic disorders were 4.6%–6.2% in first-degree relatives of probands with OCD, compared with 1%–1.7% among relatives of controls (Pauls et al. 1995; Grados et al. 2001). Tics were reported in 16% of parents of youth diagnosed with OCD (Leonard et al. 1992). Familial rates of OCD and tic disorders are also high for probands with Tourette’s disorder (16%–23% familial rate of OCD and 13.6%–17.6% of tic disorders) (Walkup et al. 1996; Hebebrand et al. 1997). Despite the growth of OCD and tic genetics research (Samuels et al. 2006; Nestadt et al. 2010), familial associations of similar symptoms in a subgroup of patients with possible autoimmune etiology remain understudied (Loungee et al. 2000; Murphy et al. 2010). Termed pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus* (PANDAS), these cases of childhood-onset OCD resemble a psychiatric dominant presentation of Sydenham chorea but have an acute and dramatic onset of either OCD or tics or both following a streptococcal infection, with mild neurological signs but no chorea, and an episodic or sawtooth course (Swedo et al. 1998; Murphy et al. 2004). Loungee et al. (2000) provided the first evaluation of OCD or tic symptoms in 139 family members of 54 probands with PANDAS. The authors found that rates of OCD (12%) and tic disorders (15%) in first-degree relatives of PANDAS probands were comparable to family aggregation studies among non-PANDAS probands with OCD or tic disorders (Lenane et al. 1990; Pauls et al. 1995; Walkup et al. 1996). However, the concordance rate among siblings of PANDAS probands remains unstudied.

Dranitzki and Steiner (2007) provided the first description of PANDAS among siblings (Dranitzki and Steiner 2007). The authors described the acute onset of facial tics, rhythmic jerking of all four limbs, and nervousness in a 10-year-old girl, which followed the onset of a group A streptococcal infection (group A *Streptococcus* [GAS]). Following oral therapy with penicillin, symptoms subsided. Remission continued over 6 months of prophylactic therapy and no recurrence was observed in 3 years of follow-up. Three years later, the patient’s 6.5-year-old brother developed OCD symptoms and facial and vocal tics. He tested positive for GAS and his symptoms also remitted after several weeks of amoxicillin therapy.
The aim of the present report was to describe the presentation of pediatric probands with PANDAS as well as their genetically identical sibling(s). (Fig. 1). This report builds upon the existing literature by presenting probands with a significantly higher genetic concordance than the studies between first-degree relatives. First, we describe a set of triplets with extensive GAS exposure whose presentation ranged from severe to mild to asymptomatic. Second, we report on mirror-image twins whose neuropsychiatric responses to GAS varied from significant OCD symptomology in one brother to stuttering in the other. Finally, we present two twins, both with frequent strep exposure, from a family with significant autoimmune risk. Parents provided consent for inclusion of their sons’ histories in this case report.

FIG. 1. Genograms of case participants. GAS = Group A beta-hemolytic Streptococcus; OCD = obsessive compulsive disorder; ITP = idiopathic thrombocytopenic purpura; PANDAS = pediatric autoimmune neuropsychiatric disorders associated with Streptococcus; ASO = anti-streptolysin O titer; DNASE-B = anti-deoxyribonuclease B titer.
The triplets were three Caucasian boys, Emmitt, Steve, and Billy, who presented at age 7 years. The brothers reside with both biological parents; there are no other siblings. According to the patient’s mother, family psychiatric history is positive for the following indications: subclinical obsessive symptoms (mom and maternal aunt; mental counting rituals); adult-onset of OCD (treated with medication; maternal grandmother); attention-deficit/hyperactivity disorder (treated with stimulant medication in dad and two of his brothers); unipolar depression (in extended family members on the paternal side of the family). There was no family history of tic disorders, movement disorders, autism, psychosis, bipolar depression, or neurological disorders.

