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Review

Evaluation of autoimmune phenomena in patients with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

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ABSTRACT

The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) are basically characterized by obsessive-compulsive symptoms and/or tics triggered by group-A beta-hemolytic *Streptococcus* infections. Poor data are available about the clear definition of PANDAS's autoimmune origin.
The aim of our study was to evaluate the prevalence of autoimmune phenomena, including thyroid function abnormalities, specific celiac disease antibodies, and positivity of organ- or nonorgan-specific autoantibodies in a large cohort of Caucasian children and adolescents with PANDAS.
Seventy-seven consecutive patients (59 males, 18 females; mean age 6.3 ± 2.5 years, range 2.0–14.5 years) strictly fulfilling the clinical criteria for PANDAS diagnosis were recruited. In all subjects we evaluated serum concentrations of free-T_3, free-T_4, thyrotropin, and the following auto-antibodies: anti-thyroperoxidase, anti-thyroglobulin, anti-thyrotropin receptor, anti-gliadin, anti-endomysium, anti-tissue transglutaminase, anti-nuclear, anti-smooth muscle, anti-extractable nuclear antigens, anti-phospholipid, plus lupus-like anticoagulant. The results were compared with those obtained from 197 age- and sex-matched healthy controls (130 males, 67 females; mean age 6.8 ± 2.9 years, range 2.3–14.8 years).
The frequencies of subclinical (3.8% *vs* 3.6%) and overt hypothyroidism (1.2% *vs* 0%), autoimmune thyroiditis (2.46% *vs* 1.14%), celiac disease (1.2% *vs* 0.05%), and positivity of organ- and nonorgan-specific autoantibodies (5.1% *vs* 4.8%) were not statistically significant between patients with PANDAS and controls. Evaluating the overall disease duration, we did not observe any significant difference between patients with (3.4 ± 2.15 years) and without (3.4 ± 2.89 years) autoimmune abnormalities. However, PANDAS patients with autoimmune diseases or positivity for any organ- and nonorgan-specific antibodies showed significantly higher anti-streptolysin O and anti-DNAse B titers, as well as a history of more frequent throat infections than controls ($p < 0.0001$).
Abnormalities of thyroid function and thyroid autoimmune diseases, as well as the association with celiac disease or organ- and nonorgan-specific autoimmunity seem not more frequent in children and adolescents with PANDAS than in healthy controls. A potential relationship between autoimmunity and PANDAS should be assessed further in larger studies. Children and adolescents with PANDAS should not be actually screened for thyroid function, celiac disease and/or autoimmune diseases.

Contents

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1. The evolving concept of PANDAS as a post-infectious syndrome

The term "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections" or PANDAS was coined by S.E. Swedo et al. in 1998 [1], referring to children and adolescents with abrupt onset of a variety of neurological clinical signs triggered by group-A beta-hemolytic *Streptococcus* (GABHS) infections [2]. Specifically, PANDAS are defined by five clinical criteria: (a) the presence of obsessive–compulsive disorder (OCD), Tourette's syndrome (TS), or any other tic reported by the Diagnostic and Statistical Manual of Mental Disorder IV (DSM-IV); (b) prepuberal onset (between 3 years of age and the start of puberty); (c) episodic courses characterized by an abrupt or "explosive" onset of symptoms with recurrent exacerbations; (d) a distinct association with GABHS infection; and (e) potential association with other neurological abnormalities [3]. OCD is defined by distress and anxiety resulting from recurrent obsessions, such as persistent thoughts, impulses or actions beyond the child's control, and compulsions, as repetitive behaviors used to neutralize or counteract an obsessive idea; tics are brief, repetitive, purposeless, nonrhythmic, involuntary movements or sounds, while TS is defined by the presence of involuntary motor tics, such as eye blinking, nose twitching, head jerks, or vocal tics, throat clearing, coughing, and sniffing, dramatically worsened by stress.

