

Clinical-Serological Characterization and Treatment Outcome of a Large Cohort of Italian Children with Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection and Pediatric Acute Neuropsychiatric Syndrome

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Abstract

Objective: Pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus pyogenes* infection (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS) are emerging immune-mediated encephalopathies characterized by sudden onset of seemingly inexplicable complex neuropsychiatric symptoms, including obsessions, compulsions, and heterogeneous tics, which occur in children. Main goal of this study was to report our experience in a large cohort of Italian children affected by either PANDAS or PANS and treated long term with an antibiotic regimen similar to that used for acute rheumatic fever.

Patients and Methods: The clinical charts of a cohort of 371 consecutive Italian children, 345 with PANDAS (93.0%) and 26 with PANS (7.0%), were retrospectively evaluated. Antistreptococcal, antinuclear antibodies, and serologic evaluation for a group of common autoantibodies and microbial agents were also assessed. A strict differential diagnosis with other autoimmune diseases displaying neuropsychiatric manifestations was performed.

Results: Antistreptolysin O and anti-DNase B antibody titers were tested and were positive in all PANDAS subjects, but negative in PANS. Anti-*Mycoplasma pneumoniae* antibodies and anti-Epstein–Barr virus Nuclear Antigen antibodies were found positive in 11 (42.3%) and 5 (19.2%) patients with PANS, respectively. Among PANDAS cases, a clear streptococcal infection was clinically evident at the onset of neurological symptoms in only 74 patients (21.4%), whereas the relationship with *Streptococcus pyogenes* was confirmed by serologic tests in the other 271 (78.6%). All patients fulfilling the diagnostic criteria for PANDAS ($n = 345$) received amoxicillin/clavulanic acid for 10–21 days at diagnosis, while those who were diagnosed with PANS ($n = 26$) received treatment according to the causative agent. Thereafter, all PANDAS/PANS patients received prophylaxis with benzathine benzylpenicillin for an overall period of at least 5 years to prevent subsequent potential streptococcal infections. To date, 75.0% of PANDAS patients ($n = 258$) have shown an improvement of neurologic symptoms, mainly observed within 3–5 months of treatment for PANDAS cases, while 88.4% of PANS patients ($n = 23$) have improved after 6–12 months. Infection-related relapses of neurologic manifestations were observed in both PANDAS and PANS patients ($n = 167$ out of 371; 45% of the total cohort) in the long term.

Conclusions: Our study has confirmed the usefulness of the preliminary diagnostic criteria for PANDAS and PANS, revealing also the importance of early diagnosis to reduce the risk of evolution toward disabling chronic neurologic sequelae. Long-term antibiotic prophylaxis has resulted in a substantial benefit to reduce neurological symptoms for the majority of PANDAS and PANS patients over a 7-year period.

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Introduction

PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDER associated with *Streptococcus pyogenes* infection (PANDAS) encompasses a complex of obsessive-compulsive disorders (OCDs) and/or tics, both characterized by a shocking sudden pattern of remitting and relapsing symptoms, with the initial episode occurring abruptly or even overnight (Swedo et al. 1998, 2015; Perrin et al. 2004; Murphy and Pichichero 2002; Murphy et al. 2014). Within a short time children with PANDAS may also develop a cognitive decline and behavioral regression, including attention difficulty, terrifying anxiety, deterioration in handwriting or any school performances and other fine-motor skills, night terror, or occasionally even psychosis. Urgency or frequent urination may be observed as an initial manifestation, frequently misdiagnosed as urinary tract infection in the absence of other typical neurological symptoms (Swedo et al. 1998, 2015; Perrin et al. 2004; Murphy and Pichichero 2002; Murphy et al. 2014). Shocked parents and/or caregivers describe their child as “completely new and unrecognizable.” Although the exact pathogenesis of PANDAS is still under investigation, a widely demonstrated association has been a previous group-A *Streptococcus pyogenes* (GAS) infection (Swedo 2015). Some children may also display neuropsychiatric symptoms, including moderate or severe OCD and tics, which are triggered by other infectious agents such as *Mycoplasma pneumoniae*, Epstein-Barr virus, *Borrelia burgdorferi*, varicella-zoster virus, Herpes simplex virus, and influenza virus. All of these GAS-unrelated neurologic conditions have been more precisely labeled as “pediatric acute-onset neuropsychiatric syndrome” or PANS, with the specific diagnosis requiring the exclusion of many neurologic disorders (Chang et al. 2015). In both PANDAS and PANS a relevant decline in school performance may be observed by teachers and parents, as well as visual-motor impairment, food restriction, and even aggressive behaviors. Piano playing-choreiform movements of fingers or toes have also been reported (Swedo et al. 1998).