A relatively unremarkable pregnancy was described. Their mother reported good prenatal care and no illnesses or injuries during pregnancy. There was no substance or alcohol use during gestation. Because of preterm labor, her mother was prescribed subcutaneous terbutaline injections beginning approximately 2 months before delivery. Delivery was at 34 weeks gestation via c-section. Birth order and weights were as follows: Emmitt, 3 lbs 5 oz; Steve, 4 lbs 11 oz; and Billy, 5 lbs 4 oz. Apgar scores were reportedly high and breathing was normal at birth. The boys all received bili-light treatment for jaundice for a few days following delivery. Billy and Steve were released from the hospital after 2 weeks, whereas Emmitt remained hospitalized for 1 month because of difficulties with sucking or swallowing.

The triplets’ early developmental milestones were described to be within normal limits except for a delay in communication. Subsequently, they entered speech and language therapy and each reportedly benefited from intervention. There are no current impairments in speech and language or social development and no history of movement disorders or neurologic disease. Health history is remarkable for viral meningitis in Steve (at age 5 years) and head injury without loss of consciousness for Emmitt (falling on tile floor as a toddler, resulting in an emergency room consultation). The boys attended the same preschool classroom but were in separate classrooms since beginning kindergarten. Otherwise, the boys were healthy with the exception of upper respiratory infections.

An extensive evaluation by a board-certified child psychiatrist with expertise in PANDAS (T.K.M.) determined that Emmitt met putative diagnostic criteria for PANDAS based on the Swedo et al. (2004) criteria. A brief overview is presented: at age 6 years, Emmitt developed an acute onset of verbal tics (throat clearing appeared first, followed by exhaling, humming, and loud whistling/screeching tics). Tic symptoms displayed a progressive sawtooth pattern over several weeks, and Emmitt’s neuropsychiatric symptoms were consistently exacerbated with GAS infections. The complexity of Emmitt’s tics remained simple (mostly phonic). Deoxyribonuclease B (anti-DNASE-B) antibody was tested at that time and was found to be above 1,360; anti-streptolysin O (ASO), was 699. Despite a 30-day course of amoxicillin (standard dose per weight) prescribed by his pediatrician for presumptive PANDAS, tic symptoms did not improve (with no notable change in laboratory findings: anti-DNASE-B antibody >1,360; ASO = 744). Over the next 8 months, Emmitt’s verbal tics worsened (more noticeable, more intense, and more frequent) and egodystonic OCD symptoms developed (e.g., counting compulsions). No throat cultures were obtained.

At approximately 5 months after tic onset, a magnetic resonance imaging (MRI) using ultrahigh resolution was ordered by his neurologist and a focal area of abnormal signal intensity at the junction of the genu of the right internal capsule and the right basal ganglia was identified; electroencephalogram (EEG) findings were unremarkable. The MRI (with and without contrast) was repeated approximately 6 months later and showed no changes. No elevated cerebral blood flow was observed and the lesion was thought to be benign or a grade 1–2 neoplasm. Multivoxel (chemical shift) spectroscopy was performed and findings were not suggestive of malignancy. At the time of his evaluation at this clinic (6 months after onset), DNASE-B antibody was 960 and ASO was 533. Subsequently, over the past 6 months, Emmitt’s symptoms have almost completely subsided.

The history of Emmitt’s identical triplet brother (Steve) was notable for an acute onset of neuropsychiatric symptoms just before the onset of Emmitt’s symptoms (also at age 6 years). Although his presentation may not have met the full conservative criteria for PANDAS (insufficient documentation of GAS/symptom exacerbation history), his symptoms were consistent with many aspects of PANDAS. Steve had a positive streptococcal culture approximately 3 months prior to the onset of his symptoms. Steve’s symptoms included mild facial tics (eye movements and switches) and were always of lower intensity than Emmitt’s tics. Tic symptoms would develop rapidly (either overnight or within a few days) and remit rapidly as well (within 1–2 weeks). When Steve presented for assessment by his pediatrician, his anti-DNASE-B was 240 and his ASO was 158. Following a 30-day course of amoxicillin, his symptoms completely remitted; posttreatment streptococcal titers were also without notable change with the anti-DNASE-B of 240 and ASO of 169. Finally, the third identical triplet (Billy) has no history of PANDAS symptoms or other neuropsychiatric symptoms. His antibody levels were not checked.