Basal ganglia dysfunction combined with molecular mimicry and autoimmune-mediated altering neuronal signaling are the most plausible pathogenetic mechanisms to explain PANDAS: a susceptible host might produce antibodies against GABHS that cross-react with neuronal tissues, resembling what is known for other GABHS-related sequelae or post-infectious diseases, as glomerulonephritis, reactive arthritis, and rheumatic fever [4,5]. Detecting alterations in the central and peripheral nervous systems by conventional magnetic resonance imaging is infrequent in children and adolescents with PANDAS, unlike patients with neuropsychiatric systemic lupus erythematosus [6,7]. Various studies have indicated that PANDAS are autoimmune disorders derived from the presence of anti-neuronal (anti-brain and anti-basal ganglia) antibodies [8,9]. Nevertheless, other studies failed to identify significant differences of autoantibody levels between patients with PANDAS and controls [10,11]. A strong support for PANDAS as immune-mediated disorders derives from the excellent response of these children to immunotherapies (plasma exchange and intravenous immunoglobulin) [12]. In addition, prospective data have also shown that azithromycin or oral penicillin have effectively decreased the number of streptococcal infections and neuropsychiatric symptom exacerbations [13]. Yet, despite the fact that PANDAS are regarded as autoimmune disorders, poor incontrovertible data are actually available [14]. For example, a 1998 study – related to 13 adults with OCD – evaluating neuron-specific autoantibodies and other organ- and nonorgan-specific autoantibodies failed to reveal any humoral evidence of autoimmunity [14]. Other data, on the other hand, seem to suggest a link between maternal autoimmune diseases and both OCD/tics and PANDAS, indicating a greater frequency of autoimmune disorders in mothers of subjects with PANDAS than in the general population [15]. Thus, the purpose of our study is to evaluate the prevalence of autoimmune phenomena in a large cohort of children and adolescents with PANDAS, including abnormalities of thyroid function and positivity of autoimmunity tests, such as those for celiac disease and organ- or nonorgan-specific autoantibodies.

2. The cohort of children and adolescents recruited for PANDAS

Seventy-seven consecutive Caucasian patients (59 males, 18 females; mean age 6.3 ± 2.5 years, range 2.0 to 14.5 years) who strictly fulfilled the diagnostic criteria for PANDAS [1,3,16] were collected from July 2009 to November 2013. Ethical approval was obtained from the Ethics Committee of our University Hospital, and a written informed consent was obtained from the patients' parents after a full explanation of the nature of the study.

2.1. Case definition and study protocol

Diagnoses of PANDAS were carried out according to the DSM-IV criteria in combination with Affective Disorders and Schizophrenia—Present and Lifetime (KSAD-S-PL) and Children Yale–Brown Obsessive Compulsive Scale (CY-BOCS). Moreover, PANDAS criteria established by the American National Psychiatry Institute were also employed for the diagnosis [1,16]. Participants who were included in the PANDAS group met the five clinical criteria [1]. In making a diagnosis of PANDAS, we required two "spikes" in OCD and/or tics, each associated with pharyngitis and laboratory documentation of a streptococcal infection (e.g., positive rapid strep test, positive strep culture, and/or elevation in the anti-streptolysin O and/or anti-DNAse B titers) [17]. All recruited patients were assessed with a structured diagnostic interview at the time of the serological examination; the documentation was obtained retrospectively by reviewing patients' records. The age of symptom onset was determined using all available information, including pediatric records as well as reports from parents and teachers. In our cohort of study all children had OCD and/or tics, and their onset of symptoms occurred in pre- or early puberty. Out of the 77 participants, 42 were considered in a period of exacerbation at the time of our assessment and 35 were in remission. Our definition of exacerbation was CY-BOCS >15, while remission was when CY-BOCS <16. Among PANDAS subjects, 12 (15.4%) were taking psychotropic medications at the time of the study, 8 were taking only one medication (10.2%), and 4 were taking two medications (5.2%). Six subjects were also taking serotonergic agonists, including sertraline, fluvoxamine, and fluoxetine; 4 were taking dopamine antagonists, including haloperidol, risperidone, and fluphenazine; and 2 were taking tricyclic antidepressants, namely clomipramine and imipramine. Exclusion criteria were a previous diagnosis of autism, mental retardation, schizophrenia-spectrum disorder, or chronic degenerative neurological diseases.

2.2. The control group

One hundred ninety-one age/sex-matched healthy Caucasian children and adolescents (129 males, 62 females; mean age 6.6 ± 2.7 years, range 2.3 to 14.8 years) were recruited as controls. These patients had no infectious or neurologic disorders at the time of our evaluation. Studies regarding this group of children and adolescents have been previously published [18].

2.3. Methods of investigation

In all subjects we evaluated the serum concentrations of free-T_3, free-T_4, and thyrotropin [TSH]. The following autoantibodies were also evaluated: anti-thyroperoxidase [TPOA], anti-thyroglobulin [TgA], anti-thyrotropin receptor [TSHrA], anti-gliadin [AGA], anti-endomysium [EmA], anti-tissue transglutaminase [tTGA], anti-nuclear [ANA], anti-smooth muscle [ASMA], anti-extractable nuclear antigens [ENA], and anti-phospholipid [APA], plus lupus-like anticoagulant [LAC]. All autoantibodies were evaluated at least three times during the follow-up period. In the PANDAS group serum samples were