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.

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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

collected during acute exacerbations of their disease, associated with evidence of a streptococcal pharyngeal infection. Additionally, continuous data such as pubertal staging, weight, height, and body mass index were collected. All serum samples were coded and stored. Anti-streptolysin O titers [ASOT] were measured using the Dade Behring BN II nephelometer (http://www.dadebehring.com). Anti-DNAse B titers were measured by the commercially available kit (Streptonase-B, Wampole Laboratories, NJ, USA) according to the manufacturer's instructions. ASOT or anti-DNAse B titers above 200 IU/mL were considered to indicate a recent infection (WHO guidelines). Free T_3, free T_4, and TSH serum levels were measured by immunometric assays (Immulite™ 2000, Third Generation, DPC Diagnostic Products Corporation, Los Angeles, CA, USA), and inter-run coefficients of variation were <9.1% for free T_3, <7.5% for free T_4, <8.5% for TSH, respectively. Subclinical hypothyroidism was defined as a TSH level above the upper reference limit for age in combination with normal serum thyroid hormone levels. Overt hypothyroidism was defined as persistently increased TSH levels with decreased serum thyroid hormone levels. Thyroid autoimmunity was evaluated by fluorescence enzymatic immunoassays for TPOA and TgA; positive TPOA and TgA values were considered to be ≥100 IU/mL and 50 IU/mL, respectively. TSHrA were measured with THBIA (DiaSorin Spa, Vercelli, Italy) using a two-step radioreceptor assay; TSHrA levels were considered to be positive when values were >9 U/L. Regarding celiac disease, all patients underwent evaluation of serum IgA, AGA [both IgG and IgA], EmA, and tTGA [IgA]: diagnosis of celiac disease was confirmed by performing a small intestine biopsy if the specific autoantibody profile was positive [19]. ANA were assessed using an immunofluorescent method with HEp-2 cell (Scimedx Corp., Denville, NJ, USA). ENA were detected by an ELISA method (QUANTA Lite assay, INOVA Diagnostics, San Diego, CA); ELISA test was used for the semiquantitative detection of 6 extractable nuclear antigens, including SS-A, SS-B, RNP, Scl-70, Sm and Jo-1 antigens, as well as dsDNA. ASMA were detected using cryostat frozen sections of rat kidney, starting from a 1:20 dilution of serum: the results were scored as follows: SMA-V (vessels), staining of small/medium-sized vessel walls; (b) SMA-G [glomeruli], in addition to vessels, staining of glomerular mesangial cells; and (c) SMA-T (tubuli), staining of vessels and glomerular and peritubular structures. The determination of APA class IgG and IgM was performed using citrated plasma and a standardized ELISA test (Diagnostica STAGO, Paris, France). The results were expressed as GPL units for IgG [positive ≥ 5 GPL units/mL] and MPL units for IgM [positive ≥ 5 MPL units/mL]. APA positivity was accepted only if confirmed on a different sample collected at least 12 weeks later. The determination of the LAC was performed using coagulation analyzer BCS Siemens. Simplified dilute Russell's viper venom test (dRVVT) was performed using LA1 screening reagent and LA2 confirmatory reagent (Siemens), following the manufacturer's instructions. A dRVVT ratio (LA1 screen/LA2 confirmation) above 1.2 was considered positive for LA activity. Activity of LA was quantified as follows: low positive (LA1/LA2 = 1.2–1.5), medium (LA1/LA2 = 1.5–2.0), and high positive (LA1/LA2 > 2.0).

3. Statistical evaluation and results

Statistical analyses were performed by using SPSSX (SPSSX Inc., Chicago, IL, USA). The χ^2-test or Fisher's exact test, when appropriate, were used to compare differences between patients and controls. Bonferroni's correction for multiple comparisons was also applied under selected instances. Summaries of the continuous variables are given as mean ± standard deviations (SD) and ranges. Statistical tests were two-tailed and considered to be significant when p was < 0.05.

The basic features of our study cohort and controls are summarized in Table 1.

As expected, ASOT were raised in 71.8% of children with recent streptococcal infections (mean 570 IU/mL, 95%CI, 291 to 1100), whereas anti-DNAse B titer was raised in 67.9% (mean 670 IU/mL, 95%CI, 253 to 1234).

The main feature of our patients with PANDAS was their abrupt and dramatic onset of symptoms associated with the streptococcal infection (present in 69 of 77 patients) or the relapsing–remitting course associated with new streptococcal infections (present in 46 of 77 patients).