Percy and Tim, mirror-image twins (right and left handed, respectively),2 are 6-year-old Caucasian boys who also presented with PANDAS or seemingly related symptoms. The brothers live with their biological parents. Pregnancy was noteworthy for bedrest at 23 weeks gestation, terbutaline by mouth at 26 weeks, terbutaline injections at 30 weeks, and magnesium sulfate on the day of delivery. Delivery was at 32.5 weeks. Percy’s birth weight was 4 lbs 4 oz and Tim’s was 4 lbs and 11 oz. Breathing and swallowing abnormalities were reported at birth and the brothers remained hospitalized for 11 days. Percy required 6 hours of treatment in an oxygen hood post-delivery. Developmental milestones appeared within normal limits. Family history is remarkable for subclinical anxiety (mother) and PANDAS (presenting with tic and OCD symptoms) in a second-degree relative and idiopathic thrombocytopenic purpura (ITP) in another second-degree relative. Tim and Percy attended preschool together in the same classroom. Beginning at age 5 years, the twins were placed in separate classrooms in the same school.

Percy was diagnosed with PANDAS following an extensive clinical evaluation by the final author. Percy’s presentation is noteworthy, at approximately age 4 years, for five confirmed GAS infections over an 8-month period (treated with antibiotics) resulting in removal of his tonsils and adenoids. There was an additional episode of GAS exposure (twin brother) during the 8-month

---

1The upper limit of normal for preschoolers is 120–160 for the ASO titer and 60–320 for DNASE-B (Kaplan et al. 1998); commercial labs often employ lower cutoffs, for example, 60 for ASO.

2Mirror image is a descriptive term for monozygotic twins who develop asymmetric features, for example, one is left handed and the other is right handed, birthmarks on opposite sides of the other; about 25% of identical twins are mirror image (Burn 1991).
period. Percy’s mother reported one additional positive GAS infection within the month following tonsillectomy and GAS exposure (via family member with a positive culture) at 2 months postsurgery. Two months postoperatively, he had an abrupt onset of inappropriate touching (nonsexual tapping/rubbing of self and objects), followed by germ fears, repetitive behaviors (touching/tracing), frequent urination urges (medical and laboratory data were negative), and fears of offending God (and other religious obsessions). Over the next 3–6 months, symptoms fluctuated dramatically in an episodic course. Percy’s titers at the time of assessment in our clinic were ASO = 200, anti-DNAsB = 80, anti-Group A carbohydrate (ACHO)3 = 2.71; all except the anti-DNasB were on cusp of the non-age-adjusted threshold for elevation (Ayoub and Harden 2002). Obsessive-compulsive symptoms fluctuated with GAS and GAS exposure and improved with antibiotics.

Tim has a history of GAS infections (treated with antibiotics) generally overlapping with Percy’s (including tonsillectomy and adenoidectomy at the same time). Tim’s neuropsychiatric symptoms presented as throat clearing but resolved within a few weeks postoperatively. Other symptoms included stuttering, which was remarkable for occurring when GAS cultures were positive and ameliorating with antibiotic treatment. Stuttering and throat clearing symptoms remitted following tonsillectomy at age 4 years. Tim’s course remained stable.

