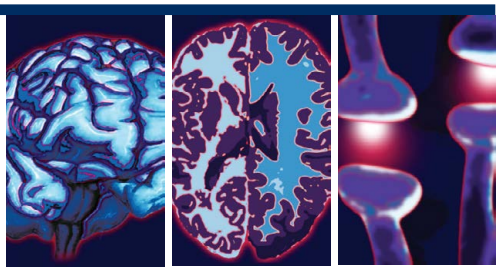

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection (PANDAS): Clinical Manifestations, IVIG Treatment Outcomes, Results from a Cohort of Italian Patients

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Abstract

Pediatric Autoimmune Neuropsychiatric Disorder associated with Streptococcal Infection (PANDAS) is characterized with main clinical features including obsessive-compulsive disorders and tics, acute-onset in prepubertal age, relapsing-remitting course, association with neurological abnormalities (mainly choreiform movements and motor hyperactivity), and temporal relationship with group A streptococcal infections. Thirty- four children with a serious- severe grade of PANDAS were enrolled in Italian Institutions with the aim to report clinical manifestations of the patients and their response to the intravenous immunoglobulin (IVIG) treatment. All patients were selected according to the Swedo's criteria and specific laboratory investigations as suggested by Chang for the PANS and treated with IVIG at the dosage of 2 g/kg/day for two consecutive days. At the onset, all patients presented with at least, one psychiatric manifestation including anxiety, emotional lability, bedwetting, enuresis, and phobia, and oppositional behavior including temper tantrums, personality changes, and deterioration in math skills and handwriting. At the laboratory investigations, positivity of pharyngeal swab for streptococcal infection in most of the patients and variable titers of anti-DNase B and ASO were found. In 29 patients reduction or disappearing of the motor symptoms were reached after 1 or 2 cycles of IVIG treatment, while in 5 patients the symptoms reappeared after the third cycle of IVIG. PANDAS may present with polymorphic clinical signs involving behavioral and psychiatric manifestations. In this study, IVIG has been shown to be effective in most of the cases and no complications have been reported during the treatment. Since there is no general agreement on PANDAS treatment, further more extensive researches in this topic are to be hoped.

Keywords

PANDAS, PANS, Tic, Obsessive-compulsive disorders, Tourette's Syndrome, Group-A-beta-hemolytic streptococcal infection

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List of Abbreviations

RF: Rheumatic Fever; SC: Sydenham Chorea; GABHS: Group-A-Beta Hemolytic Streptococcal Infection; TS: Tourette Syndrome; OCD: Obsessive Compulsive Disorder; PANS: Pediatric Acute-Onset Neuropsychiatric Syndrome; PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections; CANS: Childhood Acute Neuropsychiatric Symptoms; PCC: PANS Consensus Conference; ASO: Anti-Streptolysin O; A-Dnaseb: Anti-Deoxyribonuclease; PRC: PANS Research Consortium; OSAS: Obstructive Sleep Apnea Syndrome

Introduction

Streptococcal infections in children are very common, but usually self-limited. In some cases, the infection may have harmful effects that cause body-organ disturbances, involving also the central nervous system (CNS). Among the infection-linked disorders, rheumatic fever (RF) and Sydenham chorea (SC) are the most widely defined and well-known disorders. More recently, a condition has been related to streptococcal infection: the pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection and registered as the PANDAS acronym. This condition was first reported by Swedo et al. [1] in 1998 to describe children affected by a set of clinical signs linked to group-A-beta-hemolytic streptococcal infection (GABHS). These authors indicated five clinical criteria to diagnose this disorder: Neuropsychiatric abnormalities, mainly tic and obsessive-compulsive disorder (OCD), onset in the pre-pubertal age (3-14 years), a remitting and relapsing course, association with GABHS, presence of other neurologic abnormalities including hyperactivity, choreiform movements and Tourette's syndrome (TS) [1-6]. Clinical phenotypes of PANDAS have been broadened to provide new insight and boundaries to the disorder; new types have also been recognized that share clinical manifestations with PANDAS: PANS (pediatric acute-onset neuropsychiatric syndrome) and CANS (childhood acute neuropsychiatric symptoms [7]. PANDAS are now considered as a sub-group of PANS.

PANS is diagnosed by the abrupt onset of psychiatric symptoms with OCD or food restriction, and at least two of the following associated symptoms: anxiety, emotional lability and/or depression, irritability, aggression and/or severe oppositional behaviors, behavioral regression, deterioration in school performance, sensory or motor abnormalities, and other signs and symptoms which include sleep disturbances, enuresis, or urinary incontinence [7-10]. In PANS, identification of the causal events (including infections, immune dysfunction, and/or environmental events) is not always found. The definition of CANS requires only the acute dramatic onset of OCD and other associated neuropsychiatric disturbances [7,9,11].

