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PANS and PANDAS: Case series of patients in a Danish pediatric clinical cohort.

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Abstract

Objectives: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) have been suggested to be a result of a disordered immune response after an infection causing neuropsychiatric symptoms. Although the diagnosis has been controversial, more focus has come on the diagnosis, pathophysiology, and treatment during the recent years.

Methods: We reviewed patient charts of 15 pediatric patients with suspected PANS/PANDAS from the Danish national Tourette syndrome clinic; charts were reviewed for demographics, symptoms, examinations, treatment, and outcome.

Results: 11 patients met either full criterion for PANDAS or PANS. Four patients did not fulfill all diagnostic criteria due to age at onset, absence of GAS infection and/or sub-acute onset of symptoms. Most reported symptoms were tics (86.7%), sleep disturbance (66.7%), behavioral disturbances (60.0%), anxiety (53.3%), motoric control abnormalities (53.3%) and Obsessive Compulsive Disorder (40.0%). Streptolysin-O antibody and streptococcus throat culture were positive in respectively 61.5% and 38.4%. Anti-neuronal antibody titers were taken; Calmodulin-dependent kinase II and anti-beta-tubulin antibodies were most often positive. Acute antibiotic treatment was given to all patients and had an effect in 73.3%. Prophylactic antibiotic was given to 53.3% of patients and had an effect in all patients. Some patients were treated with standard psychiatric treatment, intravenous immunoglobulin or steroid, and non-steroidal anti-inflammatory drugs.

Conclusion: This study has shown a positive effect of acute and prophylactic antibiotic-, psychiatric- and immunomodulating treatment, according to parental reports. Until further evidence regarding diagnostic tests and treatments exists, current literature and clinical experience must guide clinicians.

Keywords: PANS; PANDAS; Pediatric autoimmune neuropsychiatric disorders; Obsessive-Compulsive Disorder (OCD); Tics Disorders

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Introduction

During the last years, there has been increasing focus on Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection (PANDAS) and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), although the diagnoses have been described as controversial.

In 1995, Allen et al. described some cases with sudden, severe onset or worsening of tics or Obsessive Compulsive Disorder (OCD) after a recent group A beta-hemolytic streptococcus (GAS) infection or after recent viral infections [1]. Some years later, the diagnostic criteria for PANDAS were described [2]:

1. **Presence of OCD and/or a tic disorder:** The patient must meet lifetime diagnostic criteria (DSM-III-R or DSM-IV) for OCD or a tic disorder.
2. **Pediatric onset:** Symptoms of the disorder first become evident between 3 years of age and the beginning of puberty.
3. **Episodic course of symptom severity:** Clinical course is characterized by the abrupt onset of symptoms or by dramatic symptom exacerbations. Symptoms usually decrease significantly between episodes and occasionally resolve completely between exacerbations.
4. **Association with GAS infection:** Symptom exacerbations must be temporally related to GAS infection, i.e., associated with positive throat culture and/or elevated anti-GAS antibody titers.
5. **Association with neurological abnormalities:** During symptom exacerbations, patients will have abnormal results on neurological examination. Motoric hyperactivity and adventitious movements (including choreiform movements or tics) are particularly common.

There are several other central nervous system diseases that might be triggered by post-streptococcal autoimmunity, like Sydenhams Chorea (SC), OCD, movement disorders like dystonia and dystonic choreoathetosis, and acute disseminated encephalomyelitis (ADEM) [3].

The pathogenesis of PANDAS is not fully understood, but a disordered immune response after an infection with GAS

directed at both GAS antigens and host proteins is suggested [4]. It has been suggested, that antibodies raised in response to the infection cross-react with autoantigens in cortical structures and the basal ganglia [5].

No specific autoimmune antibody for PANDAS has been found yet and results from studies are inconsistent [4]. It has been suggested that the elevated antibodies can activate intracellular signaling pathways, which might affect neuronal function [6,7]. This might be responsible for alterations in behavior and movement control [7]. A pilot study has shown significantly different concentrations of cytokines in patients with PANDAS compared with patients with obstructive sleep apnea and patients with chronic tonsillitis with GAS [8]. Abnormal production of cytokines is suggested to result in disruption of the blood-brain-barrier.