The final set of twins, Noah and Joakim (age 10 years), presented with a significant family history of marked autoimmune disease: Hashimoto’s thyroiditis (mother); rheumatoid arthritis (two older sisters); ITP (Joakim and his older brother). The twins’ pregnancy was unremarkable for occurring when GAS cultures were positive and ameliorating with antibiotic treatment. Delivery milestones were within normal limits for both boys. Noah presented for evaluation after an 18-month history of OCD symptoms, which included touching rituals, washing, ordering/arranging, perfectionist tendencies, and contamination obsessions. A sawtooth pattern was noted with intermittent exacerbations including the present episode. Noah’s presentation was consistent with putative PANDAS criteria. Obsessive-compulsive symptoms were in the moderate to high range during Noah’s clinical evaluation. Physical examination revealed enlarged cervical nodes and tonsils, red arch, and white pustules. Rapid GAS test was positive. The patient’s mother reported that Noah’s brother (Joakim) cultured positive for GAS 1 week prior and that Noah’s symptoms exacerbate during GAS infections among family members. Additionally, she indicated that she has a significant lifetime history of GAS infection including two hospitalizations for tonsillitis secondary to severe esophageal ulceration. Prior to Noah’s presenting episode, at least two OCD symptom exacerbations were noted at the time of family GAS exposure. Noah’s twin brother (Joakim) has a similar GAS exposure history with no neuropsychiatric symptoms. Notably, Joakim was diagnosed with tonsillitis at age 4 years (requiring hospitalization) and was rehospitalized at age 6 years for tonsillitis and onset of ITP. Otherwise, his presentation is unremarkable.

Discussion and Implications

Recent infections may indicate undetected immune deficiencies that increase the risk of autoimmunity (Mackay et al. 2010). Immune deficiencies and autoimmune predisposition are reported to occur at increased frequencies among family members. It is therefore possible that these susceptibilities could be at play in developing an autoimmune response to GAS as hypothesized in PANDAS. Nevertheless, as seen in many autoimmune disorders, concordance among monozygotic twins varies tremendously (Ballestar) (Javierre et al. 2010). Similarly, these cases highlight the potential for environmental influences for discordant presentations in genetically identical siblings (Wong et al. 2005). Discordant presentations have also been reported in cases of mirror-image twins (James 1983; Lohr and Bracha 1992; Sommer et al. 1999; Kato et al. 2005). Thus, from a neuropsychological perspective, being a mirror-image twin may explain the differences in the specific type of neuropsychiatric symptom (e.g., language vs. visuo-motor impairment) but not the course (e.g., sawtooth or episodic) of presentation, as Tim presented with symptoms that affected his language fluency but remitted with a more stable course than Percy. Emmitt was the most severely affected with neuropsychiatric symptoms, which were not unexpected given that his low birth weight and complicated postnatal course perhaps put him at a higher neurological risk (Leckman et al. 1987; Hyde et al. 1992; Burd et al. 1999; Pringsheim et al. 2009). Further, his abnormal MRI (perhaps an inflammatory reaction) in the area of known involvement for OCD and tic neuropathology (Giedd et al. 2000) and his notably higher streptococcal antibody levels without a different GAS exposure risk from his siblings is interesting. Emmitt’s triplet brother, Steve, presented with a similar GAS history but with borderline titers and attenuated neuropsychiatric symptoms. Noah’s history of interest is the very high degree of familial autoimmune disease (in each of his siblings and mother). Other than OCD and GAS, Noah has been comparatively healthy.

Despite supposed identical genetic susceptibility and very similar environmental exposures, clinical presentations differed significantly. Variations in the degree of postinfectious molecular mimicry (a cross-reactive antibody response to host tissue in addition to the invading pathogen) may explain differences in the symptom severity seen in the triplets. Epigenetic factors are believed to play a role in autoimmune and neuropsychiatric disorders (Bagot and Meaney 2010; Gropman and Batshaw 2010). Pre- and postnatal difficulties and early exposure to GAS may impact immune development by modifying, for example, T helper cell or cytokine differentiation (Brooks et al. 2010) or human glucocorticoid receptor responses (Groom et al. 2010) at the epigenetic level. Epigenetic changes are primarily due to methylation of the DNA or modifications in the way histones package the DNA but not influence the sequence of the DNA. Exploration of the process involved in these modifications should inform on the pathophysiology of many complex diseases including psychiatric and autoimmune disorders. Further research into environmentally driven influences that may influence the manifestation of these pediatric neuropsychiatric disorders will promote our understanding of their prevention and treatment (Fraga et al. 2005; Kaminsky et al. 2009).