The mechanism related to the onset of PANDAS is believed to be autoimmune and probably related to molecular mimicry. Auto-antibodies might be responsible for targeting brain structures, such as dopamine D1 and D2 receptors, leading to the alteration of dopaminergic transmission [12]. Dale et al. [13] in a study conducted in patients with autoimmune movements and psychiatric disorders report increased D2 receptors immunoglobulin G in 10 out 33 patients with SC and in 4 out 44 in patients with TS while no increase of D2 receptor was found in 22 PANDAS patients. However, these authors [13] concluded that assessment of D2 receptor antibodies may be useful in defining autoimmune movement and psychiatric disorders. As reported by Dale et al. [13] increased D2 receptor antibodies are also present in SC, this finding is not specific enough for the diagnosis of PANDAS.

The etiological events causing the disorder are not always detectable; therefore no guideline for treating patients is homogeneously recognized. PCC (PANS Consensus Conference) proposed guidelines for PANDAS/PANS to treat patients according to grade of the symptoms, from mild to severe [14,15] . According to that, the treatment can be differently graded according to the degree of the symptoms mild, moderate, serious, severe. In some children, the use of antibiotics may be justified to prevent new infections in association with anti-inflammatories like naproxen and corticosteroids; in the more severe cases, use of cycles of intravenous immunoglobulin (IVIG), plasmapheresis (PEX), and monoclonal antibodies (Rituximab) has been advanced [14]. Tonsillectomy has also been proposed in the treatment of patients with PANDAS. Clinical evidence reveals that tonsil removal has no efficacy in delaying or changing the course of the disease. Pavone et al. [16] analyzed 120 patients diagnosed for PANDAS according to five clinical criteria. The results between the two groups (PANDAS and control subjects) showed

that tonsillectomy did not reduce the severity of neuropsychiatric symptoms [16].

The aim of this study is to describe clinical features and psychiatric manifestations in data from the Italian Center of PANDAS on behalf of the Italian Society of Pediatric Neurology and to evaluate treatment efficacy with IVIG in children with a serious-severe grade of PANDAS disease.

Methods

The present study focuses on 34 patients with a serious-severe form of PANDAS diagnosed and clinically followed by the participants to this study. Before the use of IVIG all patients' parents signed a consent form for using IVIG and for data collection to write the present study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as revised in 2000, and was approved by the ethic committee of the University Hospital Vittorio Emanuele of Catania, Italy (nd 1385 04/12/2015). At the diagnosis, laboratory and diagnostic evaluation were carried out according to Chang et al. [14] regarding PANDAS/ PANS disorder. At the diagnosis, all of them were submitted to a Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) Total Severity Score was >15, for be included in the study. The patients were clinically followed up for three years. Participants reviewed the presentation features of OCD, tics, and choreiform movements, results of pharyngeal swab, anti-streptolysin O (ASO) titer, anti-deoxyribonuclease (Anti-DNase B) titer, EEG findings, brain MRI findings when performed. All 34 patients were treated with one to three cycles of IVIG at 2 g/Kg per day for two consecutive days and evaluated treatment efficacy with IVIG. The study results were elaborated with Microsoft Cloud: a Azure SQL relational database to store the structured data and Microsoft Power BI to extract the insights. The software was created with runs in the Cloud to obtain data rapidly, and to gain even more information in further studies.

Results

A total of 34 patients include 18 males and 16 females, with an average age of 9.4 years, along with a serious-severe form of PANDAS. All patients showed at least one psychiatric manifestations, specifically anxiety, enuresis, phobia, oppositional behavior. Their daily activity was compromised, as the OCD manifested with episodes of selective feeding, eating refusal, excessive food intake, and behavioral disorders such as psychosis, suicidal thoughts, aggression, and self- harm. The tics were motor and phonic types, both simple and complex: eye blinking, whistling, shoulder shrugs, facial grimaces, pulling at clothes, jumping, sniffing, throat cleansing, coughing, and spitting. Choreiform movements were found in three patients, and they were largely localized in the arms. In Tables 1-3, the single clinical features and psychiatric manifestations are reported.

Pharyngeal swab was as positive in 28 children, 4 negative in 4 children, and not available in 2 children. ASO titer measured in all patients was extremely variable, ranging from 296 IU to 2141 IU (982.7± 457.9 IU). Anti-DNase B titer measured in 26 patients ranged from 299 to 1160 U/mL (539.8 ± 214.1 U/mL). The ASO and the Anti-DNase B titers are higher comparing to the average data from other centers, these discordances may be due to the different strains of involved streptococci. The EEG was normal in almost all cases, with exceptions in three consisting of basal rhythmic asymmetry. The ECG and cardiac ultrasound were normal in all patients.

Table 1: Psychiatric manifestations.