Genetics also seem to play a role in the pathogenesis of PANDAS. It is suggested that patients who develop PANDAS might have inherited a specific vulnerability to sequelae after a streptococcal infection [9].

Since patients with symptoms of PANDAS without a previous GAS infection have been described, PANS was defined [10]:

1. Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake
2. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories:

1) Anxiety, 2) emotional lability and/or depression, 3) irritability, aggression and/or severely oppositional behaviors, 4) behavioral (developmental) regression, 5) deterioration in school performance, 6) sensory or motor abnormalities, 7) somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency

3. Symptoms are not better explained by a known neurologic or medical disorder, such as SC, systemic lupus erythematosus, Tourette disorder or others.

There has not been found a microbe that was consistently associated with PANS, but infections with mycoplasma pneumoniae, influenza, Epstein Barr virus and Borrelia burgdorferi have been described [6]. The pathogenesis of PANS is assumed to be the same as for PANDAS.

Although evidence-based treatment is lacking [5], newly published guidelines by the PANS research consortium suggest three complementary modes of intervention in patients with PANDAS/PANS: (1) treatment of the symptoms with standard psychiatric care, behavioral treatment, and supportive interventions, (2) removal of the source of inflammation with antimicrobial interventions, and (3) treatment of disturbances of the immune system with anti-inflammatory and/or immunomodulatory therapies [11,12]. In a newly diagnosed patient, an initial course of antimicrobial treatment for acute streptococcal infection usually is provided, regardless of identification of an infection with GAS or not [13]. Currently, there is insufficient evidence to support antimicrobial prophylaxis, except for the most severely affected children and those with multiple GAS-associated exacerbations [13]. With mild symptoms, watchful waiting combined with behavioral treatment and other supportive interventions is suggested. If the symptoms last more than two weeks or are worsening, treatment with Non-Steroidal Anti-Inflammatory Drug (NSAID) during 6 weeks or brief courses of oral corticosteroids might be considered [12]. In the case of moderate to severe symptoms, immunomodulatory therapy (corticosteroids and/or intravenous immunoglobulin (IVIG)) may be warranted [12]. IVIG is shown to be effective in case of exacerbations and recurrences (see for review [14,15]), but has potential risks and complications during and after administration (see for review [14]). Therapeutic plasma exchange, which is supposed to remove offending auto-antibodies [16], is the first-line therapy if extreme or life-threatening impairment due to PANDAS/PANS symptoms is present [12]. Tonsillectomy is not shown to be effective in patients with PANDAS/PANS and indications should be limited to those for the general population, like sleep-disordered breathing [14].

In the Danish national Tourette syndrome clinic patients with various movement disorders are evaluated and treated. Therefore, it has been natural to refer patients with suspected PANDAS/PANS to the clinic.

Due to lack of evidence in the field we have conducted a retrospective case series on the first clinical cohort of 15 Danish children and adolescents with suspected PANDAS/PANS in order to raise awareness and give an insight in assessment and treatment options used so far in Denmark, while we wait for valid and well-designed randomized controlled trials (RCTs) as mentioned in Sigra et al. [5].

Materials and Methods

We reviewed medical charts on 15 patients with suspected PANS/PANDAS evaluated in the Danish national Tourette syndrome clinic in the period February 2014 until June 2017. Patients were referred to the clinic from their general practitioner, pediatricians or the emergency department. All patients were initially seen by a pediatric neurologist and a nurse with specific training in movement disorders and examined according to the local guidelines [17].

Patients with an atypical debut of neuropsychiatric symptoms, compared to chronic tic disorders, were evaluated in the department´s multidisciplinary team and if there was consensus for suspected PANS/PANDAS diagnosis they were given the diagnosis PANDAS/PANS and later included in this review.