Disclosures

The authors have approved this document and report no conflict of interest with respect to this manuscript. Dr. Lewin receives funding from the National Alliance for Research in Schizophrenia and bolts.
and Affective Disorders, the International OCD Foundation, and the Joseph Drown Foundation. Dr. Storch receives grant funding from the NIMH, NICHD, All Children’s Hospital Research Foundation, Centers for Disease Control, National Alliance for Research on Schizophrenia and Affective Disorders, Obsessive Compulsive Foundation, Tourette Syndrome Association, Janssen Pharmaceuticals, and Foundation for Research on Prader-Willi Syndrome. He receives textbook honorarium from Springer publishers and Lawrence Erlbaum. Dr. Storch has been an educational consultant for Rogers Memorial Hospital. Dr. Murphy has received research support from NIMH, Forest Laboratories, Janssen Pharmaceuticals, Endo, Obsessive Compulsive Foundation, Tourette Syndrome Association, All Children’s Hospital Research Foundation, Centers for Disease Control, and National Alliance for Research on Schizophrenia and Affective Disorders. Dr. Murphy is on the Medical Advisory Board for Tourette Syndrome Association. She receives textbook honorarium from Lawrence Erlbaum.

References

Nestadt G, Grados M, Samuels JF: Genetics of obsessive-compulsive
Nestadt G, Samuels J, Riddle M, Bienvenu OJ, III, Liang KY, LaBuda
M, Walkup J, Grados M, Hoehn-Saric R: A family study of
obsessive-compulsive disorder. Arch Gen Psychiatry 57:358–363,
2000.
O’Rourke JA, Scharf JM, Yu D, Pauls DL: The genetics of Tourette
Pauls DL: The genetics of obsessive compulsive disorder: A review of
2008.
Pauls DL, Alsobrook JP, Goodman W, Rasmussen S, Leckman JF: A
family study of obsessive-compulsive disorder. Am J Psychiatry
Pauls DL, Raymond CL, Stevenson JM, Leckman JF: A family study
of Gilles de la Tourette syndrome. Am J Hum Genet 48:154–163,
Price RA, Kidd KK, Cohen DJ, Pauls DL, Leckman JF: A twin study
Pringsheim T, Sandor P, Lang A, Shah P, O’Connor P: Prenatal
and perinatal morbidity in children with Tourette syndrome and
attention-deficit hyperactivity disorder. J Dev Behav Pediatr 30:
Riddle MA, Scahill L, King R, Hardin MT, Towbin KE, Ort SI,
Leckman JF, Cohen DJ: Obsessive compulsive disorder in children
and adolescents: Phenomenology and family history. J Am Acad
Samuels JF, Riddle MA, Greenberg BD, Fyer AJ, McCracken JT,
Rauch SL, Murphy DL, Grados MA, Pinto A, Knowles JA, Pia-
centini J, Cannistraro PA, Cullen B, Bienvenu OJ, 3rd, Rasmussen
SA, Pauls DL, Willour VL, Shugart YY, Liang KY, Hoehn-Saric R,
Nestadt G: The OCD collaborative genetics study: Methods and
Sommer IE, Ramsey NF, Bouma A, Kahn RS: Cerebral mirror-
S, Lougee L, Dow S, Zamkoff J, Dubbert BK: Pediatric
autoimmune neuropsychiatric disorders associated with strepto-
coccal infections: Clinical description of the first 50 cases. Am J
Swedo SE, Leonard HL, Rapoport JL: The pediatric autoimmune
neuropsychiatric disorders associated with streptococcal infection
(PANDAS) subgroup: Separating fact from fiction. Pediatrics
Walkup JT, LaBuda MC, Singer HS, Brown J, Riddle MA, Hurko O:
Family study and segregation analysis of Tourette syndrome: Evi-
693, 1996.
Wong AH, Gottesman, II, Petronis A: Phenotypic differences in ge-
etically identical organisms: The epigenetic perspective. Hum Mol

Address correspondence to:
Adam B. Lewin, Ph.D.
Department of Pediatrics
Rothman Center for Neuropsychiatry
University of South Florida College of Medicine
800 Sixth Street South
Fourth Floor North
Box 7523
Saint Petersburg, FL 33701
E-mail: alewin@health.usf.edu