Microbes and Infectious Diseases 2023; 4(4): 1255-1265

Microbes and Infectious Diseases

Journal homepage: https://mid.journals.ekb.eg/

Original article

Clinicolaboratory characteristics of pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections: A cross-sectional study

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ARTICLE INFO

Article history:
Received 5 August 2023
Received in revised form 25 August 2023
Accepted 27 August 2023

Keywords:
Anti Dnase B
ADH
ASO
GABHS infection
PANDAS
OCD
Tic disorders
Tourette syndrome

ABSTRACT

Background: A B-hemolytic streptococcal infections (GABHS) have been linked to obsessive-compulsive disorder (OCD) and tic disorders, leading to pediatric autoimmune neuropsychiatric diseases associated with streptococcal infections (PANDAS). This study aims to characterize the clinical and laboratory profile of a group of PANDAS patients and to relate between GABHS infection and their neuropsychiatric manifestations. **Methods:** a cross-sectional study was conducted between January2022 and January2023. We included all pediatric patients who had PANDAS using the following criteria: tic disorder and/or OCD; Presence of relationship between GABHS infection and disease onset and/or exacerbations. Streptococcal diagnosis for all cases was conducted using throat swab culture and measuring serum anti-streptolysin O(ASO) antibody titer, anti-deoxyribonuclease B (Anti Dnase B). **Results:** We diagnosed PANDAS in 76 patients. The mean age of patients was 6.8 ± 1.90 years. Motor tics occurred in 37 patients (48.7%), verbal tics in 6 patients (7.9%) and combined tics in 33 patients (43.4%). Attention deficit hyperactivity (ADH), Tourette syndrome, and OCD were identified in 27.6%, 18.4% and 15.8% of patients, respectively. Of all patients, 31 (40.8%) had pathologic Anti Dnase B antibody titer, 27 (35.5%) had pathologic (ASO) antibody titer, and GABHS were isolated from throats in 14 patients (18.4%). There was moderate agreement between GABHS throat culture and both ASO antibody titer (Kappa=0.58; p<0.001) and Anti Dnase antibody titer (Kappa=0.49; p<0.001). Of note, there was substantial agreement between ASO and Anti Dnase antibody titers (Kappa=0.78; p<0.001). **Conclusion:** The diagnosis of PANDAS requires careful assessment, including documentation of neuropsychiatric symptoms associated with evidence of GABHS infection.

Introduction

The abrupt onset of new neuropsychiatric symptoms in children can be challenging for parents and physicians. Physicians must consider a wide variety of differential diagnoses, and decisions must

DOI: 10.21608/MID.2023.227202.1582
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be made regarding the selection of diagnostic studies as well as the choice of therapy [1].

The pediatric autoimmune neuropsychiatric syndrome associated with streptococcal infection (PANDAS) is a distinct subtype of Pediatric acute neuropsychiatric syndrome that describes patients with acute onset obsessive-compulsive disorder (OCD) and/or tic disorders associated with group A Beta-hemolytic streptococcal infections (GABHS) [2-4]. Experts hypothesized that PANDAS is caused by streptococcal antibodies by molecular mimicry, cross-reactive antigens are molecules on the group A streptococcus that mimic host molecules and during infection or immunization induce an autoimmune response against host tissues leading to the autoimmune group A streptococcal sequela [5]. Neuroinflammation persists as dopamine receptors in the basal ganglia and other kinds of neurons in the cortex are dysregulated [6, 7].

Pediatricians suspect PANDAS in children with sudden onset of neuropsychiatric symptoms, recent GABHS infection, and remission of these symptoms following antibiotic therapy. PANDA patients should be monitored for recurrence of neuropsychiatric symptoms and/or GABHS infection since approximately 50% experience a second episode. Early detection and treatment of GABHS may assist in avoiding the development of illness and limit relapses [8, 9].

