Case Report

Sudden Onset Complex Tic Associated with Streptococcal Infection in a Neonate: The First Case of Neonatal PANDAS

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Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) is defined by acute onset of neuropsychiatric symptoms, most notably simple or complex motor or vocal tics, with an abrupt onset before adulthood associated with a Group A Streptococcal infection. This disorder is most commonly diagnosed in childhood presumably because of the high incidence of Group A Streptococcal infections during this time in development. This is the first report of a neonate with PANDAS. The neonate presented with clinical and laboratory evidence of a non-invasive Group A Streptococcal infection and concomitantly developed a complex tic. The complex tic waned as the Group A Streptococcal antibody titers decreased suggesting a temporal relation between the two. Infection and other triggers should be considered when abrupt changes in behavior or development occur early in life. Such an increased index-of-suspicious of PANDAS or Pediatric Acute-Onset Neuropsychiatric Syndromes (PANS) early in life may lead to improved neurodevelopmental outcomes.
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INTRODUCTION

The etiology of many childhood neurological disorders is not clear at this time and current research is extremely active in determining novel biological pathways that may be resulting in childhood neurodevelopmental disorders. For example, in autism spectrum disorder, recent reviews have pointed out that a wide array of abnormalities in various biological systems, including various metabolic systems and the immune system, may be related to neurodevelopmental abnormalities.[1] Despite this insight there remain a significant number of unanswered questions and we are still learning about the variation in clinical presentation in many well-defined and less-well-defined disorders.

One disorder that has been gaining significant attention in neurological, neurodevelopmental and psychiatric disorders of childhood is Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) that is related to the more well known immunological disorder known as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS). PANDAS is defined by acute onset of neuropsychiatric symptoms, most notably simple or complex motor or vocal tics, with an abrupt onset before adulthood associated with a Group A Streptococcal (GAS).[2,3] This disorder is just beginning to be better defined in regards to the symptoms that define it[4,5] and its biomarkers.[6,7] In contrast PANS represents a sudden onset of neuropsychiatric symptoms as a result of a wide variety of causes including metabolic, environmental and a various infectious agents.[5,8]

Movement disorders in the neonatal period are rather uncommon. When they occur, they are usually caused by brain injury,[9] drug withdrawal,[10] severe metabolic disorders[11] or are a benign condition only occurring during sleep.[12] Additionally, GAS infections are rather rare during the neonatal period and when they occur they usually cause invasive disease such as sepsis[13] or serious skin infections.[14] This report describes a neonate who presented with clinical and laboratory evidence of a non-invasive GAS infection that concomitantly developed a movement disorder. The movement disorder waned as the GAS antibody titers decreased suggesting a temporal relation between the two. This is the first description of a case of PANDAS during the neonatal period.

CASE REPORT

A 23-day-old boy presented to the neurology service after a one-week history of constant head turning that started abruptly and was increasing in severity over one week. Approximately 10 days prior to admission he developed a diffuse, erythematous maculopapular sandpaper type rash that started on his face and progressed to his lower body and then the inguinal area. Shortly after developing the rash, back-and-forth head turning, resembling nodding "no-no" developed. These movements occurred periodically at first,

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lasting several minutes in duration, but then progressively became almost constant, except for sleep, over a one-week period. The head movements were exacerbated by excitement and stimulation and only abated with sleep. Consciousness was preserved throughout the episodes and the child reacted to visual, auditory and tactile stimuli throughout the episodes. Initially, lateral eye deviation immediately preceded the head deviation in the same direction. The movements could not be suppressed by restraining the head and the movements inferred with breast-feeding, resulting in decreased oral intake. The child also started to have emesis with some of the feeds. As the movement worsened, the parents felt that the child had become sleepier and less active during the day. Although the patient had no upper respiratory tract or gastroenterological abnormalities, both parents had pharyngitis and an upper respiratory infection just prior to the appearance of the child's rash. The parents' symptoms started approximately one week after the birth of the child.

The patient was a full-term product of a normal gestation complicated by an upper respiratory infection in the second trimester. The child's mother suffered from Hashimoto's thyroiditis and received synthroid 88 mcg per day throughout the gestation. All prenatal laboratory values were normal, including group-B streptococcus. Normal spontaneous vaginal delivery was not prolonged or complicated and, at delivery, Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. There were no perinatal antibiotic given to the mother. Family history was unremarkable for neurological, developmental, psychiatric or genetic disease.