A panel of clinicians and researchers with a specific interest in PANDAS and PANS has proposed recommendations for diagnosis of these conditions in 2013 (Chang et al. 2015). PANDAS was defined as a subtype of PANS, and it was stated that not all PANS cases have an underlying mute streptococcal infection, while all PANDAS cases are associated with a clearly confirmed streptococcal infection, at least temporally (Chang et al. 2015). Days or weeks after an infection, neurologic symptoms may follow abnormalities occurring in the central nervous system, mainly involving the basal ganglia, similar to Sydenham's chorea. Specifically, these patients were found to have a history of tonsillitis, positive throat cultures for GAS infection, and increased antistreptolysin O (ASO) and/or anti-DNase B titers, which frankly suggest a preceding streptococcal infection (Swedo et al. 1998, 2015; Perrin et al. 2004; Murphy and Pichichero 2002; Murphy et al. 2014; Chang et al. 2015; Swedo 2015). Unfortunately, due to conflicting opinions and reports about PANDAS/PANS recognition, many children are left undiagnosed and may even receive psychiatric medications, including selective serotonin reuptake inhibitors, which often result as ineffective (Esposito et al. 2014; Chang et al. 2015).

Herein, we report our experience with a cohort of 371 Italian children who fulfilled the diagnostic criteria for PANDAS/PANS

and received antibiotic prophylaxis, similar to secondary prophylaxis performed for cases of acute rheumatic fever. The antibiotic prophylaxis resulted in a substantial benefit to patients, reducing neurologic manifestations for the majority of PANDAS and PANS cases over a 7-year period.

Patients and Methods

A retrospective study was started by a thorough evaluation of medical charts related to 371 consecutive children with PANDAS or PANS who were managed between May 1, 2009 and August 31, 2016, at the University of Florence. Patients were recruited from the University of Florence, University of Brescia, and Università Cattolica Sacro Cuore of Rome: inclusion in the study required that patients were aged <18 years at the time of diagnosis. All patients were evaluated by the single leading physician involved in the recognition of PANDAS/PANS symptoms (Lepri is rheumatologist; Falcini, Meini, and Rigante are pediatricians): patients were unselected and sent to our clinics due to the occurrence of specific PANDAS and/or PANS symptoms. The almost totality of patients was from Northern and Central Italy, and the largest number of children with PANDAS/PANS was evaluated in Florence by Falcini and Lepri. The preliminary diagnostic criteria for PANDAS/PANS were adopted for all patients, and their general management was in Florence. A formal written consent was obtained by each child's parent or caregiver before analyzing retrospective data in an anonymous manner. A strict differential diagnosis with other autoimmune diseases displaying neuropsychiatric manifestations was performed. Patients who presented with other types of inflammatory brain diseases such as central nervous system vasculitides, autoimmune encephalitides or postinfectious inflammatory brain diseases, neurosarcoidosis, and inflammatory channelopathies, as well as demyelinating disorders (e.g., acute disseminated encephalomyelitis or multiple sclerosis), were excluded from the study. Clinical characteristics were inferred from medical charts. Acuity of onset <3 days was noted in all cases, and laboratory investigations were performed in every recruited child. Demographic, clinical, and laboratory data, including serum autoantibody profile, were recorded for all cases. A psychologist evaluated all patients: 27 of them had received psychiatric medications, including risperidone (5 patients, 0.5–1 mg/day), aripiprazole (6 patients, 10 mg/day), and haloperidol (8 patients, 0.5 mg/day), the benzodiazepine lorazepam (1 patient, 2 mg/day), the selective serotonin reuptake inhibitor sertraline (6 patients, 10 mg/day), and rotigotine (a dopamine receptor agonist) transdermal patch (1 patient) before arriving to our attention, but none of these patients treated had shown any clinical efficacy after these treatments. Of note, except for 6 patients who received only 1 psychiatric medication, 21 received 2-to-3 drugs at the same time, but caregivers did not observe any significant amelioration of symptoms. Five patients had been on psychiatric medications for a median period of 6 months before our first visit. All subjects recruited in the study had been evaluated with the Childhood Yale Behavioral Obsessive Compulsive Scale for the assessment of specific neuropsychiatric signs or symptoms (Melli et al. 2015).