During the first examination and during flares, patients were examined with a throat culture and blood samples; antistreptolysin-O (ASO) (reference value, positive >200) and anti-deoxyribonuclease B (DNase B) (reference value, positive ≥ 800) to evaluate for the presence of GAS. Furthermore, anti-neuronal antibody titers were measured in serum; CAM-KII (reference value, elevated ≥ 131%), lyso GM1 antibodies (reference value, elevated ≥ 321 titer), anti-beta-tubulin antibodies (reference value, elevated ≥ 1001 titer), dopamine D1 (reference value, elevated 2001 titer) and dopamine D2 antibodies (reference value, elevated ≥ 8001 titer) [18]. Both the titers of the anti-neuronal antibodies and CaM kinase II activity

are positively correlated with disease activity meaning that the higher the value, the more severe symptoms are present. Some patients were furthermore examined with lumbar puncture, MRI and/or EEG, depending on the presenting symptoms.

Patient charts were reviewed with focus on diagnostic criteria, patient demographics, symptom onset, laboratory tests, and treatment. Treatment effect was evaluated by parents and patients themselves. Diagnoses of PANDAS and PANS were made according to the diagnostic criteria. Those who did not fulfill all PANDAS or PANS diagnostic criteria were categorized as having "PANDAS minus the missing criteria" or "Acute onset movement disorder not associated to streptococcal disease".

Results/Observations

Most patients included in our cohort were male (66.7%) and the mean age at onset was 8.0 years ± 4.1. The mean age of the patients at time of referral was 8.2 years ± 4.0 (Table 1). Preexisting but low-level neuropsychiatric symptoms were seen in 20.0% and included behavioral disturbances, sleep disorder and anxiety (these were not included as symptoms in the PANS/PANDAS evaluation seen in Table 1). Psychiatric disorders in first-degree family members were reported in 13.3% of the cases, these included ADHD and stutter.

Of the 15 patients included in this study, nine fulfilled the diagnostic criteria of PANDAS (60%) and two fulfilled the PANS criteria (13.3%) (Table 1). Four patients (26.7%) did neither fulfill the PANDAS or PANS criteria. Of these four patients, two had abrupt onset of tics, but did not fulfill PANDAS criteria due to post-pubertal age of onset (14 and 17 years old respectively) and absence of association with GAS infection. They did not fulfill PANS criteria either due to absence of OCD and/or restricting food intake. These two patients were categorized as "Acute onset movement disorder not associated to streptococcal disease". The third patient neither fulfilling PANDAS nor PANS criteria did have clinical symptoms and association with GAS infection, but age of onset was post-pubertal (15 years old)." age of onset was post-pubertal (15 years old). He did not have OCD and/or restricted food intake. He was categorized as "PANDAS minus age criteria". The fourth patient fulfilled all PANDAS criteria except acute onset and was therefore categorized as "PANDAS with sub-acute onset".

Symptoms started acutely (within 3 days) in 93.3% of the patients and sub-acutely (within 2 months) in 6.7%. The prevalence of symptoms is reported in Table 1. Tics were the most prevalent symptom followed by sleep disturbance, behavioural disturbances including irritability and aggression,

Demographic characteristics and symptoms of 15 children with suspected PANS/PANDAS*		
Demographic characteristics and past medical history of 15 patients		
Age at first contact to the clinic (mean ± SD)	8.2 years ± 4.0	
Age at symptoms onset (mean ± SD)	8.0 years ± 4.1	
Male gender	10/15 (66.7%)	
Preexisting neuropsychiatric disorders	3/15 (20.0%)	
First degree family member with history of neuropsychiatric disorder	2/15 (13.3%)	
Symptoms of 15 children with suspected PANS/PANDAS		
Symptoms	**Total cohort n=15**	
	n	**%**
Obsessive Compulsive Disorder	6	40.0
Tics (motoric and/or vocal)	13	86.7
Vocal tics only	2	13.3
Motoric tics only	5	33.3
Eating restriction	3	20.0
Anxiety	8	53.3
Behavioral disturbances including irritability and aggression	9	60.0
Enuresis	1	6.7
Sleep disturbance	10	66.7
Somatic symptoms	3	20.0
Motoric control abnormalities	8	53.3
Elective mutism	1	6.7
Stutter	1	6.7
Symptom onset		
Acute onset	14	93.3
Sub-acute	1	6.7
Patients meeting diagnostic criteria		
PANDAS criteria	9	60
PANDAS minus age criterion	1	6.7
PANDAS with sub-acute onset	1	6.7
PANS criteria	2	13.3
Acute onset movement disorder not associated to streptococcal disease	2	13.3

*Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)/Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)

Table 1. *Demographic characteristics and symptoms of 15 children with suspected PANS/PANDAS.*

anxiety, motoric control abnormalities (described as altered handwriting, reduced use of extremities and/or altered balance), OCD, and eating restrictions. Somatic symptoms including nausea, vomiting, headache and joint pain were the least common presenting symptoms. Stutter, elective mutism and enuresis were reported in one patient each.

Six patients (40.0%) had both OCD and tics, seven patients (46.7%) had only tics with no OCD and two patients (13.3%) had only OCD without any tics. All patients had a relapsing/ remitting course of the symptoms.

All patients were examined with ASO and/or a throat culture at the first visit in the hospital. Positive GAS infections were found in 11 patients (73.3%) and most often, streptolysin-O AB was found to be positive (Table 2). DNAse B was not performed routinely. In most cases, it was unknown whether the patients had been evaluated for streptococcal infection prior to symptom onset and/or prior their first visit in the clinic.

Anti-neuronal antibody titers were taken in 14 patients (besides dopamine D2 only taken in 13 patients). CaM kinase II and anti-beta-tubulin antibodies were most often positive. In two patients, anti-neuronal antibody titers were repeated in a period without symptoms, where decreased values of CaM kinase II were found and normalized values of anti-beta-tubulin and dopamine D2 antibodies.

If presenting symptoms raised suspicion of another acute neurological disease, the patient was examined with lumbar puncture, MRI and/or EEG. Nine patients were examined with at least one of these tests. No pathological findings were found on MRI or EEG, but two lumbar punctures showed elevated cell counts and protein and these patients were treated with intravenous antibiotics. Culture of cerebral spinal fluid was negative in both cases.

Treatment used is reported in Table 2. All 15 patients (100%) were treated initially with antibiotics which had a positive effect in 11 (73.3%) patients. In eight patients (53.3%) prophylactic antibiotic was tried with a positive effect in all patients. Antibiotic drugs used were amoxicillin, benzylpenicillin, phenoxymethylpenicillin, clarithromycin, amoxicillin and potassium clavulanate, azithromycin and dicloxacillin. Furthermore, all patients who were bothered by their symptoms were offered standard psychiatric treatment consisting of behavioral therapy and/or medication. Positive effect was

Laboratory tests of 15 children with suspected PANS/PANDAS				
Test	**Number of patients test performed in**		**Positive finding in taken tests**	
	n	%	n	%
Anti-streptolysin-O and anti-deoxyribonuclease B	13	86.7	8	61.5
Streptococcus throat culture	13	86.7	5	38.4
Anti-neuronal antibody titers				
Anti-beta-tubulin	14	93.3	9	64.3
Dopamine D1	14	93.3	4	28.6
Lyso GM1	14	93.3	3	21.4
Calmodulin-dependent kinase II	14	93.3	10	71.4
Dopamine D2	13	86.7	4	30.8
Lumbar puncture	7	46.7	2	28.6
MRI	8	53.3	0	0
EEG	4	26.7	0	0
Treatment of 15 children with suspected PANS/PANDAS				
Treatments	**Number (n) of patients treatment given to**		**Number of patients with treatment effect (some or good effect)**	
Type of treatment	n	%	n	%
Acute antibiotic treatment	15	100	11	73.3
Prophylactic antibiotic treatment	8	53.3	8	100
Steroid	2	13.3	1	50
Intravenous immunoglobulin	4	26.7	4	100
Ibuprofen	3	20	3	100
Tonsillectomy	2	13.3	2	100
Psychiatric standard treatment				
Cognitive therapy	1	6.7	1	100
Behavioural therapy	2	13.3	1	50
Clonidinhydrochlorid	4	26.7	3	75
Methylphenidate	3	20	2	66.7
Aripiprazole	2	13.3	1	50
Risperidone	2	13.3	2	100
Sertraline	2	12.5	1	50
Lisdexamfetamine	1	6.7	0	0
Atomoxetine	1	6.7	0	0

