Editorial

Original version accepted in English

PANDAS: To treat or not to treat?

PANDAS: Tratar ou não tratar?

The concept of PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection) remains controversial as to its validity, possible prevalence, potential pathogenic mechanisms, and clinical implications.[1-2] In the face of these many uncertainties, the clinician is faced with several practical challenges concerning treatment.

To review, the criteria proposed by Swedo et al characterize PANDAS as: 1) cases of OCD and/or tic disorder; 2) with prepubertal onset; 3) a history of sudden, severe symptom onset and an episodic course characterized by remissions and abrupt exacerbations; 4) evidence of temporal association between symptom onset (or exacerbation) and Group A Beta-hemolytic strep (GABHS) infection; and 5) adventitious movements or clumsiness.[1]

Applying these criteria to confirm or disconfirm a possible PANDAS diagnosis is often difficult in individual cases.

Firstly, the criterion of temporal association of symptom onset with strep infection is ambiguous. Swedo noted that Sydenham's chorea can occur up to 6 months after a strep infection, and suggested a time window of 12 weeks between infection and onset, with a more stringent limit of 7-14 days between infection and exacerbation. Although the longitudinal course of illness over many months may suggest a PANDAS diagnosis, in the short run, it is impossible to tell in any given new case whether the connection between a strep infection and the acute onset of symptoms is causal or merely coincidental.[1] GABHS pharyngitis and carrier states are very common in the general pediatric population. Given prevalence estimates for childhood OCD or tic disorder of at least 3%, it is clear that many children experience the co-occurrence of GABHS infection and tic/OCD symptom onset on a purely coincidental basis. Furthermore, like other stressors, GABHS (and other febrile illnesses) may exacerbate pre-existing tics or OC symptoms on a non-specific basis.

A recent prospective study from our group at Yale illustrates this dilemma.[3] A group of 47 children with TS or OCD and 19 healthy controls, all age 7-17 years were followed longitudinally with regular monitoring of tic/OCD symptom severity and strep culture and antibody titer status. Using empirically derived criteria for symptom exacerbation, the overall rate of tic/OCD exacerbations was 0.56 per patient per year. The average rate of new GABHS infection was 0.42 per subject per year. However, the temporal association between tic/OCD symptom exacerbation and new GABHS infection was no greater than expected by chance. Although these findings do not preclude the existence of a small subgroup of PANDAS, they suggest that the symptom fluctuations in the majority of this unselected sample were not related to GABHS.

Natural history is another putative PANDAS criterion. Swedo et al describe PANDAS as often characterized by explosive "overnight" onset of severe symptoms.[1] However, Singer et al noted that in a series of 80 consecutive unselected children with TS, parents described 53% as having "sudden explosive onset or worsening of tic symptoms."[4] Hence, because even abrupt onset of tics/OCD with a positive throat culture may be coincidental, Swedo et al caution that "a single positive throat culture or elevated antibody titer is not sufficient to determine that a child's neuropsychiatric symptoms are associated with streptococcal infections (...) Instead the determination that a child fits the PANDAS profile is made through prospective evaluation (...)."

The absence of specific biological markers for PANDAS complicates diagnosis. Many lay people and even physicians are under the mistaken impression that elevated Anti Streptolysin O or Anti Strep DNAase B titers are markers for PANDAS. All these antibodies indicate however is that a child has had a strep infection and mounted a normal immunological response; there is no evidence that these antibodies play any role in PANDAS or other autoimmune post-streptococcal disease.

Confronted with a child with a positive GABHS throat culture and sudden onset of tics or OCD, what is the clinician to do? In order to minimize the risk of rheumatic fever, infection disease guidelines clearly mandate a 10 day course of antibiotic treatment, irrespective of tic or OCD symptoms. A more difficult decision is called for in children who have had a recent onset of tics or OCD and have a positive GABHS throat culture but no history recent of pharyngitis or antibody elevation. As many as 10% of children may be such asymptomatic carriers, often for many weeks. Although there is debate as to whether asymptomatic strep carriers require antibiotic treatment, treatment is probably advisable if there has been a recent onset or change in tic/OCD symptoms.

Long-term prophylactic antibiotic treatment should be reserved only for children with a longitudinal course clearly compatible with PANDAS. The hazard of fostering antibiotic resistance is a serious one, as many communities have seen the explosive emergence of erythromycin resistant strains of GABHS in recent years. Low levels of adherence to antibiotic treatment, even in children with acute strep pharyngitis, underline the practical problems of adherence to long term prophylactic regimens. A second-generation NIMH trial of azithromycin prophylaxis vs. placebo is currently underway.

The apparently promising NIMH trial of plasmapheresis (PEX) and intravenous immunoglobulin in children meeting PANDAS criteria has led many parents to seek out these treatments for their children. However, these treatments have their hazards (e.g. central line placement, hypotension in the case of PEX); furthermore, PEX was not helpful for children with tic/OCD who did not meet the PANDAS criteria. NIMH recommends that such immunomodulatory treatments should only be done in the context of properly reviewed research protocols.

Other potential immunomodulatory interventions exist. Some, like omega-3 fatty acid (fish oil) supplementation, are probably benign. Others, such as monoclonal antibodies have been effective in other autoimmune illnesses, but have potentially severe side effects.

To summarize, the prudent clinician will:

1) Obtain throat cultures of children with abrupt onset or dramatic exacerbation of tic/OC symptoms;

2) Treat positive GABHS cultures;

3) Reserve antibiotic prophylaxis to only those cases with a longitudinal course of abrupt exacerbations linked to GABHS;

4) Reserve immunomodulatory treatments for only those cases meeting the PANDAS criteria and unresponsive to standard treatments.

Robert A King
Medical Directory, Tourette's/OCD Clinic
Yale Child Study Center

References

1. Swedo SE, Leonard HL, Rapoport JL. The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) subgroup: separating fact from fiction. Pediatrics. 2004; 113(4):907-11.

2. 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(4):883-6.

3. Luo F, Leckman JF, Katsovich L, Findley D, Grantz H, Tucker DM, et al. Prospective longitudinal study of children with tic disorders and/or obsessive-compulsive disorder: relationship of symptom exacerbations to newly acquired streptococcal infections. Pediatrics. 2004;113(6):e578-85.

4. Singer HS, Loiselle C. PANDAS: a commentary. J Psychosom Res. 2003;55(1):31–9.