

Acute Myoclonus Secondary to Group A β -Hemolytic Streptococcus Infection: A PANDAS Variant

The acute onset of obsessive-compulsive behavior or tic has been associated with group A β -hemolytic streptococcus infection, or pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, known by the acronym PANDAS.¹ The postulated etiology of this disorder is similar to that proposed for Sydenham's chorea, in which an autoimmune process is triggered in response to group A β -hemolytic streptococcal infections. In PANDAS, the result is the development of behaviors characteristic of obsessive-compulsive disorder or tic, as in Tourette syndrome. This disorder appears to respond to immunomodulation, and repeated streptococcal infections may explain the occasional transient worsening of these illnesses in susceptible individuals.¹ Although it is not likely to be an explanation as an etiology for all individuals with these disorders, there does seem to be a population characterized by a sensitivity to streptococcal infections.

We report three children with the acute onset of generalized and segmental myoclonus associated with recent streptococcal infection indicated by elevation of antistreptococcal antibodies. We believe these children may represent a postinfectious variant of the PANDAS syndrome.

Case Reports

Case 1. C.E. is a 5-year-old, right-hand-dominant boy who presented to his pediatrician with a chief complaint of acute onset of abnormal movements. The movements were characterized by brief, lightning-like jerks of the upper extremities and trunk upon initiation of movements, and disappearing during sleep. His symptoms had started several days prior to presentation, and his mother reported no other complaints. There were no associated systemic symptoms. The family history was noncontributory. No previous upper respiratory tract symptoms or pharyngitis were noted. The examiner noted no obvious pre- or postictal abnormalities, and the patient appeared to be in no distress. General medical examination was normal. Neurologic examination was notable for the presence of multiple, rapid, myoclonic jerks involving the trunk, neck, and both upper extremities. Work-up was initiated with results as noted (Table 1). Treatment for streptococcal pharyngitis was begun with oral penicillin and cardiology evaluation was requested. Despite treatment, ASO/anti-DNAase titers were persistently positive 1 month later. However, the myoclonic activity had diminished significantly on follow-up examination, with complete resolution within several weeks of this visit.

Approximately 2 months after initial treatment, the patient had a recurrence of symptomatic streptococcal pharyngitis, associated with sore throat, fever, and mild rhinorrhea. These symptoms were again associated with the acute onset of myoclonus, identical in nature to his previous episode. His abnormal movements resolved after therapy with intramuscular penicillin, with continued complete resolution of myoclonus since.

Case 2. The patient is a 12-year-old, right-hand-dominant African-American boy with a chief complaint of acute onset of "belly twitching" feeling like a "heart beat." His symptoms started several months prior to referral to the neurology clinic. The patient was otherwise healthy, without preceding illness or history of movement disorder. Family history was unremarkable. General medical examination was normal. Neurologic examination was normal except for rhythmic, synchronous, bilateral abdominal musculature contractions, which were rapid and associated with bilateral latissimus dorsi muscle contracture. The remainder of the examination was normal. Fluoroscopic evaluation of the patient's diaphragm prior to referral was normal except for evidence of abdominal musculature movements. Laboratory, radiographic, and neurophysiologic data are shown (Table 1). Treatment with appropriate antistreptococcal antibiotic was initiated, without resolution of movements. Conventional treatment for myoclonus was also unsuccessful. To date, the patient continues to demonstrate abnormal abdominal movements.

Case 3. The patient is a 10-year-old, right-hand-dominant white boy seen in the neurology clinic for a complaint of "whole body jerks." The patient reported symptoms starting approximately 2 months prior to his visit, and occurring with variable frequency, initially two or three times per day, and at their peak, up to 50 times per hour. These movements continued for approximately 2 months prior to his referral to the neurology clinic. At the time of his neurology referral, the movements were occurring 15 to 20 times per day. The patient was described as more aggressive and hyperactive by his mother during the period that he manifested movements. The patient's medical history was otherwise unremarkable, there were no preceding illnesses, and the family history was noncontributory.

The general medical examination was normal; the neurologic examination was normal except for myoclonic jerks characterized by rapid, symmetric flexion of the patient's trunk and upper extremities. Laboratory, radiographic, and neurophysiologic results are shown (Table 1). The patient was treated empirically with erythromycin for a 10-day course, with complete resolution within 2 weeks of the treatment course. He remains asymptomatic at this time, and by parental report his behavioral difficulties also have resolved.