Despite ongoing research, the association between GABS and PANDAS remains controversial. Pediatricians are frequently unaware of or dismiss the PANDAS diagnosis. Unfortunately, many healthcare providers are unaware of PANDAS or have no experience diagnosing it. Before accepting an accurate diagnosis, parents frequently consult multiple healthcare providers. A pediatrician or PANDA specialist may be able to provide appropriate care [10]. As a result, this study aimed to describe the clinical and laboratory profile of a group of patients diagnosed with PANDAS and to examine the association between streptococcal infection and their neuropsychiatric manifestations [10].

Subject and methods

This is a cross-sectional study, it was conducted between January 2022 and January 2023, in the Pediatric Neuropsychiatry Unit of Zagazig University Children's Hospital and Microbiology and immunology department. This study included all pediatric patients under 18 years of age at the time of diagnosis of PANDAS who did not meet the exclusion criteria, including chromosomal abnormalities, neurological syndromes, brain injury, cerebral abnormalities, systemic diseases associated with neuropsychiatric symptoms, and other predefined neuropsychiatric disorders, resulting in the enrollment of 76 consecutive children with PANDAS, aged 4 to 12 years, in the Zagazig University ethical approval (IRB approval) and informed consents were obtained from parents.

Definitions

PANDAS: PANDAS patients were diagnosed based on the following criteria, which include: Tic disorder (Tourette syndrome, chronic motor tic disorder, or vocal tic illness) and/or OCD (according to DSM IV criteria); onset in childhood (between the ages of three and puberty); Tics are rapid, recurrent, non-rhythmic, and stereotyped movements or vocalizations that can be simple or complex) [3];Symptoms may appear suddenly and progress in an episodic manner; The link between GABHS infection and the onset and/or progression of the disease; Neurologic abnormalities such as motoric hyperactivity, choreiform movements, or tics may arise during exacerbations [11,12]. A pediatric neurologist performed a thorough somatic and neurologic assessment on all children, measuring motor and cognitive abilities as well as dyskinesia. To measure OCD, behavioral traits, nonverbal IQ, and tics, the Yale Global Tic Severity Scale (YGTSS) [13, 14] and Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) were used [15].

Laboratory assessment of GABHS infections

Microbiological throat swabs were taken in duplicate. A sterile cotton swab was used to swab any apparent exudates or hyperaemic areas on the tonsillar walls, and the tongue was pressed down as needed with a wooden spatula. All swab samples were forwarded to the Microbiology laboratory as soon as possible. Swabs were cultured on blood agar (BA), chocolate agar (CA), and MacConkey (MAC) agar (Himedia, India) for 48 hours at 37°C. Chocolate agar was incubated in a candle jar with 5% CO_2, whilst BA and MAC were incubated at normal conditions [16,17].

Beta-haemolytic streptococci isolates were taken by being white to grey colony with a zone of beta haemolysis of 2-3 mm in diameter surrounding each

colony plus, Gram positive cocci grouped in a chain and were both coagulase and catalase negative [18].

Blood samples were taken from patients, and serum separated from the collected samples was maintained at 20°C for further immunological investigations.

Antistreptolysin O tests were performed using the ASO-latex slide agglutination test developed by Biomed Diagnostics. The results were compared to positive and negative controls. ASO titre is evaluated as a baseline followed by a second measurement 6 - 8 weeks later to identify a rise of 2 to 4 times, suggesting recent infection in children with negative throat culture[19].

ELISA assay for anti Deoxy ribonuclease B using (Human anti deoxyribonuclease B antibody) ELISA Kit, MyBiosource, Inc.