Regarding the prevalence of celiac disease, only 1 patient was found positive for specific celiac autoantibodies, and diagnosis of celiac disease was confirmed histologically in this case; moreover this patient had also an autoimmune thyroiditis. This result is not statistically significant in comparison with controls (1 case, 0.05%; p = NS). In addition, 2 patients (2.46%) with PANDAS (comprising the above reported patient) were positive for TPOA and TgA, without statistical differences in respect to controls (1.14%; p = NS). Not one of these patients was positive for TSHrA. The overall frequency of other organ- and nonorgan-specific autoantibodies did not significantly differ between PANDAS patients and controls (5.1% vs 4.8%, p = NS). In particular, we disclosed 4 ANA-positive patients (5.1%), but no positivity for other organ- and nonorgan-specific autoantibodies was demonstrated.

Subclinical hypothyroidism was diagnosed in 3 patients (3.8%) and overt hypothyroidism in 1 (1.2%). The frequency of subclinical (7 patients, 3.6%) and overt (0 subjects) hypothyroidism was not significantly different from that in the control group. The 2 patients with subclinical hypothyroidism had autoimmune thyroiditis. L-thyroxine treatment became necessary in 1 patient with autoimmune thyroiditis and overt hypothyroidism, because of the persistently increased TSH levels, while 3 patients with subclinical hypothyroidism were simply followed over time. In patients positive for thyroid autoantibodies we also observed a heterogeneous echo texture and diffuse hypoechogenicity on thyroid sonography. Evaluating the time between the first symptoms' appearance and diagnosis of PANDAS, we did not find significant differences between patients with (3.4 ± 2.15 years) and without (3.4 ± 2.89 years) autoimmune phenomena.

However, PANDAS patients with history of autoimmune diseases or positivity for organ- and nonorgan-specific antibodies had significantly higher ASOT (705 ± 222 IU/mL) and anti-DNAse B titers (1231 ± 913 IU/mL), as well as a history of more frequent throat infections than in controls (respectively: 125 ± 45 IU/mL, 143 ± 37 UI/mL; p < 0.0001).

4. Autoimmune phenomena are not more frequent in PANDAS patients

Our data show that children and adolescents with PANDAS do not seem to develop autoimmune phenomena more frequently than the general healthy pediatric population. Our study confirms data from J.L. Black et al. revealing no humoral evidence of autoimmunity involving organ- and nonorgan-specific autoantibodies in a population with pediatric onset obsessive–compulsive disorders [14]. PANDAS patients with history of autoimmune diseases or positivity for organ- and nonorgan-specific antibodies showed significantly higher ASOT and anti-DNAse B titers than healthy controls. This is of great concern

Table 1
Main demographical and clinical features of subjects with PANDAS and healthy controls.

	Subjects	Controls	p
Number	77	191	–
Males:females	59:18	129:62	–
Mean age ± SD [years]	6.3 ± 2.5	6.6 ± 2.7	NS
Exacerbation/remission	42/36	–	–
Anti-streptolysin O [IU/mL]	705 ± 222	125 ± 45	<0.0001
Anti-DNAse B [IU/mL]	1231 ± 913	143 ± 37	<0.0001
Subclinical hypothyroidism	3.8%	3.6%	NS
Overt hypothyroidism	1.2%	0%.	NS
Autoimmune thyroiditis	2.46%	1.14%	NS
Coeliac disease	1.2%	0.05%	NS
Organ- and nonorgan-specific autoantibodies	5.1%	4.8%	NS

NS = not significant.

