Editorial

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PANDAS - Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection - is it a specific clinical disorder?

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"There are a terrible lot of lies going around the world, and the worst of it is half of them are true."
Sir Winston Churchill British politician (1874 - 1965)

In 1998, Swedo and colleagues[1] proposed the existence of a subset of children with tic disorders and/or obsessive compulsive disorder (OCD) who have the abrupt onset/exacerbation of symptoms that are temporally associated with a streptococcal infection. Labeled pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (acronym PANDAS), diagnostic criteria include: the presence of OCD and/or tic disorder; prepubertal age at onset; sudden, "explosive" onset of symptoms and/or a course of sudden exacerbations and remissions; a temporal relationship between symptoms and Group A â-hemolytic streptococcal infection (GABHS); and the presence of neurological abnormalities, including hyperactivity and choreiform movements. In subsequent reports, proponents have clarified several requirements.[2] For example, diagnosis necessitates at least two exacerbations of neuropsychiatric symptoms with distinct intervening periods of remission – during which throat cultures and anti-streptococcal antibody titers are negative. Explosive tic exacerbations are defined as the simultaneous appearance of several different motor and phonic tics with an intensity that causes parents to seek immediate medical attention. These acute recurrences must begin simultaneously with a positive throat culture or within 7 to 14 days after the infection. Lastly, choreiform movements are described as fine piano-playing finger movements. The existence of this entity remains controversial, however, with advocates and opponents taking firm positions on either side of the clinical issue.[2-5]

Evidence interpreted to support the existence of PANDAS stems from clinical, radiographic, and laboratory studies. Additional cohorts have been reported indicating that criteria can define cohorts of patients with common characteristics and a predictable course. Unfortunately, in this author's opinion, the proposed diagnostic rigor is not achieved in most publications. Higher rates of tic disorders and OCD in first degree relatives of children with PANDAS are often cited as evidence for the presence of an environmental trigger in a genetically vulnerable population. It is possible, however, that the proband will develop tics even without any preceding infection. Magnetic resonance volumetric analyses in children with PANDAS have shown a larger average size of the caudate, putamen, and globus pallidus, but a variety of regional differences also occur in children and adults with classical Tourette syndrome (TS). A trait marker for susceptibility in rheumatic fever, the monoclonal antibody D8/17, has been shown to have an expanded expression in individuals with PANDAS. Unfortunately, the reproducibility and accuracy of assay systems have been questioned and the test remains a research tool. Lastly, despite claims of a clinical analogy to rheumatic fever, an association between GABHS and PANDAS has not yet

been supported by formal epidemiologic studies or by prevention with penicillin. Moreover, several recently published longitudinal studies have failed to show that children are more likely to have tic exacerbations associated with streptococcal infections.

This investigator also believes that legitimate concerns and inconsistencies remain in five required PANDAS diagnostic criteria. *Tic or OCD diagnosis*: If PANDAS were truly similar to Sydenham's chorea (SC), then the majority of affected patients would be free of neuropsychogical issues before the initial "inciting" GABHS infection. In contrast, most children diagnosed with PANDAS have preexisting tic or OC symptoms before any acute exacerbation. Is it appropriate to limit clinical symptoms to tics and OCD or should, as others have suggested, then also include other movement and behavioral disorders? In turn, if everything is permissible, is PANDAS a truly definable entity? *Prepubertal onset:* Limiting PANDAS to a prepubertal disorder is understandable, but this age restriction merely puts it into the most common time period for the onset of tic disorders. Do adults reported with PANDAS-like symptoms have a subtype of this syndrome or a different disorder? *Explosive exacerbations:* Although the operational definition of a PANDAS exacerbation has been improved, abrupt fulminant changes are not uncommon in non-PANDAS tic patients. Additionally a variety of external factors, such as stress, anxiety, fatigue, viral infections, temperature, and medication usage, all dramatically affect tic severity. *Temporal association between tic/OCD onset and a GABHS infection:* Both tics and GABHS are common in children and there is a distinct possibility of overlap merely by chance. The permissible latent period between GABHS and the first acute exacerbation of symptoms remains ill-defined. In SC, the frequently cited model for PANDAS, chorea typically appears 3 to 5 months after the streptococcal infection, at a time when microbiologic and serologic evidence of a streptococcal infection are often absent. Thus by analogy, it could be possible to have the abrupt onset of tics in PANDAS without clear confirmation of infection. Physicians diagnosing PANDAS must recognize that its founders have established strict criteria for confirming an association between symptoms and GABHS, i.e., rising titers/positive throat culture with symptom exacerbation and falling titers/negative throat culture with symptom remission times two. Diagnoses made without appropriate longitudinal laboratory data should not be permitted and all asymptomatic streptococcal carriers and patients with persistently elevated antistreptococcal titers should be excluded. *Presence of neurological abnormalities:* This criterion requires the co-occurrence of tics, hyperactivity, or choreiform movements during exacerbations. The proposed definition of "choreiform" does not conform to standard terminology.

In summary, this author believes that the proposed poststreptococcal autoimmune disorder PANDAS deserves careful study, but, to date, its validity remains unproven. Although the focus of this editorial was on issues relating to clinical criteria, significant controversies also exist concerning its hypothesized immune-mediated mechanism. For clinicians considering making this diagnosis, I would suggest strict adherence to the formal published criteria, recognition that the diagnosis requires longitudinal assessments, realization that a single measurement of antistreptococcal antibodies has limited value, and that treatment with prophylactic antibiotics or immunomodulatory therapies is controversial and accompanied by potentially serious side-effects. Until further clarification is available, I suggest that therapy should continue to focus on standard approaches to control tic and OCD symptoms. Along with the scientific community, we eagerly await the result of longitudinal case-controlled studies now in progress.

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