Initial examination demonstrated normal vital signs and growth parameters. General exam was unremarkable except for a mild erythematous, diffuse maculopapular rash over the left face and body which extended slightly below the waist but did not include the inguinal region.

Table 1. Laboratory Values Results.

Laboratory Test	***Value***
Infectious	
Leukocyte Count	$7.02x10^3$ / uL
Antistreptolysin O Antibody	1:400 (Normal < 1:200)
Anti-deoxyribonuclease-B Antibody	Positive [1:170 (Normal < 1:60)]
Anti-Neuronal Antibodies	Negative [14 (0-54 Normal)]
CSF Culture	No Growth
Blood Culture	No Growth
Urine Culture	No Growth
C-reactive protein	0.04 mg/dL
Total IgM	33 [Normal 5-30] mg/dL
Toxoplasmosis IgG & IgM	None Detected
Rubella IgG	Positive [76 IU/mL (>14 Positive)]
Cytomegalovirus IgM & IgG	None Detected
Urine Cytomegalovirus	Negative
Herpes Simplex Virus-I/II IgG	None Detected
Urine Analysis	Normal
Metabolic	
Serum amino acids	Essentially Normal
Plasma lactic acid	1.4 mmol/L
Plasma ammonia	60 mcg/dL
Urine organic Acids	Normal
Plasma pyruvate	0.06 mmol/L
Inflammatory	
Anti-nuclear antibodies	Not Detected
Rheumatoid factor	<12 IU/mL
Erythrocyte Sedimentation Rate	10 mm/hr
Systemic	
Electrolytes	Normal
Hematocrit	42.6
Platelet Count	364
Endocrine	
Thyroid Stimulating Hormone	1.76 uU/mL
Neurological	
Electroencephalogram	Normal in Sleeping and Awake State
Brain magnetic resonance imaging	Normal
Spine magnetic resonance imaging	Normal
Neoplastic	
Chest magnetic resonance imaging	Normal
Abdomen magnetic resonance imaging	Normal
Pelvis magnetic resonance imaging	Normal
Urine Homovanillic Acid	Normal
Urine Vanillylmandelic Acid	Normal

Neurological examination revealed prominent constant back and forth head movement that decreased in amplitude, but notably persistent, during sleep, and increased with stimulation and agitation. The child was slightly lethargic and cranky. The eyes were deviated to the right most of the time but crossed midline and moved to the left on occasion.

Volitional eye movements were conjugate and were not related to head movements. Vestibular-ocular reflex was intact. Little visual interest was observed, tracking was not observed, but visual threat response could be elicited. Pupils were equal, round and reactive to light. Tongue was midline but non-rhythmic thrusting of the tongue straight out of the mouth did occur at times. Face was symmetric, palate elevated easily and gag was present. Axial and appendicular tone was slightly decreased, head lag was apparent and head stability was poor. Moro, plantar and palmar grasps, suck, root, step and place reflexes were intact but slow. Deep tendon reflexes were brisk but no spread or clonus was appreciated.

A metabolic and infectious work-up was obtained as depicted in **Table 1**. A TORCH panel, which included cytomegalovirus IgG and IgM and toxoplasmosis IgG and IgM as well as herpes simplex virus titers, was unremarkable. Despite a comprehensive metabolic workup no specific inflammatory or metabolic cause could be found. However, the Antistreptolysin O (ASLO) Antibody and Anti-deoxyribonuclease-B Antibody were suspiciously elevated, outside the range of normal (see **Table 1**).

To examine the structure of the brain, a magnetic resonance imaging scan with sagittal T1, axial T2, axial Fluid Attenuated Inverse Recovery and axial T1-weighted images was obtained. No evidence of mass lesion, midline shift or infarction was found. Small bilateral posterior fossa subdural hematomas along the tentorium were noted, and a choroid plexus cyst was noted in the occipital horn of the left lateral ventricle. These were considered normal variants of the neonatal period. An magnetic resonance imaging scan of the entire spine, consisting of sagittal T1 and T2 weighted imaging and axial T1 and T2 weighted images in the lumbar region, demonstrated a spinal cord normal in contour and signal intensity with no mass lesion, syrinx or tethering. The conus tip ended normally at the L1 level.