because pathogenetic mechanisms of PANDAS involve autoimmune-mediated disrupted signaling [3], and recent data support a hypothetical link between maternal autoimmune diseases and the occurrence of PANDAS [15]. Therefore, frequent GABHS reinfections might trigger the appearance of autoimmune processes or organ- and non-organ-specific antibodies in susceptible hosts, though more data are needed to corroborate this hypothesis. It is established that autoimmune diseases result from a complex interplay of genetic, environmental, and endogenous factors [20]. The administration of various vaccines (against influenza, human papilloma virus, hepatitis A and B, rabies, and measles) has also been related to the appearance of different autoimmune diseases, including central nervous system demyelinating diseases, multifocal disseminated demyelination, optic neuritis, and encephalomyelitis [21]. Many inflammatory mediators, such as CXCL10, also named interferon gamma-induced protein 10, secreted by monocytes, endothelial cells, fibroblasts, keratinocytes, thyrocytes, and preadipocytes, may stimulate the directional migration of Th1 cells, and might have a role in triggering different autoimmune diseases [22]. Nevertheless, autoimmunity may be considered not only a cause of disease. In fact, human T cell repertoires naturally comprise autoimmune lymphocytes, naturally helping heal damaged tissues and contributing to health and benefit self-maintenance [23]. Among the environmental factors, infections have been implicated in the onset and/or promotion of autoimmunity [24,25]. Rheumatic fever is a classic example of an autoimmune illness triggered by an infection: the pathogen involved is GABHS, the most common cause of childhood bacterial pharyngitis [26]: GABHS infection is followed by a latent period before the onset of symptoms and, during the latent period, immunological perturbations occur to initiate the biologic process of rheumatic fever. The persistence of anti-heart antibodies in patients with recurrences of rheumatic fever suggests that repeated GABHS infections can maintain this process and worsen cardiac complications [27,28].

GABHS infections have been implicated as triggers of PANDAS [1,29], but the exact relationship between PANDAS and autoimmune disorders remains equivocal. Some data seem to hypothesize a causal role of streptococci at least in a subset of patients with both OCD and tic disorders [4,30–32], as well as the existence of a neuropsychiatric risk deriving from repeated GABHS infections [33–35]. Patients with Sydenham's chorea, systemic lupus erythematosus, and other autoimmune diseases might display a high rate of comorbid OCD [35,36]. In fact, individuals with systemic lupus erythematosus are 10 to 15 times more likely to develop OCD [36–38]. Further, OCD is more prevalent among relatives of subjects with rheumatic fever than in controls [39], suggesting that psychiatric disturbances can be associated with autoimmune diseases in both affected patients and their relatives. In many studies evaluating PANDAS patients, the duration of illness at the time of evaluation is generally not mentioned, but it may have a significant impact on the level of evidence for autoimmunity. For example, studies in diabetes have shown levels of markers for autoimmunity depending on both time of onset and overall duration of illness [40,41].

Our data do not seem to support the importance of disease duration in the development of autoimmune diseases or organ- and nonorgan-specific antibodies in PANDAS. Nevertheless we hypothesize that the frequency of GABHS infections may be crucial in triggering the start of an autoimmune disorder. More data are surely necessary for better delineating subgroups of PANDAS patients who may develop an overt autoimmune disease. In addition, our data do not seem to support the necessity of follow-up for potential autoimmune disorders or for evaluating serum organ- and nonorgan-specific autoimmunity tests in these patients.

In conclusion, abnormalities of thyroid function and thyroid auto-immunity, as well as celiac disease and organ- or nonorgan-specific autoimmunity are not more frequently observed in children and adolescents with PANDAS than in the general pediatric population. Their potential relationship should be evaluated in larger studies, though the causal role of GABHS infection in the development of autoimmune disorders and organ- or nonorgan-specific autoantibodies should be further confirmed. Actually, asymptomatic children and adolescents with PANDAS should not be screened for thyroid function and/or autoimmune diseases.

5. Take-home messages

- "Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections", collectively named PANDAS, refer to an abrupt onset of obsessive–compulsive symptoms, motor or vocal tics and Tourette's syndrome, all triggered by group-A beta-hemolytic *Streptococcus* infections in children and adolescents.
- Various studies indicate that PANDAS derive from autoimmune abnormalities related to the presence of anti-neuronal antibodies directed against basal ganglia.
- Seventy-seven consecutive patients with a mean age of 6.3 ± 2.5 years, who strictly fulfilled the clinical criteria for PANDAS diagnosis were recruited, undergoing evaluation of serum free-T_3, free-T_4, thyrotropin, 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 antibodies and lupus-like anticoagulant.
- Abnormalities of thyroid function and thyroid autoimmunity, as well as specific autoantibodies related to celiac disease or organ- and nonorgan-specific autoimmunity were not more frequently observed in children and adolescents with PANDAS in comparison with controls.
- The potential relationship of autoimmune phenomena with PANDAS as well as the causal role of GABHS infection in their development should be evaluated and confirmed in larger studies.
- Our data show that asymptomatic children and adolescents with PANDAS should not be screened for thyroid function, celiac disease and/or autoimmune diseases.

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