Table 2. *Laboratory tests and treatment of 15 children with suspected PANS/PANDAS.*

reported in more than half (50 - 100%). Three patients (20%) with persisting symptoms despite antibiotic and psychiatric treatment were treated with IVIG for five days. Two patients with persisting severe symptoms despite above mentioned treatment, were treated with intravenous steroids. Two patients (13.3%) underwent tonsillectomy at another hospital department on parental request and both experienced a positive effect.

Discussion

Although the diagnosis PANDAS/PANS has been controversial, more focus has come on the diagnosis, pathophysiology and treatment during the recent years. In our study we have evaluated 15 patients who had abrupt onset of tics and/or OCD with significant comorbid neuropsychiatric symptoms including sleep disturbance, behavioral disturbances, anxiety, motoric control abnormalities, selective mutism and stutter. Somatic symptoms including nausea, vomiting, headache, joint pain and enuresis were seen also. Common for all patients was that parents and the patients described symptom start very acuity.

GAS infection

Although there is found evidence for an association between GAS and PANDAS from clinical, epidemiological, prospective studies and animal models (see for review [13]), it can be difficult to identify a GAS infection in patients presenting with a sudden onset of neuropsychiatric symptoms.

Two of the patients in our study (13.3%) did not fulfil the criteria for PANDAS, among others due to lack of association with GAS infection. In a study by Swedo et al. it was found that 22% of the community cases failed to meet PANDAS criteria due to absence of documented GAS infection [19]. Both throat cultures and GAS antibodies titers can be false negative or false positive and there might be a latent period between GAS infection and the onset of PANDAS symptoms [13]. Furthermore, as recognized in the PANS criteria, infections other than GAS may trigger acute onset or exacerbations of neuropsychiatric symptoms, probably through nonspecific immune activation mechanisms [13]. Therefore, we argue that the sudden onset of neuropsychiatric symptoms on PANDAS/PANS should be related to an infection, but not necessarily a GAS infection.

Anti-neuronal antibody titers

In our clinic, we have routinely evaluated anti-neuronal antibody titers and we found that minimum one anti-neuronal antibody titer was positive in 92.8% of the 14 patients tested. Most often, protein CaM kinase II was positive. Some studies have found elevated titers of antibodies against lysoganglioside, tubulin, dopamine D2 receptor and dopamine D1 receptor in serum samples from acutely ill children with PANDAS [6,12], while others have not [4]. As far as we know, anti-neuronal antibody titers are not described as a part of the regular examination in a child with suspected PANDAS/PANS. Further prospective and longitudinal studies are needed in order to examine whether these titers can be used both in the diagnostic process and in evaluation of treatment efficacy.

Diagnostic criteria

Major criteria: Although acute onset of neuropsychiatric symptoms triggered by an infection is part of the diagnostic criteria of both PANS and PANDAS, the major criteria of the two diagnoses are different. For example, tics are not included in the criteria of PANS.

In the first 50 cases of PANDAS described in 1998 [2], Swedo et al. found that 16% had tics only, 64% had (subclinical) OCD and tics, and 10% had OCD-only. In our study a larger part of the cohort had tics only (46.7%) or both OCD and tics (40.0%). This is probably due to the fact that our clinic is a tertiary Tourette syndrome clinic with specialty in tic disorders. Probably a larger part of PANDAS suspected patients with OCD-only will be referred to a child and adolescent psychiatric department. Although the pathophysiology of the diseases is not fully understood yet, in both PANDAS and PANS it is suggested that antibodies generated against an infectious agent cross-react with neuronal components in the basal ganglia, caudate, putamen and globus pallidus [4,12]. Some of these structures are involved both in the pathophysiology of OCD and of tics [20-22], and therefore one might suspect the same symptoms in both PANS and PANDAS. In our cohort, three patients could not be diagnosed with PANS due to absence of OCD and/or eating restriction, although these patients presented with acute onset of tics and other neuropsychiatric symptoms after a suspected infection.