To search for a paraneoplastic source, especially neuroblastoma, sagittal and coronal fast spin-echo inverse recovery, axial fast spin-echo T2 with fat saturation, coronal T1 and post-gadolinium axial T1 weighted fat saturation, of the chest, abdomen or pelvis regions were obtained, but no abnormalities were identified.

Over a one-week period, the frequency of head turning movements decreased and the rash substantially improved. Since the patient was feeding well, afebrile with stable vital signs, he was discharged on the 7th hospital day.

The patient was seen in the outpatient neurology clinic 6 weeks after discharge for follow-up. At follow-up the child's neurological and developmental examination was normal and he had no further neurological abnormalities or episodes of abnormal movements. The ASLO Antibody titer had normalized to 1:120 when measured during follow-up. The family was instructed to return to the clinic if the movement disorder reoccurred but did not up to two years following the original admission.

DISCUSSION

This report describes a 3 1/2 week old boy with a scarlatiniform rash and an abrupt onset involuntary movement of his head and eyes consistent with a movement disorder. The movements were not choreiform or dystonic, were involuntary and appeared to involved muscle groups in the eyes and neck, making this movement most likely a complex tic. The constant nature of the movements was somewhat unusual for a tic disorder but this is the best category of movement disorders to describe the movements. Although, in general, tics are commonly thought to not persist in sleep, studies on Tourette's syndrome suggests that tics persist in sleep in many patients.[15]

Table 2. Comparison of Symptoms of Neonatal Case to PANDAS Symptoms.

Characteristic	Neonatal Case
Remissions of neuropsychiatric symptoms	Yes
With Antibiotic Therapy	No Antibiotic Therapy
Dramatic onset of symptoms	Yes
Definite Remissions	Yes
Elevated streptococcal titers	Yes
Elevated Antistreptolysin O Antibody Titer	Yes
Episodes of fever and/or sore throat at onset and/or flare up	No
Positive GAS throat culture with onset and/or flare-up of symptoms	No Throat Culture Done
Clumsiness	Not Applicable

In **Table 2** we compare the characteristics of PANDAS that have been carefully studied[16] to the case of the neonate described within. Many of the symptoms characteristics of PANDAS were consistent with the case reported in the article including the specific elevation of the ASLO antibody titer. Some characteristics could not be directly compared.

For example, antibiotics were not given and clumsiness cannot be well judged in a neonate. Although there was not a fever or sore throat with the onset of PANDAS symptoms, the neonate did have a scarlatiniform rash, which is another sign of a GAS infection. In the case described, the PANDAS symptoms resolved without treatment with antibiotics or immunomodulation agents. Currently there is only limited evidence to support the use of antibiotics during PANDAS symptoms due to the fact that the many studies were non-blinded[17] and that the results of double-blind placebo-controlled studies are inconsistent.[18] In addition, recurrent or chronic antibiotic use can result in the development of resistant microbes that could have long-term health consequences. Thus, antibiotics may be useful as a prophylactic agent in some cases, but the particular cases need to be considered carefully.[18]

Dysfunction basal ganglia circuit function is the most likely cause of this movement disorder. The neonate did not manifest a tremor, nystagmus or dysmetria, making dysfunction of the cerebellar circuitry less likely and further supporting the notion that this movement was best described as a complex tic. In addition, the movements were unlike that of spasmus nutans since spasmus nutans presents later in infancy and does not have a correspondence between eye and neck movements.

The positive ASLO Antibody titer and scarlatiniform rash suggest an acute GAS infection, presumably transmitted from the parents as they had symptoms of GAS pharyngitis prior to the development of the boy's symptoms. With the evidence of a GAS infection and an abrupt onset tic disorder, a diagnosis of PANDAS is most likely. A comprehensive investigation of other important disorders associated with movement disorders in the neonatal period was negative, supporting the diagnosis of PANDAS.