Children who demonstrated an association with a previous GAS infection fulfilling the diagnostic criteria for PANDAS were treated

with amoxicillin/clavulanic acid (80–100 mg/(kg·d) in two doses for a period ranging from 10 days to 3 weeks) and then maintained on benzathine benzylpenicillin (600,000–1,200,000 every 21 days according to subject's weight) for at least 5 years. Subjects without a previous GAS infection were eventually treated with the specific drug according to the identified infection: macrolide was used for treatment of *Mycoplasma* infection (revealed by immunoglobulin M antibodies), acyclovir for varicella-zoster virus, and amoxicillin or cephalosporin for *Borrelia* infection. Prophylaxis with benzathine benzylpenicillin was prescribed also in PANS children without a specific causative agent identified, as suggested by the recent article by Cooperstock et al. (2017). In addition, five subjects with a more severe disease, who were refractory to previous antibiotic treatments, received intravenous immunoglobulin (IVIG) [at a dose of 2 g/(kg·d)]: in particular, three subjects received six cycles of IVIG infusions at an interval of 1 month each, and two received only three IVIG infusions due to adverse events (high fever, severe headache, vomiting, or anaphylaxis). However, all five patients had recurrence of symptoms after 2 months, and for this reason they were retreated with the prophylactic antibiotic regimen. All patients were followed up for a period of at least 7 years.

Results

A total of 371 patients, 276 males (74%) and 95 females (26%), came to our attention due to the abrupt occurrence of OCD and/or vocal or motor tics starting before puberty. The frequencies of neurological symptoms are presented in Table 1. Of these, 348 patients (93.8%) were full-term born, and of these 332/348 (95.4%) were born from a regular pregnancy, whereas 16/348 (4.6%) after Cesarean section. Data about maternal pregnancy or family history were not available in 23 out of 371 patients, as they were adopted children. All patients attended regularly nursery, primary, and secondary schools according to their age, with overall good performances in most cases, and 236/371 (63.6%) had a regular physical activity. A total of 183 patients (51.1%) had relatives with OCD/tics or other various neurological diseases, such as anxiety, depression, and obsessive disorders.

Out of 371 patients, 137 (36.9%) had no clinically-evident infectious disease before the onset of OCD/tics symptoms, while 74 (20%) reported a previous GAS infection, which was indicated if throat culture was positive or if antistreptococcal antibodies were found outside the expected range for patients' age. Five patients presented with a history of transient hip synovitis, two had a typical

TABLE 2. FREQUENCIES OF INFECTIONS AND INFECTION-RELATED CONDITIONS OBSERVED IN OUR COHORT OF CHILDREN WITH PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDER ASSOCIATED WITH *STREPTOCOCCUS PYOGENES* INFECTION/PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME

Group-A <i>Streptococcus pyogenes</i>	74
Impetigo	4
Scarlet fever	12
<i>Mycoplasma pneumoniae</i> infection	11
Upper respiratory infection	145
No apparent infectious trigger	137
Hip synovitis	5
Henoch–Schönlein purpura	2

noncomplicated Henoch–Schönlein purpura, and five had had Kawasaki disease several years before, which was regularly treated with IVIG without any cardiac complications. In addition, out of 371 patients, 11 (3%) had antibodies positive for a previous *M. pneumoniae* infection, whereas anti-Epstein–Barr virus Nuclear Antigen antibodies were positive in five patients. A total of 145 of 371 (39%) patients had had nonspecific upper airway infections, 12 scarlet fever, and 4 suppurative acute skin infection, which were related to GAS. All of these cases were placed in the group of poststreptococcal disorders. Table 2 shows the relationship with a previous infection shown by our patients, which was used to classify the groups into PANDAS or PANS.