Discussion

At present, there are multiple examples of infectious causes for acute onset of behavioral abnormalities, as well as movement disorders.¹⁻⁵ Classically, this is manifest by the prototypic postinfectious

Table 1. Laboratory and Radiographic Test Results

Test	Normal Value	Case 1	Case 2	Case 3
Antistreptolysin-O (ASO) titer	(< 170 dilutions)	> 1360	1:340	1:340
Anti-DNAase B titer	(< 170 dilutions)	> 1360	1:480	1:170
Throat culture		Positive	Negative	Negative
White blood cell count	(5-14.5 th/cumm)	9.5	7.9	8.0
Erythrocyte sedimentation rate	(0-15 mm/hr)	20	12	NT
Cross-reacting protein	(0.0-0.8 mg/dL)	< 0.1	NT	< 0.1
Antinuclear antibody titer	(negative)	Negative	1:80	Negative
Lyme enzyme immunoassay	(0.00-1.10)		0.70	NT
Free T ₄	(0.89-1.80 ng/dL)	0.94	NT	1.15
Thyroid-stimulating hormone	(0.35-5.50 μ IU/mL)	0.79	NT	2.06
Ceruloplasmin	(18-45 mg/dL)	53.5	43.2	NT
Copper	(590-1180 μ g/L)	1740	NT	1273
Cerebrospinal fluid protein	(< 40 mg/dL)	12	NT	NT
Magnetic resonance imaging		Normal	Normal	Normal
Electroencephalogram		Normal	Normal	Normal

tious movement disorder, Sydenham's chorea. Recently, however, obsessive-compulsive disorder has been associated with transient increases in antistreptolysin titers in children.^{2,4,6,7} These patients have presented with a variety of symptoms, including adventitious movements (tic, choreiform movements) and severe obsessive manifestations. Not only do these children demonstrate evidence of an invasive streptococcal infection, but additionally, it has been demonstrated in these cases that there are elevated levels of antineuronal antibodies specific for epitopes within the basal ganglia.^{4,6} Radiographic evidence of abnormalities within these areas also have been demonstrated both in patients with Sydenham's chorea and PANDAS.^{2,8} Husby et al initially described the presence of these antibodies in a population of Egyptian children particularly prone to Sydenham's chorea.⁹ Present in a large majority of children with a history of Sydenham's chorea, these antibodies became more prevalent in children who were repeatedly exposed to recurrent streptococcal infections. The antibody was not demonstrable in other patients with myriad neurologic diseases, and antibody binding was prevented by absorption with streptococcal antigen. Both characteristics indicated to the authors that the antibody itself was specific for a process caused by streptococcus. Although this was initially demonstrated in Sydenham's chorea, a known rheumatic complication, the presence of elevated antineuronal antibodies in the subset of children with obsessive-compulsive disorder may indicate that they also mediate a similar process causing neuropsychiatric symptoms in PANDAS. That the symptoms are in fact associated with the elevation of antibody titers has been further substantiated by the apparent response to immunomodulation in these patients. Several have had apparent dramatic responses to the administration of immunoglobulin or plasmapheresis.¹ To our knowledge, there have been no reports of the acute onset of myoclonus, whether generalized or segmental, associated with streptococcal infections, though other infectious precipitants have been related to the onset of myoclonus, such as the herpes zoster and coxsackie viruses.³ Individuals have been reported with the acute onset of myoclonus after nonspecific upper respiratory infection, and even suspected group A β -hemolytic streptococcal infections.³ These individuals may have represented previous unrecognized occurrences of antibody mediated movement disorder.

Our patients demonstrated the acute onset of symptoms, without obvious infectious precipitants, but with moderately to remarkably elevated serum titers to antistreptococcal antibodies. There were no other indicators of obvious central nervous system abnormalities that could have served as an explanation for the acute onset of the movement disorder and rapid resolution in two patients.

That two patients had transient symptoms also seems to indicate a possible infectious process, with symptoms that resolved once active production of antibody was diminished. A mechanism for this process could involve antibody production that, similar to Sydenham's chorea, affects areas in the central nervous system. Antibody mediated dysfunction of areas previously associated with the pathologic appearance of myoclonus potentially may provide a target for the antineuronal antibodies. Although originating from throughout the central and peripheral nervous system, one area implicated in the development of myoclonus is the nucleus gigantocellularis,

located in the caudal medulla.^{10,11} Interestingly, Husby et al's initial description of antineuronal antibodies included a significant amount of antibody binding against medullary extracts as well as the basal ganglia. This may imply that neuronal injury similar to that postulated for PANDAS could occur in this region, with the resultant injury causing myoclonus. Case 2 demonstrated segmental myoclonus, and if indeed secondary to recent streptococcal infection, this would imply that the antibody directed effect could affect multiple remote areas within the central nervous system. This would include the spinal cord, which has been noted to be involved in other cases of segmental myoclonus with infectious precipitants.⁵ Given the multiple sites within the central nervous system that have been implicated in the onset of various types of myoclonus, the etiology in these cases could likewise be expected to be heterogeneous.

Another possible etiology is that these children have a predisposition to movement disorder, which itself becomes manifest after a triggering exposure to antineuronal antibodies. The familial occurrence of Sydenham's chorea provides precedence for this, and a trait marker has been associated with both Sydenham's chorea and PANDAS: the D8/17 B-lymphocyte antigen.^{7,12} The presence of this trait marker, coupled with antineuronal antibody production, could lead to the acute onset of movement or neuropsychiatric abnormalities. This genetic predisposition may explain the relatively rare occurrence of these syndromes associated with the much more common streptococcal infection. This marker has not been determined in our patients to date, but potentially this or a similar marker could serve as an identifier for these children with myoclonic manifestations.

