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Restless Legs Syndrome as an Atypical Case of PANDAS?

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Abstract

Background: Restless legs syndrome, also known as Willis-Ekbom disease or Wittmaack-Ekbom syndrome, is a neurological disorder characterized by an irresistible urge to move the body to stop uncomfortable or odd sensations. Moving the affected body part modulates the sensations, providing temporary relief. PANDAS is an acronym for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections, a hypothetical subset of conditions in which children are thought to exhibit an extremely abrupt onset of obsessive-compulsive disorder and/or tic disorders symptoms following Group A Beta-Hemolytic Streptococcal (GABHS) infections, with a relapsing-remitting (not waxing-waning) course. Our data highlight the close clinical similarity between Restless Legs Syndrome and PANDAS; in our opinion these two disorders may be distinguishable using laboratory test with the aim of identifying the etiologic agents of PANDAS. This case report presentation could be useful for the pediatrician that may chance upon a similar case.

Case Presentation: Our objective is to describe clinical features of an atypical presentation of PANDAS in an Italian boy presenting restless leg syndrome. A 7 year-old boy that suffered for about one year from intense itching, forcing him to make continuous movements and stereotyped patterns of rotation of the limbs in order to find relief. The patient undergone in another hospital routine and specific laboratory data, including anti-streptolysin O titer. In addition he was investigated with neurologic and cardiologic assessment with EEG, SEP, MEP, polysomnography and medullary MRI, cardiologic examination, ECG and echocardiography: these were all normal. Blood tests showed only mild hypereosinophilia, elevated Antistreptolysin O antibody titers (ASO 329IU/ml) and low iron levels. He was discharged with the diagnosis of "Restless Legs Syndrome" (RLS) and began therapy with gabapentin 100mg twice daily and iron, without benefit. Suspecting movement disorders associated with GABHS infection, we started, after previous ineffective therapy, administration of benzyl penicillin every 20 days, until the next follow-up. After three months of follow-up the boy's disorders had disappeared and the ASO titer was stable. The boy was in good clinical condition and no other movement disorders had appeared.

Conclusions: Our data confirm that patients with suspected restless leg syndrome could present PANDAS.

Keywords: Group-A beta hemolytic streptococcal infection; PANDAS; Obsessive-compulsive symptoms; Autoimmunity; Restless legs syndrome

Background

Restless Legs Syndrome (RLS), also known as Willis-Ekbom Disease (WED) or Wittmaack-Ekbom syndrome is a neurological disorder characterized by an irresistible urge to move the body to stop uncomfortable or odd sensations. It most commonly affects the legs, but can affect the arms, torso, head, and even phantom limbs. Moving the affected body part modulates the sensations, providing temporary relief.

RLS sensations range from pain or an aching in the muscles, to "an itch you can't scratch", an unpleasant "tickle that won't stop", or even a "crawling" feeling. The sensations typically begin or intensify during quiet wakefulness, such as when relaxing, reading, studying, or trying to sleep. Additionally, most individuals with RLS suffer from periodic limb movement disorder (limbs jerking during sleep), which is an objective physiologic marker of the disorder and is associated with sleep disruption.

RLS can be caused by low iron levels. Treatment is often with levodopa or a dopamine agonist such as pramipexole. Some controversy surrounds the marketing of drug treatments for RLS. It is a "spectrum" disease, with some people experiencing only a minor annoyance and others suffering major sleep disruption and impaired quality of life.

PANDAS is an acronym for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections, a hypothetical subset of conditions in which children are thought to exhibit an extremely abrupt onset of Obsessive-Compulsive

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Table 1: Diagnostic criteria for PANDAS.

1	Presence of Obsessive-Compulsive Disorder (OCD) and/or tic disorder.
2	Pediatric onset of symptoms (age 3 years to puberty).
3	Acute onset and episodic course (relapsing-remitting, not waxing-waning).
4	Association with neurological abnormalities (chorei form movements).
5	Temporal relationship between symptom exacerbations and GABHS infections.

Disorder (OCD) and/or tic disorders symptoms following Group A Beta-Hemolytic Streptococcal (GABHS) infections, with a relapsing-remitting (not waxing-waning) course [1]. The proposed link between the infection and these disorders is that an initial autoimmune reaction to a GABHS infection produces antibodies that continue to interfere with basal ganglia function, causing symptom exacerbation [2,3]. The PANDAS hypothesis was based on observations in clinical case studies at the US National Institute of Health and in subsequent clinical trials where children appeared to have dramatic and sudden OCD exacerbations and tic disorders following infection [4]. There is supportive evidence for the link between streptococcal infection and onset in some cases of OCD and tics, but proof of causality has remained elusive [5-7]. The PANDAS hypothesis is controversial; whether it is a distinct entity differing from other cases of Tourette Syndrome (TS)/OCD is debated [3,8-11]. It has not been validated as a disease entity [4] and is not listed as a diagnosis in the International Statistical Classification of Diseases and Related Health Problems (ICD) or the Diagnostic and Statistical Manual of Mental Disorders (DSM).

Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) was proposed in 2012 to describe another subset of acute-onset OCD cases including "not only disorders potentially associated with a preceding infection, but also acute-onset neuropsychiatric disorders without an apparent environmental precipitant or immune dysfunction" [12].

We report on a boy in whom restless leg syndrome was an atypical presentation of PANDAS.