The most striking evidence was that the clinical onset of neurological manifestations was dramatically “sudden” in all cases, that is, occurring in less than 3 days, as well as completely unexpected by parents and/or caregivers. The first symptoms occurred at a mean age of 76.7 months (6.4 years) $\pm$ 30.3 months (2.5 years). Clinical manifestations at onset were characterized by motor tics in 308 subjects (83%) and concomitant vocal tics in 70 children (18%). Eighteen patients (4.9%) presented with only vocal tics. Out of 371 subjects, 152 (41%) presented with OCD and 137 (36.9%) with inappropriate mood or behavioral disturbances. Urinary or

TABLE 1. FREQUENCIES OF CLINICAL SIGNS AND SYMPTOMS IN OUR COHORT OF CHILDREN WITH PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDER ASSOCIATED WITH *STREPTOCOCCUS PYOGENES* INFECTION/PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME

Motor tics	156 (42%)
Vocal tics	12 (3.2%)
OCD	40 (10.8%)
Motor and vocal tics	47 (12.7%)
Motor tics and OCD	83 (22.4%)
Vocal tics and OCD	6 (1.6%)
Motor/vocal tics and OCD	23 (6.2%)
Anxiety	26 (7%)
Sleep disturbance	1
Mood and behavioral symptoms	137 (37%)
Urinary problems	14 (3.8%)
Food restriction	4 (1%)

OCD, obsessive compulsive disorder.

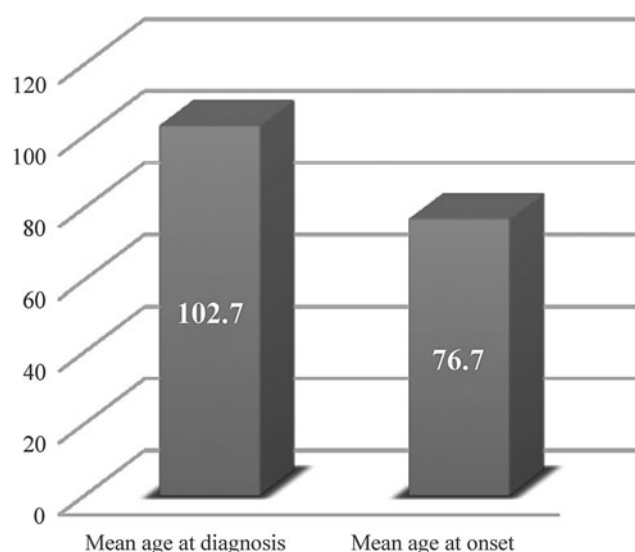


FIG. 1. Mean age at diagnosis (expressed in months) and mean age at onset of pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus pyogenes* infection/pediatric acute-onset neuropsychiatric syndrome in our cohort of patients.

TABLE 3. ANTISTREPTOLYSIN O AND ANTI-DNASE B ANTIBODY TITERS EVALUATED IN OUR COHORT OF CHILDREN WITH PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDER ASSOCIATED WITH *STREPTOCOCCUS PYOGENES* INFECTION/PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME

ASO (n: 342)	No. of patients
Negative	69 (20.2%)
Positive	273 (79.8%)
Anti-DNase B (n: 213)	No. of patients
Negative	41 (19.3%)
Positive	172 (80.8%)

ASO, antistreptolysin O.

fecal incontinence was observed in 14, lack of appetite in 4, and a sleep disorder in only 1 patient. The mean age at diagnosis of PANDAS/PANS was 102.7 ± 32.2 months (8.5 years), showing a considerable delay in comparison with the mean age at onset of symptoms (6.4 years) (Fig. 1).