Principle of the Assay: The competitive enzyme immunoassay approach is used in the Anti-DNA-B ELISA kit, which includes Deoxyribonuclease B antigen and an Anti-DNA-B-HRP conjugate. In a pre-coated plate, the test sample and buffer are incubated for one hour with the Anti-DNA-B-HRP conjugate. The wells are emptied and washed five times after incubation. The wells are then treated with an HRP enzyme substrate. The result of the enzyme-substrate reaction is a blue complex. Finally, a stop solution is added to cease the reaction, which causes the solution to become yellow. Colour intensity is measured spectrophotometrically in a microplate reader at 450nm. Because anti-DNA-B from samples and anti-DNA-B-HRP conjugate compete for the Deoxyribonuclease B antigen binding site, the intensity of the colour is inversely proportional to the concentration of anti-DNA-B. A standard curve is constructed that relates the colour intensity (OD) to the concentration of standards. The concentration of anti-DNA-B in each sample is estimated from this standard curve.

ASO titres more than 240 Todd units and Anti Dnase B titres greater than 300 IU/mL were deemed to be diagnostic of recent streptococcal infection.

Data collection

A thorough medical history that includes age, gender, developmental, and psychiatric history, as well as past and present symptoms of psychiatric, neurological, neurodevelopmental, infectious, autoimmune, and rheumatic diseases. Each patient underwent a thorough clinical examination, and laboratory data such as ASO titers, Anti Dnase B titers, and throat swab culture were taken for GABHS diagnosis.

Statistical analysis

All data were collected and statistically analyzed using IBM SPSS Statistics for Windows 20.0, Armonk, NY: IBM Corp. We performed descriptive analysis for variables in this study, including mean with standard deviation (SD) and median with interquartile range (IQR) for quantitative variables and frequencies with percentages for categorical variables. A Chi-square test was used to compare between clinical characteristics of the studied patients and evidence of streptococcal infection. Cohen's Kappa test of agreement, Mann-Whitney, and Kruskal-Wallis tests were used. The statistical significance level was present if $p \leq 0.05$.

Results

Basic and clinical features of the study participants

We diagnosed PANDAS in 76 patients (44 females and 32 males) during the study period. The mean age of the examined patients at the time of diagnosis of PANDAS was 6.8 ± 1.90 years. Of all patients, 21 patients (27.6%) had attention-deficit hyperactivity (ADH), 14 patients (18.4%) had Tourette syndrome, and 12 patients (15.8%) had OCD. Motor tics were noticed in 37 patients (48.7%), verbal tics in 6 patients (7.9%) and combined tics in 33 patients (43.4%) **(Table 1).**

The laboratory evidence of GABHS infection

Positive throat cultures for GABHS, pathologic ASO antibody titer (if >240 Todd Units), and pathologic Anti Dnase B antibody titer (if >300 IU) were found in 18.4 %, 35.5 % and 40.8 % of patients, respectively. There was moderate agreement between GABHS throat culture and ASO antibody titer (Kappa=0.58; $p<0.001$) and Anti Dnase B antibody titer (Kappa=0.49; $p<0.001$). In addition, there was substantial agreement between ASO and Anti Dnase B antibody titers (Kappa=0.78; $p<0.001$) **(Table 2).**

Relation between GABHS and clinical characteristics of the studied patients

Pathologic ASO antibody titer was significantly found in patients with combined tics and OCD (p 0.005; p 0.01; respectively), while pathologic Anti Dnase B antibody titer was significantly found in patients with combined tics, OCD, Tourette syndrome and ADH (p 0.003; p 0.04; p 0.01; p 0.02; respectively) **(Table 3).**

The ASO antibody titer was significantly increased in patients with combined tics (p 0.003), ADH (p 0.04), and OCD (p 0.03). Furthermore, Anti Dnase B antibody titer was significantly increased in patients with combined tics (p<0.001), ADH (p 0.03), OCD (p 0.03), and Tourette syndrome (p 0.04) **(Table 4).**

Table 1. Clinical characteristics of the studied group

Characteristics	**(N=76)**
Age (years)	
Mean ± SD	6.8 ± 1.90
Range	4 - 12
Sex	
Male	32 (42.1%)
Female	44 (57.9%)
Type of tics	
Motor tics	37 (48.7%)
Vocal tics	6 (7.9%)
Combined tics	33 (43.4%)
ADH	
No	55 (72.4%)
Yes	21 (27.6%)
OCD	
No	64 (84.2%)
Yes	12 (15.8%)
Tourette syndrome	
No	62 (81.6%)
Yes	14 (18.4%)

ADH; Attention-deficit hyperactivity, OCD; obsessive–compulsive disorder, SD: Standard deviation

Table 2. Evidence of GABHS infection among the studied group.