Type of psychiatric manifestations	Number of patients
Anxiety	8
Enuresis	6
Oppositional behavior	5
Worse school and social performance	5
Phobia	5
Anorexia	4
Separation syndrome	4
Aggression	3
Evening obsessive cleaning rituals	3
Food selectivity	3
Ritual behavior	2
Psychomotor agitation	2
Nightmares	2
Fear of being abandoned before sleeping	2
Obsessive thoughts	2
Bad school results	2
Psychotic symptoms	2
Trash talking	1
Compulsive and repetitious gesture	1
Unusual gesture	1
Psycosis	1
Stranger refuse	1
Abandonment issue	1
Severe food selectivity	1

All patients showed at least one psychiatric manifestations, specifically anxiety, enuresis, phobia, oppositional behavior.

Table 2: Clinical presentation of tics.	
Type of tic	**Number of patients**
Vocal tics	7
Stereotyped limb movements	5
Trichotillomania	4
Blinking	4
Whistling	4
Nodding	4
Motor tics to the shoulders	4
Face grimacing	3
Twitching	3
Eye tics	2
Mouth grimacing	2
Blowing	2
Motor and vocal tics	2
Hand tics	2
Tics to head and upper part of the body	2
Phonations tics	1
Motor tics to the shoulders and arms	1
Simple mouth tics	1
Face tics	1
Vocal tics associated to head twitching	1
The tics were motor and phonic types, both simple and complex.	

Table 3: Clinical presentation of choreiform movements.	
Type of choreiform movements (3 patients) different in time	**Number of patients**
Limb and chest stiffness	3
Tongue protrusion	2
Stereotyped movements	2
Choreiform movements of the arms	2
Hang up	1
Flexion-extension of the wrist	1
Clonus of the arm	1
Choreiform movements were found in three patients, and they were largely localized in the arms.	

Brain MRI showed abnormalities in 3 cases: a mild asymmetry of the lateral ventricles in two cases, prevalently left asymmetry and a mild bilateral enlargement of the perioptical sheath in one. The remaining cases showed normal.

All patients showed impressive tics in high frequency which tends to vary in intensity during the time, and OCD symptoms not responsive to treatment with antibiotics. Treatment with IVIG, at 2 g/Kg per day for two consecutive days performed from one to three times according to the clinical response gave the following results: 29 out of 34 children treated with IVIG had noticeable reduction or disappearance of symptomatology for at least one year after the last dose of IVIG. Among these 29 patients, eight patients (5 females and 3 males) with the age range between 9-11 years old were treated with IVIG at 2 g/kg/day for two consecutive days with complete remission and no relapse of symptoms. The remaining 21 patients (12 males and 9 females) were treated at the same IVIG dosage for two different cycles; in the first cycle (IVIG with 2 g/Kg per day for two consecutive days), the patients showed improvement of symptoms for up to 3 months, but a second cycle (IVIG with 2 g/Kg per day for two consecutive days) was necessary for the resolution of the symptomatology. In 5 (15%) cases (3 males and 2 females), a partial but temporary response to second cycle of IVIG treatment was yielded, but symptoms reappeared after the third cycle of treatment. Gender played no role in the results obtained.

Discussion

In this cohort with serious-severe PANDAS, choreiform movements were not constantly noted, however, they were largely localized in the arms when they were present. The pharyngeal swab analyses were quite informative. EEG and brain MRI showed normal in most patients. IVIG treatment seems to be useful in the most severe cases.

PANDAS is a childhood disorder with abrupt onset of motor and behavioral symptoms, mainly OCD and tics, related to GABHS infection. The course is variable with different phases, depending on the re-appearance of new infection [1-5]. In PANDAS patients, the clinical features may be ranging from mild to particularly severe and are similar to those presented by individuals with TS. Therefore, a differential diagnosis between the two disorders is difficult to be performed. A linkage between PANDAS and TS has been suggested based on similar clinical signs, such that it has been proposed that PANDAS and TS may be considered as the spectrum of the same disorder. This represents an exciting gap that future research will be able to bridge. As reported by Spinello et al. [17] preclinical evidence indicates that the immune response to repeated streptococcal immunization is associated with behavioral and neurological phenotypes reminiscent of TS. Hypotheses on the relationship between these disorders are limited by the lack of evidence in behavioral phenotypes and etiologic events causative of TS.

Present patients have a serious/severe form of PANDAS with tics that present in different ways. The OCD manifests in various forms, but some show a serious and dangerous psychiatric involvement, such as OCD-related suicidal

behavior. As with clinical features, pharyngeal swab analyses were quite informative, yielding positive results in the pharyngeal swab in 30 out 34 (88%) of the affected children, in three cases negative, and in another one not available, possibly due to treatment with antibiotics given by parents shortly before recovery. Both ASO and Anti-DNase B titers were extremely variable.