In our cohort of patients, ASO (pathologic if >200 Todd Units) and anti-DNase B (pathologic if >200 IU) antibody titers were assessed; they were increased in 273/342 (79.8%) and in 172/213 subjects (80.8%), respectively (Table 3). Antinuclear antibodies were positive at a low titer in only 2 patients. Other autoantibodies, such as anti-dsDNA, anti-ENA, and antiphospholipid antibodies (including anticardiolipin antibodies and lupus-like anticoagulant), were negative. Treatments administered for the different types of infections observed in the group of 26 PANS patients are shown in Table 4.

Actually, 75.0% of PANDAS patients ($n=258$, out of 345) have shown an improvement of neurologic symptoms after prophylaxis with benzathine benzylpenicillin, based on reports by children's parents and/or caregivers in terms of improved school performances, reduction or disappearance of OCD symptoms and/or motor/vocal tics, weakened anxiety, and reduced hyperactivity; in addition, 88.4% of PANS patients ($n=23$, out of 26) showed a substantial improvement, and 5 of these have discontinued therapy (Figs. 2 and 3). In fact, an emerging medical literature has reported therapeutic benefits of antibiotics in PANS with and without an evident infectious trigger (Cooperstock et al. 2017). The clinical improvement was observed 3-to-5 months after starting antibiotic therapy in the group of PANDAS, while the amelioration of symptoms was evident after a mean period of 6-to-12 months for patients with PANS.

TABLE 4. TREATMENT ADMINISTERED FOR DIFFERENT TYPES OF INFECTIONS OBSERVED IN THE GROUP OF 26 PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME PATIENTS

No. of PANS pts	Infectious agent	Treatment
11	<i>Mycoplasma pneumoniae</i>	Macrolide
5	Epstein-Barr virus	None specific
5	Varicella-zoster virus	Acyclovir
2	<i>Borrelia burgdorferi</i>	Amoxicillin/cephalosporin
3	Presumed virus infection	None specific

PANS, pediatric acute-onset neuropsychiatric syndrome.

In addition, 45.0% of the total number of PANDAS/PANS patients ($n=167$, out of 371) displayed relapses of different neurologic manifestations, occurring concurrently with or soon after new infections, including nonspecific viral infections, during the long-term antibiotic treatment regimen. Finally, five antibiotic-refractory subjects treated with IVIG who had recurrence of symptoms were again treated with the prophylactic antibiotic regimen and showed a progressive clinical improvement after about 1 month.

Discussion

To date, the relationship of different infections, and specifically GAS infection, with the onset of neurologic symptoms caused by an immune response against both infectious antigens and specific neuronal antigens of basal ganglia in predisposed children is not completely understood (Esposito et al. 2014; Chang et al. 2015; Cooperstock et al. 2017). Among the different postinfectious sequelae induced by GAS infection, a spectrum of childhood-onset OCD and motor/vocal tics with a presumed autoimmune origin has been identified, and PANDAS is the most widely known disease expression.

In general terms, OCD, mainly characterized by the presence of obsessions (i.e., recurrent and persistent thoughts, urges, or images that are experienced as intrusive and unwanted) and/or compulsions (i.e., repetitive behaviors or mental acts that an individual feels driven to perform in response to an obsession or according to rules that must be rigidly applied), shows a lifetime prevalence of 1%–3% in the general population, with fluctuation of symptoms (waxing and waning), even if episodic courses are also described (Swedo et al. 1998; Chang et al. 2015; Cooperstock et al. 2017). The bimodal age onset of OCD suggests that different etiological factors may be implicated in the genesis of such a disturbance. A genetic component with biological or environmental influence in patients with early onset is also postulated. Family studies confirm a higher familial aggregation among relatives of children with early onset disease (Geller 2006).

Tics, that is, rapid recurrent nonrhythmic and stereotyped movements or vocalizations, are considered the most prevalent movement disorder in childhood, although their exact prevalence in the general population is unknown: onset might occur between 2 and 7 years, and the worst period of tic expression usually peaks around preadolescence (9–12 years), with a following phase of stabilization and attenuation of symptoms in adolescence or early adulthood. In the majority of cases, the first tics are motor and ocular. About 40% of children have no more tics during adulthood, while 40% have minimal or mild tics that cause no interference in their lives, and only 20% continue to show moderate or severe symptoms. In several cases, vocal tics (crying, vocalizations, and whooping) jeopardize the quality of social life, and other motor tics (hand wringing, arm jerking, trunk spasms, or complex movements) can be the first sign of the disorder (Scahill et al. 2014). In PANDAS/PANS the acute onset of tics, often overnight, is a matter of great distress for parents and caregivers and can be highly difficult to manage, treat, and eradicate.