Variable	**(N=76)**
Throat culture for GABHS	
-ve	62 (81.6%)
+ve	14 (18.4%)
ASO antibody titer	
Non pathologic if ≤ 240 Todd Units	29 (64.5%)
Pathologic if >240 Todd Units	27 (35.5%)
Mean ± SD	200.87 ± 183.1 Todd Units
Median (IQR)	115 (68-307.5) Todd Units
Range	45 – 816 Todd Units
ADB antibody titer	
Non pathologic if ≤ 300 IU	45 (59.2%)
Pathologic if > 300 IU	31(40.8%)
Mean ± SD	212.49 ± 133.28 IU
Median (IQR)	150 (89.25-333) IU
Range	43 – 450 IU
Agreement	
ADB antibody titer and throat culture	Kappa=0.49 (*P*<0.001**)
ADB and ASO antibody titers	Kappa=0.78 (*P*<0.001**)
Throat culture and ASO antibody titer	Kappa=0.58 (*P*<0.001**)

ADB; anti-deoxyribonuclease B, ASO; anti-streptolysin O, GABHS: Group A B-hemolytic streptococcal infections, IQR: Inter quartile range, SD: Standard deviation

Cohen's Kappa test of agreement

**Highly significant (p<0.001)

Table 3. Clinical characteristics and GABHS infection of study patients.

Clinical features	**N**	**Throat Culture for GABHS**		***P*** χ^2	**ASO antibody titer**		***P*** χ^2	**ADB antibody titer**		***P*** χ^2
		-ve N (%)	**+ve N (%)**		**Non pathologic N (%)**	**Pathologic N (%)**		**Non pathologic N (%)**	**Pathologic N (%)**	
Tics										
Motor	37	28 (75.7)	9 (24.3)	0.29	28 (75.7)	9 (24.3)		26 (70.3)	11 (29.7)	
Vocal	6	6 (100)	0 (0)	NS	6 (100)	0 (0)	0.005	6 (100)	0 (0)	0.003
Combined	33	28 (84.8)	5 (15.2)		15 (45.5)	18 (54.5)	*	13 (39.4)	20 (60.6)	*
ADH										
No	55	46 (83.6)	9 (16.4)	0.45	39 (70.9)	16 (29.1)	0.06	37 (67.3)	18 (32.7)	0.02*
Yes	21	16 (76.2)	5 (23.8)	NS	10 (47.6)	11 (52.4)	NS	8 (38.1)	13 (61.9)	
OCD										
No	64	53 (82.8)	11 (17.2)	0.52	45 (70.3)	19 (29.7)	0.01*	41 (64.1)	23 (35.9)	0.04*
Yes	12	9 (75)	3 (25)	NS	4 (33.3)	8 (66.7)		4 (33.3)	8 (66.7)	
Tourette syndrome				0.23			0.06			0.01*
No	62	49 (79)	13 (21)	NS	43 (69.4)	19 (30.6)	NS	41 (66.1)	21 (33.9)	
Yes	14	13 (92.9)	1 (7.1)		6 (42.9)	8 (57.1)		4 (28.6)	10 (71.4)	

ADB; anti-deoxyribonuclease B, ADH; Attention-deficit hyperactivity, ASO; anti-streptolysin O, GABHS: Group A B-hemolytic streptococcal infections, OCD; obsessive–compulsive disorder

χ^2: Chi square test NS: non-significant (p>0.05) *: Significant (p≤0.05)

Table 4. Clinical characteristics and serologic evidence of GABHS infection of study patients.