In this cohort, the EEG was normal with the exception in a few patients of basal rhythmic asymmetry. Abnormal brain activity was registered at EEG records in 7 out 42 PANS patients, as well as sleep disturbances or obstructive sleep apnea syndrome (OSAS) at polysomnography by Chang et al. [14] and episodes of parasomnia were described by Hommer et al. [18] in 11 children with PANDAS. In the present patients no specific brain anomalies were found at brain MRI and mild asymmetry of the left lateral ventricle and bilateral enlargement of the peri-optical sheath may not be correlated with the PANDAS symptomatology. However, brain MRI with T2 weighted images may be useful for revealing inflammatory changes in basal ganglia as reported by Giedd et al. [19]. These different results of EEG and brain MRI could be linked to the etiology underlying these disorders.

Also functional studies with hexamethyl propilene amine oxime single-photon emissions computed tomography (HMPAO-SPECT) could be helpful for better understanding symptoms often observed in patients with PANDAS: study carried out in 7 cases of SC and 2 cases of Streptococcal tic disorders revealed a hyperperfusion pattern in 2, and a hypoperfusion pattern localized in the striatum and thalamus in 5 SC patients and in 2 patients with tic disorder [20].

Recently Kumar et al. [21] reported on a study conducted in 17 children affected by PANDAS and in 12 affected by TS, with 15 normal adults as controls. The study performed dynamic positron emission tomographic study using 11C-[R]-PK11195 and used binding potential values, specifically calculated for basal ganglia and the thalamus. An activated microglia-mediated neuro-inflammation was found in the bilateral caudate and the bilateral lentiform nucleus in PANDAS as well as in the bilateral caudate nuclei in TS compared to control groups. The authors concluded that the pattern and extension of neuro-inflammation may be linked to different pathophysiology underlying PANDAS and TS.

Treatment in PANDAS patients has been widely debated. One type of treatment advised in Italy is use of IVIG. Williams et al. [22] report on 35 children presenting criteria for PANDAS and moderate to severe OCD. The treatment consisted of a 6-week trial of IVIG (1 g/kg/day on 2 consecutive days), followed by optional open-label treatment for non-responders, with follow-up at 12 and 24 weeks. The patients were tested previously with the CY-BOCS and the Clinical Global Impressions-Improvement (CGI-I) rating. According to the results of this study, IVIG treatment was safe and well tolerated, but the double-blind comparison failed to demonstrate it as being more effective than placebo.

In 1999, Perlmutter et al. [23] carried out a randomized trial in children with severe infection-triggered exacerbation, also affected by OCD or tics. In 10 patients, the treatment consisted of five single-volume plasma exchanges (PEX) over 2 weeks, and in 9 patients, with IVIG at 1 g/kg daily on 2 consecutive days, in comparison with ten placebo controls. The results were assessed by standard scales for OCD, tics, and other psychiatric disturbances, with patients followed up after 1 and 12 months of treatment. At 1 month, the IVIG and PEX group showed striking improvements, both in OCD and tics, and gains were also maintained for 1 year.

Kovacevic et al. [24] reported on treatment of 12 youth PANDAS patients treated with IVIG. The dosage was 1.5 g/Kg/day in two divided doses used in association with antibiotics to prevent further infection-triggered symptom exacerbations. All patients included in this case-series had benefits from IVIG treatment, including those with a preceding lengthy and persisting symptomatic course. These authors concluded that IVIG may be useful in the management of children with moderate-severe symptoms. A recent systemic review of IVIG performed in young patients with neurological and psychiatric disorders, Gadian et al. [25] obtained speed recovery in patients with SC, reduced recovery in patients with TS, improved tic movements in selected cases of TS and improved symptoms in PANDAS patients. As reported by Nosadini et al. [26] the IVIG treatment is expensive and it should be used in selected patients and with adherence to guidelines.

In this cohort, 29 out of 34 of children treated with IVIG showed a reduction or disappearance of the symptomatology, while in 5 cases

(15%), despite 3 IVIG courses, there was only temporary improvement of clinical symptoms, with their reappearance within 1 to 6 months. According to the results of literature and ours no definitive conclusions may be drawn from IVIG treatment for PANDAS. Limitations of the present study include the absence of case-controls and long-term follow up. However, in our opinion, treatment with IVIG has been shown to be effective in PANDAS children with a serious-severe type and to be well tolerated. As it has been reported by Frankovic et al. [27] most of the PANS Research Consortium (PRC) members prefer use of IVIG in treatment of patients with this disorder in moderate to severe forms.

In our serious-severe PANDAS patients, all showed various psychiatric problems and tics. The pharyngeal swab analyses were quite informative. 29 out of 34 of children treated with IVIG showed a reduction or disappearance of the symptomatology. Further studies need to be performed to better understand pathogenesis of this heterogeneous disorder and to confirm that IVIG is an appropriate treatment.

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