Data from our cohort of patients confirm that abrupt occurrence of OCD and/or vocal or motor tics before puberty should be evaluated for inflammatory, infectious, and immunological abnormalities with a comprehensive diagnostic workup. Moreover, our data show that PANDAS is mainly observed in males (74% of cases) with a familiar recurrence of different motor disturbances in more than half of the cases. Following the PANDAS diagnostic criteria, the clinical onset occurred at a mean age of 6 years and 4 months,

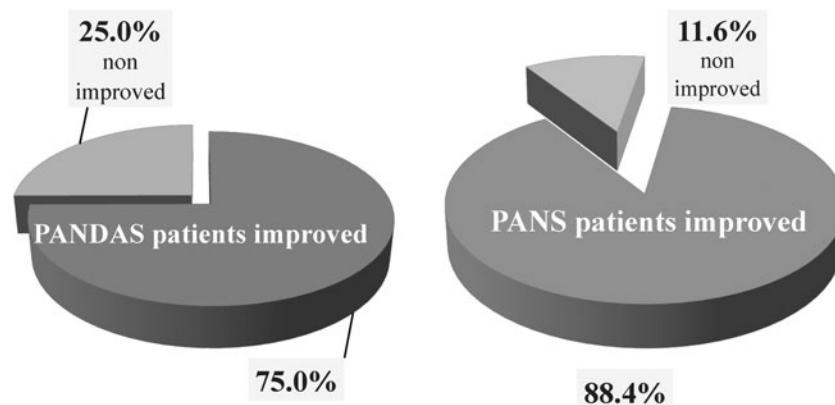


FIG. 2. Outcomes of patients with PANDAS/PANS who showed improvement of neurologic manifestations as reported by children's parents and/or caregivers after diagnosis and proper antibiotic prophylaxis. PANDAS patients improved were 258 (out of 345); PANS patients improved were 23 (out of 26). PANDAS, pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus pyogenes* infection; PANS, pediatric acute-onset neuropsychiatric syndrome.

mostly with motor tics or the coexistence of OCD and motor tics. It is important to note that diagnosis was made after 8.5 years, that is, with a significant delay observed from disease onset, highlighting the need to increase clinicians' awareness of this condition. Indeed, the majority of patients had received diagnosis after several visits with different specialists (otorhinolaryngologist, allergologist, ophthalmologist, neurologist, psychologist, or psychiatrist).

In our study, all patients diagnosed with PANDAS had an association with a previous GAS infection, which was detected following increased ASO or anti-DNase B titers. All other patients showing other infectious triggers, without increased ASO and/or anti-DNase B titer, were classified as PANS (Chang et al. 2015; Cooperstock et al. 2017). In both PANDAS and PANS patients, tics and OCD could not be explained by other known neurologic disorders. Although not used in our study, there are immunological assays available, which identify antineuronal autoantibodies usually present in these conditions (Ben-Pazi et al. 2013; Cox et al. 2015; Singer et al. 2015). Multiple etiologic or contributing factors