Age of onset: Age of onset is part of the diagnostic criteria of PANDAS, but not of PANS. In our cohort, one patient could not be diagnosed with PANDAS because of late onset (15 years old), although he fulfilled the other diagnostic criteria. One might suspect the pathophysiological mechanisms of PANS/PANDAS to be the same both pre- and post-pubertal and thus, symptoms might theoretically be the same as well.

We argue, that it might be considered to merge the diagnostic criteria of PANDAS and PANS, since the supposed pathophysiological mechanisms behind PANDAS and PANS are expected to be similar. Therefore, one might expect the similar sudden onset of the same neuropsychiatric symptoms both in PANDAS and in PANS and regardless of the age of the patient. Thus, we suggest the diagnostic criteria to include sudden onset of tics and/or OCD in childhood (until age 18 years).

Treatment

All our patients were initially treated with antibiotics and a positive effect was reported by the parents in 73.3%. As described in the introduction, the recently published guidelines from the PANS Research Consortium recommend antimicrobial treatment in a newly diagnosed patient independent on the presence of a verified infection [13]. Although this is in contrast to the current practice regarding rational pharmacotherapy [23], our study has shown that parents report positive effect of antibiotic treatment.

Although there is no evidence for standard secondary prophylactic antibiotic treatment according to PANS Research Consortium [13], half of our patients have been treated with prophylactic antibiotics with a positive effect in all.

Immunomodulating therapy (NSAID, steroid and/or IVIG) was used in nine patients with a positive effect in all.

Limitations

This study has several limitations. Since it is a descriptive, retrospective study, limitations include reliance on history and evaluation of treatment by parental report, small number of patients, possible overlooked infections, recall bias and lack of detailed medical records.

Patients in this study were referred to the Danish national Tourette syndrome clinic, which might cause an overrepresentation of patients with tics compared with other neuropsychiatric symptoms as OCD or anxiety. Patients were only evaluated for other infections than GAS infections if there was clinical suspicion.

Conclusion

This article describes the first Danish clinical cohort of patients with unusually abrupt onset of tics and/or OCD and with significant comorbid neuropsychiatric symptoms in relation to a suspected infection. 60% of patients fulfilled the diagnostic criteria of PANDAS and 13.3% fulfilled the PANS criteria. We argue that it might be valuable to merge the diagnostic criteria of PANDAS and PANS, since the supposed pathophysiological mechanisms behind PANDAS and PANS are expected to be similar and therefore should give similar sudden onset of the same neuropsychiatric symptoms. Furthermore, we argue that debut of symptoms should be in childhood (until age 18 years) in contrast to prepubertal debut (i.e., between 3 years of age and the beginning of puberty) as stated in the present diagnostic criteria. Based on the findings of our study, we suggest that the diagnostic criteria should include sudden onset of tics and/or OCD in childhood in relation to an infection, but not necessarily a GAS infection. In this descriptive, retrospective study we have seen a positive effect of acute and prophylactic antibiotic treatment, psychiatric treatment and immunomodulating treatment, according to parental reports.

Clinical Significance

Our data on symptoms, diagnostic testing, treatment and effect should encourage further evaluations of patients with suspected PANDAS/PANS. Further clinical studies with larger cohorts of both children and adolescents with suspected PANDAS/PANS, studies on the pathophysiology, and RCTs are needed to increase knowledge and evidence regarding diagnostic tests and treatments and to evaluate diagnostic criteria. Until further research has found further evidence, the current literature including clinical experiences as described in case series, must guide clinicians in examination and treatment of patients with suspected PANS/PANDAS. The 2017 guidelines from the PANS Research Consortium are a first step to achieve consensus in the field and should result in further scientific evaluation on how to obtain consensus on international evidence-based concepts.

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