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Review article

The PANDAS subgroup of tic disorders and childhood-onset obsessive–compulsive disorder

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Abstract

Diagnosis and treatment of the PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) variant of Gilles de la Tourette syndrome (GTS) and childhood-onset obsessive–compulsive disorder (OCD) are still controversial issues. Most cross-sectional studies confirm a significant association between GTS and the development of an immune response against group A β-hemolytic streptococcus (GABHS). Moreover, longitudinal retrospective studies suggest that a recent exposure to GABHS might be a risk factor for the onset of tics and obsessive–compulsive symptoms. However, further evidence from longitudinal prospective research is needed to verify whether a temporal association between GABHS infections and symptom exacerbations is a useful and reliable criterion for the diagnosis of PANDAS. In addition, preliminary results suggest that the PANDAS spectrum might be enlarged to include attention deficit/hyperactivity disorder. Although a number of immunological biomarkers have been proposed as markers of the PANDAS variant, at present, none of these has been conclusively proved useful to diagnose and monitor disease course in children with a suspicion of PANDAS. Finally, despite their empirical use in community settings, we still lack conclusive, evidence-based data regarding the usefulness of antibiotic and immunomodulatory treatments in children with PANDAS. Given the relevance of this topic for general pediatric health, additional research efforts to solve all the pending issues and the hottest points of debate are warranted.

Keywords: Gilles de la Tourette syndrome; Obsessive–compulsive disorder; PANDAS; Group A β-hemolytic streptococcus; Immunity

Historical background

The etiology of Gilles de la Tourette syndrome (GTS) is hypothesized to be multifactorial, with genetic and environmental factors interacting to establish a neurobiological vulnerability [1]. The clinical presentation of GTS is heterogeneous with regard to tic phenomenology, course of illness, and spectrum of psychiatric comorbidities. The genetic basis of GTS also seems heterogeneous, and several nongenetic factors might have a risk-modifying and/or disease-modifying role. Among the latter, factors resulting in immune activation, particularly infections, gained the attention of clinicians and researchers in the last 15 years [1]. Among microbial agents, a potential pathogenic role of group A β-hemolytic streptococcal (GABHS) infections has been explored in greater depth.

The link between tic disorders and GABHS infections was suggested by the overlap between tic disorders and Sydenham's chorea (SC), the prototype of post-streptococcal neurological disorders [2,3]. In the late 1980s, a resurgence of rheumatic fever and SC that occurred in the Salt Lake City area and the Ohio river valley in the United States allowed the direct observation of the full spectrum of SC, which also includes, besides florid, generalized chorea, the sudden onset of anxiety, inattentiveness, obsessive–compulsive symp-

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toms, and occasionally tics [2]. This led clinicians to hypothesize that GABHS infections could be relevant to the pathogenesis of pediatric-onset obsessive–compulsive symptoms and tics. During the 1990s, sudden outbreaks of tics and obsessive–compulsive symptoms temporally linked to GABHS infections, in the absence of overt SC, were reported [2,4]. In 1998, Swedo et al. [5] coined the term *PANDAS* (*pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection*) to define the prepubertal onset of obsessive–compulsive disorder (OCD), GTS, or tic disorder with abrupt symptom exacerbation after streptococcal infection and proposed a set of working definition criteria.

In the past decade, the concept of PANDAS has been the object of intense debate [6,7]. Although new evidence in support of this concept has arisen during this period of time, clinical research has not provided as yet physicians with reliable diagnostic protocols and treatment guidelines to deal with cases of "suspect" PANDAS. This uncertainty has often brought community pediatricians, particularly in the United States, to diagnose PANDAS in an arbitrary manner, and, as a consequence, treat these cases with unwarranted antibiotic courses. Despite the lack of clear evidence-based data supporting antibiotic treatment in children with PANDAS, a recent retrospective, observational study showed that PANDAS are frequently misdiagnosed in the community and inappropriately treated with antibiotics [8]. In this study, 82% of children with a community diagnosis of PANDAS and treated with antibiotics did not have any clear laboratory evidence of a GABHS infection.

This article will provide an update on the clinical implications of the PANDAS hypothesis, revising the epidemiological evidence and the current knowledge on diagnosis and management.

An up-to-date commentary on the clinical definition of PANDAS

The original description of PANDAS

In their seminal article [5], Swedo et al. evaluated 50 children who met all the five working criteria proposed as diagnostic for PANDAS: (1) presence of OCD and/or tic disorder, according to *DSM-IV* criteria; (2) onset occurring between 3 years of age and puberty; (3) episodic course; (4) temporal association of symptom exacerbations with GABHS infections; (5) presence of abnormal results on neurological examination, in the absence of frank chorea. The primary diagnosis was OCD in 48% of these children and tic disorder in 52%; however, 86% and 80% reported some obsessive–compulsive symptoms and tics, respectively. Boys outnumbered girls by a ratio of 2.6 to 1. Children with primary diagnosis of OCD reported significantly more washing and checking behaviors than those with a primary diagnosis of tic disorder. Similar to the general population of patients with tic disorder and pediatric OCD, comorbid attention deficit/hyperactivity disorder (ADHD), affective and anxiety disorders were present in 40%, 42%, and 32%, respectively. Symptoms of these comorbid diagnoses had a relapse–remission pattern similar to tics and obsessive–compulsive symptoms. Each child had at least one exacerbation preceded by a documented GABHS infection, the latter being associated with symptom onset in 42% of cases. Adopting the stringently defined criteria of Swedo et al., the diagnosis of PANDAS in a single individual requires longitudinal follow-up of the patient.

Is GABHS infection associated with the diagnosis of tic disorders and/or OCD?

If a subgroup of children with tic disorders and/or OCD has a disease related to GABHS infections, it is plausible that cross-sectional investigation might reveal a significant association between these diagnoses and current (or past) exposure to GABHS. Cross-sectional studies cannot provide direct information on the effect of GABHS infection upon disease course, and discrepant results between this type of studies may be due to several factors, such as heterogeneity among clinical series or seasonal variability of GABHS exposure. These limitations notwithstanding, the cross-sectional methodology allows patient recruitment within tertiary referral centers, which guarantees a more rigorous clinical evaluation and diagnosis. These studies will be reviewed next.

Cardona and Orefici [9] reported a significantly higher anti-streptolysin O titer (ASOT) in 150 children with tics compared to 150 healthy children, documenting a direct relationship between ASOT and tic severity. In this study, however, throat swab culture analyses on a subsample of patients failed to detect a predominant serotype associated with tics. An American cohort of 81 GTS patients exhibited higher ASOT than age-matched healthy volunteers and a mixed group of patients with autoimmune diseases [10]. Increased ASOT, anti-deoxyribonuclease B (DNAse B), anti-streptococcal M12 and M19 titers were also observed in a smaller German sample of patients with GTS [11,12]. In a British cohort of 100 patients with GTS (50% children), ASOT was raised in 64% of children and in 68% of adults with GTS; this was significantly higher than in neurological disease and healthy control subjects [13]. Two other reports from British and Italian cohorts confirmed these findings [14,15]. However, a subsequent study failed to find a significant association with ASOT and anti-DNAse B titers using the same cross-sectional approach [16]. Table 1 provides a summary of cross-sectional studies assessing streptococcal markers in GTS.

Children with tic disorders and raised anti-streptococcal antibody titers might be more likely than age-matched children with tics but normal anti-streptococcal antibody titers to exhibit, on color Doppler echocardiography, mild to