have been proposed in PANDAS and PANS, but treatment guidelines which have been published recently suggest that there are both infectious and autoimmune triggers (Frankovich et al. 2015; Calaprice et al. 2017; Swedo et al. 2017). These neurobiological syndromes can be framed as immune-mediated encephalitic disorders that potentially complicate GAS or other infections in genetically-susceptible individuals, similar to Sydenham's chorea included in the chapter of acute rheumatic fever (Swedo et al. 1998; Kirvan et al. 2006a, 2006b; Murphy and Pichichero 2002; Murphy et al. 2014; Murphy et al. 2015; Cox et al. 2013; Esposito et al. 2015; Cooperstock et al. 2017). The first PANDAS/PANS Interdisciplinary Consensus Conference was held in 2013 at the Stanford University with the goal to develop systematic strategies for evaluating children and adolescents with suspected histories and plan specific research studies (Chang et al. 2015). When PANDAS/PANS is suspected, it is important to obtain a comprehensive individualized medical (and psychiatric) history and perform a thorough physical examination combined with a complete diagnostic workup to exclude a host of neurologic and autoimmune diseases, as reported in the recent article published by the PANDAS Consortium and other more recent articles (Cooperstock et al. 2017; Thienemann et al. 2017). Our study confirms the usefulness of the preliminary diagnostic criteria for PANDAS/PANS (Chang et al. 2015) and highlights the importance of early diagnosis leading to prompt antibiotic treatment and reduction of the risk of symptom persistence and even their evolution to more severe and frustrating manifestations. Antibiotic prophylaxis with benzathine benzylpenicillin was given to all patients. Clinical features of PANDAS/PANS patients were so severe that no parents felt that it was possible to refuse prophylaxis, after fully understanding its meaning and its value over the long term.

Limitations of this study are its retrospective nature, the absence of patients who did not receive any placebo treatment alongside with those receiving antibiotic prophylaxis, and judgment of clinical improvement following antibiotic prophylaxis based on review of chart notes.

In conclusion, pediatricians should be aware of PANDAS and PANS, consider antibiotic prophylaxis as mainstay strategy for these conditions, and reassure patients' disoriented families. Indeed, our experience has revealed that a relevant number of young patients were burdened by side effects of ineffective and unnecessary

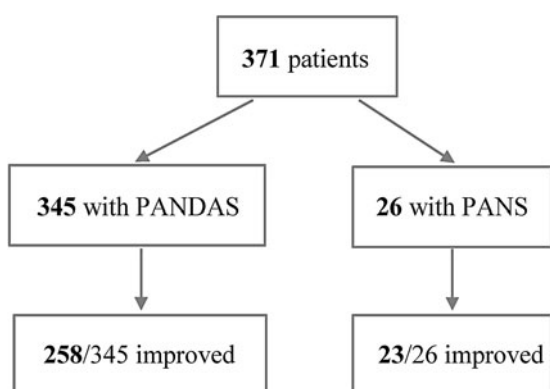


FIG. 3. Number of patients with PANDAS/PANS evaluated in the study who showed improvement of neurologic manifestations after treatment and antibiotic prophylaxis in a period of 3–5 months for PANDAS and 6–12 months for PANS. PANDAS, pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus pyogenes* infection; PANS, pediatric acute-onset neuropsychiatric syndrome.

psychiatric medications. Specifically, in our cohort of patients, long-term antibiotic prophylaxis with benzathine benzylpenicillin has resulted in a substantial benefit to patients' outcome, both for PANDAS and PANS. Improvement was obtained in 3–5 months for PANDAS and 6–12 months for PANS cases. In addition, long-term antibiotic prophylaxis appeared to prevent relapses of neurological manifestations over time in 55.0% of the overall number of PANDAS and PANS patients.

Conclusion

Our study has confirmed the complex clinical presentation of children with PANDAS and PANS and the usefulness of the preliminary diagnostic criteria in a real-life scenery, highlighting the importance of early diagnosis to reduce impairment for both affected children and their families. The retrospective evaluation of a cohort of 371 Italian children, 345 with PANDAS and 26 with PANS, shows that long term antibiotic prophylaxis with benzathine benzylpenicillin has given substantial benefits to reduce neurological symptoms in the majority of PANDAS and PANS patients and has prevented disease relapses over a 7 year period in more than half of the whole cohort.

Clinical Significance

A thorough multidisciplinary assessment can establish if children fulfill the diagnostic criteria for PANDAS and PANS and determine the most proper treatment, though a better definition of clinical manifestations, laboratory data and therapeutic responses is highly needed for these disorders. Our findings show that antibiotic prophylaxis has a role in the management of children with PANDAS and PANS, and longer term follow-up will enable a deeper understanding of the disease itself and potential usefulness of immunomodulating agents in the most severe cases.

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Disclosures

No competing financial interests exist.

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