It is possible that these children developed myoclonus independent of a preceding streptococcal infection. Elevation of anti-DNAase B and ASO titers may occur in various disease states, and may be increased in a relatively high proportion of the normal population.¹³ This may indicate previous infection or other pathology causing incidental elevation of the antistreptococcal antibodies, and may not be related to the onset of neurologic symptoms. Case 1 had a positive throat culture, and both Case 1 and Case 3 seemingly responded to antibiotic treatment, which more closely links their symptoms to a streptococcal precipitant. If this process follows the Sydenham's model, previous exposures may have sensitized the patients, with the recent infection causing a reappearance of antibody and the onset of movement disorder. This would be consistent with Husby et al's population, in which antineuronal antibody positivity was more pronounced after repeated episodes of streptococcal infection and resultant chorea. It remains to be seen whether these patients represent a subset of patients sensitive to the development of antineuronal antibodies or are instead incidental occurrences of myoclonus.

Currently, there is no uniform recommendation for treatment of patients with suspected PANDAS. In a small number of patients, therapies such as plasmapheresis and intravenous immunoglobulin have been shown to be effective in ameliorating recalcitrant symptoms. However, the potential risks of such therapies would be an important factor in determining their use, given that no large clinical data support such an approach. When considering the severity of symptoms suffered by some children, treatment of inciting infectious precipitants of myoclonus or neurobehavioral symptoms associated with PANDAS would seem to be appropri-

ate in those children who clearly have symptoms related to concurrent infections. The relative safety of a brief course of antibiotics and oral corticosteroids has been established in the practice of pediatric medicine, and in two of our three patients, antibiotic therapy seemed to lead to resolution of symptoms. However, chronic antibiotic prophylaxis has to date not been shown to prevent exacerbations of obsessive-compulsive disorder, although it ultimately may become a standard treatment for the subset of children prone to development of recurrent symptoms. Our current practice is to determine the presence of antistreptococcal antibodies in our patients with acute onset myoclonus or tic, as well as in patients with a history of Tourette syndrome. In those patients with elevated levels of antibodies or a positive throat culture, we consider using antibiotics for therapy (oral or intramuscular penicillin) after obtaining consent from the parents regarding the use of this therapy in this novel situation. We also have used prednisone, 1–2 mg/kg/day in a short burst with a noted diminution of tic in Tourette syndrome, with minimal side effects (unpublished data). To date, we have not used more aggressive therapy in our patients, and are awaiting more definitive results from ongoing studies.

In conclusion, PANDAS likely represents a newly recognized group of neuropsychiatric illnesses resulting from streptococcal infection and the concurrent development of antineuronal antibodies. We believe that our three patients represent a variant of this disorder, manifest by acute myoclonus and correlated with an elevation of antistreptococcal antibody. Two of our patients also had a temporally related response to antistreptococcal medications, with recrudescence of symptoms with recurrent infection in one. This may imply a process similar to that proposed for Sydenham's chorea, and warrants further investigation. A determination of antineuronal antibodies is indicated, as this would more conclusively identify these children with those already classified as having PANDAS. The recently described B-lymphocyte antigen D8/17 also may serve as a potential marker in those children with a genetic propensity for poststreptococcal movement disorder. Because of this possible association, new onset myoclonus warrants an investigation for streptococcal precipitants, and therapy directed toward an underlying streptococcal etiology may be effective or curative.

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A Large Lateral Parapharyngeal Heterotopic Brain Tissue Extending Into the Intracranial Area

Heterotopic brain tissue in the parapharyngeal space is an extremely rare condition that can result in respiratory distress and feeding difficulty shortly after birth.¹ The origin of the condition remains obscure. To our knowledge, only one case of heterotopic brain tissue in both the extracranial and intracranial regions has been reported.²

We here report a female newborn presenting with breathing difficulty and a large lateral mass in the left side of the neck. A computed tomographic (CT) scan revealed a large mass extending into the middle cranial fossa. Histologic findings confirmed a diagnosis of heterotopic brain tissue. We also discuss the pathogenesis.

Case Report

A 2040-gram girl was born by emergency cesarean section, necessitated by frequent deceleration of the fetal heart rate, at the 35th week of gestation. Her length and head circumference were 45 cm and 33 cm, respectively. The Apgar scores were 3 and 7 after 1 and 5 minutes, respectively, but the infant underwent an endotracheal intubation because of breathing difficulty. A large lateral cervicofacial mass involving the parotid region was noted on the left side. She was transferred to the neonatal intensive care unit of Kanazawa Medical University Hospital for further evaluation.

Both a CT scan and magnetic resonance imaging (MRI) demonstrated that a large cystic mass occupied the left parapharyngeal, oropharyngeal, soft palate, and infratemporal cranial space and extended into the middle cranial fossa through the defect of the base of the skull (Figure 1A, B, and C). The left temporal lobe was compressed by the tissue, but no connection between the mass and the central nervous system was identified (Figure 1D). The rest of the physical and neurologic examinations were normal.

Histologic findings of the mass specimen from the neck revealed a mature brain tissue suspected of being either teratoma or heterotopic brain tissue. Complete surgical excision of the mass was attempted. Removal of