Most cases of PANDAS start in childhood, when GAS infections are most common and PANDAS has not been described in infancy. Thus, this is the first description of a neonate with PANDAS. Although PANDAS is usually a recurring process, this complex tics did not appear to have recurred in this child. This could be due to the immaturity of the neonatal immune system. It is always best to demonstrate an increase in ASLO antibodies with onset of symptoms when diagnosing PANDAS, but baseline ASLO antibodies were not available. Alternatively, a demonstration of a decrease in ALSO antibody titers with resolution of symptoms can also be used to demonstrate the involvement of the immune system and symptoms. Although it is possible that the ALSO antibodies were maternal and transferred across the placenta, the lack of GAS symptoms of infection in the mother prior to the child's birth and the onset of the child's symptoms over a week following birth and the associated rash suggest that the ASLO antibodies were indeed primarily produced by the neonate.

As GAS infections are unusual in the neonatal and infancy period, the incidence of PANDAS during this period is probably uncommon, although the lack of motor and cognitive development in the neonatal period and infancy may make the detection of abnormal neurodevelopmental symptoms difficult unless severe. Having a high index-of-suspicion for GAS or other metabolic, immune or environmental triggers during times of abrupt change in behavior or cognition in early life may increase the number of recognized cases of PANS and/or PANDAS early in life.

CONFLICT OF INTEREST

The author declares no conflict of interests.

ETHICAL APPROVAL

This work meets all the ethical guidelines.

REFERENCES

1. Rossignol DA, Frye RE. A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures. Mol Psychiatry. 2012;17:389-401.
2. Swedo SE, Leonard HL, Mittleman BB, et al. Identification of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections by a marker associated with rheumatic fever. Am J Psychiatry. 1997;154:110-112.
3. Chmelik E, Awadallah N, Hadi FS, Quinn K, Franco K. Varied presentation of PANDAS: a case series. Clin Pediatr. 2004;43:379-382.
4. 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;113:883-886.
5. Chang K, Frankovich J, Cooperstock M, et al. Clinical Evaluation of Youth with Pediatric Acute Onset Neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference. J Child Adolesc Psychopharmacol. 2015;25:3-13.
6. Cox CJ, Sharma M, Leckman JF, et al. Brain human monoclonal autoantibody from sydenham chorea targets dopaminergic neurons in transgenic mice and signals dopamine D2 receptor: implications in human disease. J Immunol. 2013;191:5524-5541.
7. Lotan D, Benhar I, Alvarez K, et al. Behavioral and neural effects of intra-striatal infusion of anti-streptococcal antibodies in rats. Brain Behav Immun. 2014;38:249-262.
8. Swedo SE, Leckman JF, Rose NR. From Research Subgroup to Clinical Syndrome: Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). Pediatrics & Therapeutics. 2012;2:113.
9. Rose J, Vassar R. Movement disorders due to bilirubin toxicity. Semin Fetal Neonatal Med. 2015;20:20-25.
10. O'Brien C, Hunt R, Jeffery HE. Measurement of movement is an objective method to assist in assessment of opiate withdrawal in newborns. Arch Dis Child Fetal Neonatal Ed. 2004;89:F305-309.
11. Kayser MA. Inherited metabolic diseases in neurodevelopmental and neurobehavioral disorders. Semin Pediatr Neurol. 2008;15:127-131.
12. Suzuki Y, Toshikawa H, Kimizu T, et al. Benign neonatal sleep myoclonus: Our experience of 15 Japanese cases. Brain Dev. 2015;37:71-75.
13. Huber BM. Cellulitis-adenitis in a neonate with group a streptococcal sepsis. Klin Padiatr. 2014;226:82-83.
14. Larru B, Gerber JS. Cutaneous bacterial infections caused by Staphylococcus aureus and Streptococcus pyogenes in infants and children. Pediatr Clin North Am. 2014;61:457-478.
15. Cohrs S, Rasch T, Altmeyer S, et al. Decreased sleep quality and increased sleep related movements in patients with Tourette's syndrome. J Neurol Neurosurg Psychiatry. 2001;70:192-197.
16. Murphy TK, Storch EA, Lewin AB, Edge PJ, Goodman WK. Clinical Factors Associated with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections. J Pediatr. 2012;160:314-319.
17. 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;113:883-886.
18. Williams KA, Swedo SE. Post-infectious autoimmune disorders: Sydenham's chorea, PANDAS and beyond. Brain Res. 2014; in press.