Case Presentation

A 7 year-old boy came to our attention through a pediatric allergologic visit because for about a year he had suffered from intense itching localized predominantly in the feet and ankles, mainly occurring while falling asleep but that was still present throughout the day, forcing him to make continuous movements and stereotyped patterns of rotation of the limbs in order to find relief. His family history was unremarkable. Before coming to our attention, he had undergone cardiologic assessments (cardiologic examination, electrocardiogram test and echocardiography) and neurologic evaluations electroencephalogram, somatosensory evoked potential, motor evoked potentials, polysomnography and medullary magnetic resonance imaging) in another hospital: these were all normal. Blood tests showed only mild hypereosinophilia, elevated Antistreptolysin O antibody (ASO) titers (ASO 329IU/ml) and low iron levels. He was discharged with the diagnosis of "Restless Legs Syndrome" (RLS) and began therapy with gabapentin 100mg twice daily and iron, without benefit.

During our first check-up, the boy described his problem not as itchy but as a "deep discomfort" that compels him to move not only his ankles but also his wrists, with continuous nocturnal awakenings. Physical examination and skin prick tests were negative. Suspecting movement disorders associated with GABHS infection, we decide to repeat the blood tests, particularly ASO (525IU/ml) and neuronal antibodies (normal levels), and to prescribe azithromycin, first daily for 5 days, then weekly for 8 weeks. There was a clear improvement in symptoms during the first month of therapy, and then a new exacerbation. Blood tests showed an increase in ASO titer (678IU/ml) and physical examination showed hyperemia of the pharynx that was not present at the first examination. At this point we decide to change the therapeutic approach and started administration of benzyl penicillin every 20 days, until the next follow-up. After three months of follow-up the boy's disorders had disappeared and the ASO titer was stable. The boy was in good clinical condition and no other movement disorders had appeared.

Table 2: International Restless Legs Syndrome Study Group consensus diagnostic criteria for restless legs syndrome.

1	An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
2	The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3	The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4	The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
5	The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps etc.).

Discussion

The term PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections) describes a subset of pediatric conditions characterized by Obsessive-Compulsive Disorder (OCD) and/or tic disorders, in which symptoms worsen following a streptococcal infection such as "strep throat" and scarlet fever (NIH). They appear to be neurobiological disorders that potentially complicate GABHS infections in genetically susceptible individuals [13]. There has been extensive debate about whether or not PANDAS actually exist. Sufferers usually have a dramatic, "overnight" onset of signs and symptoms that include motor or vocal tics, obsessions and/or compulsions and remission of neuropsychiatric symptoms during antibiotic therapy [14]. This definition was formalized in 1998 by Swedo [15] and collaborators in a set of five criteria, of which the core feature was the association between newly diagnosed infections and tics and obsessive-compulsive symptoms (Table 1). While in Sydenham's chorea (SC), the prototypical post-streptococcal neuropsychiatric disorder, anti-dopamine receptor antibodies might be relevant, in PANDAS this association is not found and the pathophysiological mechanism remains undefined [16]. Unlike SC, in PANDAS the latency between GABHS infection and neuropsychiatric onset seems shorter and so the immune-mediated mechanism probably differs partly from the mechanism of SC. The remission of symptoms during antibiotic therapy (generally with penicillin and azithromycin) is more frequent in PANDAS than in other acute obsessive-compulsive symptoms and tics. Over the years the need for a reappraisal of the definition of PANDAS has become evident, given the difficulties in consistently

and reliably applying their diagnostic criteria in routine clinical practice [16]. For example, the main issue is differentiating a true "inciting" GABHS infection, whether clinical or subclinical, from GABHS carrier states [14]. In addition, streptococcal infections are common in childhood and could be just a trigger for the exacerbation of tics and obsessive-compulsive disorder.

Restless Legs Syndrome (RLS), also known as Willis-Ekbom disease, is a common pediatric neurologic condition affecting 2-4% of school-aged children and adolescents [17]. It is characterized by throbbing, pulling, creeping or other unpleasant sensations in the legs and an uncontrollable urge to move them. The pediatric diagnostic criteria were published in 2003, based on the consensus of experts at a National Institutes of Health workshop. The weakness of these criteria is their complexity. They differ from the diagnostic criteria for RLS in adults (Table 2), even if it is unlikely that the basic underlying pathophysiology is different at different ages. The severity of RLS symptoms ranges from mild to intolerable. Symptoms can come and go; they are generally worse in the evening and at night and less severe in the morning, and may cause severe nightly sleep disruption with impaired quality of life. In most cases, the cause of RLS in unknown. However, it may have a genetic component and is probably related to a dysfunction in the brain's basal ganglia dopamine pathways.

In adults, RLS is often associated with iron deficiency, pregnancy, chronic renal failure [18,19] and cardiovascular disease [20,21]. Iron deficiency and renal failure are also potential aggravating factors for pediatric RLS [22]. This may be misdiagnosed as growing pains, a common, benign condition in childhood characterized by intermittent bilateral leg pain occurring in the late afternoon or evening; the presence or absence of a need to move, which worsens with rest, is an important differential criteria. With respect to the official diagnostic criteria for restless legs syndrome (Table 2), in children there are some differences. For example, sore leg muscles generally get worse with movement, not better, and, although pain is not a usual description for RLS, children usually use the word "pain" or "hurts/hurting", therefore language and cognitive development determine the applicability of the RLS diagnostic criteria.

Conclusion

To diagnose PANDAS, the proposed criteria must be fulfilled. Evidence of GABHS infection includes a positive throat culture for GABHS or elevated or increasing antibody titers (ASO, antiDNAse B) demonstrating a recent GABHS infection. In our case, the throat culture was negative but ASO titers were very high. Furthermore, the boy started to experience restless legs syndrome - probably triggered by a recent streptococcal infection, as evidenced by the high ASO titers. The persistence of the elevated ASO titers can probably be explained by the long duration of the infection and the misdiagnosis on its onset. Intact, our patient did not respond to the standard drugs for RLS, but his symptoms disappeared with antibiotic therapy.

This case highlights the importance of differential diagnosis in patients with streptococcal infection and neurological symptoms.

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