Clinical features	**N**	**ASO antibody titer** (Todd Unit) **Median (IQR)**	**test**	***P***	**ADB antibody titer** (IU) **Median (IQR)**	**test**	***P***
Tics							
Motor	37	78 (57-245)			112 (84.5-310.5)		<0.001**
Vocal	6	76 (50-80)	KW	0.003* S	70 (65-78)	KW	HS
Combined	33	279 (120-355)	11.89		330 (160-364)	22.04	
ADH							
No	55	88 (59-280)	MW	0.04* S	120 (80-322)	MW	0.03* S
Yes	21	290 (78-370)	2.01		329 (112-350)	2.16	
OCD							
No	64	89 (62-290)	MW	0.03* S	120 (89-322)	MW	0.03* S
Yes	12	315 (130-525)	2.21		341.5(219-387)	2.14	
Tourette syndrome							
No	62	90 (60-292.5)	MW	0.27 NS	130 (86.75-320.5)	MW	0.04* S
Yes	14	280 (68-350)	1.10		333 (105-381)	2.04	

ADB; anti-deoxyribonuclease B, ADH; Attention-deficit hyperactivity, ASO; anti-streptolysin O, GABHS: Group A B-hemolytic streptococcal infections, IQR: inter quartile range, KW: Kruskal Wallis test, MW: Mann Whitney, OCD; obsessive–compulsive disorder
NS: non-significant (p>0.05) *: Significant (p≤0.05) **: Highly significant (p<0.001)

Discussion

The current study concluded that PANDAS is not an uncommon neuropsychiatric disorder that can be manifested by OCD, tics, Tourette syndrome, and ADH. The diagnosis of PANDAS requires careful assessment, including documentation of neuropsychiatric symptoms associated with evidence of GABHS infection[15,32].

Although there is a lot of evidence supporting the existence of PANDAS and related disorders, it remains a controversial diagnosis [15]. Despite increasing study, the link between GABS and PANDAS remains debatable. Many pediatricians are unaware of or disregard the PANDAS diagnosis, and many other healthcare practitioners are either uninformed of or have no expertise diagnosing it. Parents usually consult many healthcare experts before adopting a correct diagnosis [10]. As a result, the primary aim of our study was to characterize the clinical and laboratory characteristics of children with PANDAS in an Egyptian tertiary care setting, as well as to evaluate the link between GABHS infection and PANDAS clinical features.

In the current study, we diagnosed PANDAS in 76 patients (44 females and 32 males) during the study period. Motor tics were found in 37 patients (48.7%), verbal tics in 6 patients (7.9%) and combined tics in 33 patients (43.4%). Notably, ADH, Tourette syndrome, and OCD were found to be present in 27.6%, 18.4%, and 15.8% of PANDAS patients, respectively. Also, our PANDAS patients' ADH, Tourette syndrome, OCD, and tics were not caused by any known neurological conditions.

Our results are consistent with previous studies that found that PANDAS patients are more likely to present with variable neuropsychiatric manifestations besides the tic disorder or OCD [21, 22]. According to **Bernstein et al**. [23] 25% of the exacerbations identified in the PANDAS patients showed significantly higher frequency of incidence of hyperactivity, separation anxiety, worsening in handwriting, impulsivity, and deterioration in school performance during their first presentation of psychiatric disease compared to children with OCD not related to PNADAS. The prevalence of unique PANDAS features was not strongly supported by prior research; however, all clinical signs should be taken with caution because they can also be present in children with other psychiatric disorders [24]. In addition, the mean age of our patients was 6.8 years. After several visits to different specialists, most patients received a diagnosis, suggesting that there is a significant lag between the time PANDAS is diagnosed and the actual onset of the disease, underscoring the need to raise physician awareness of this condition.

In the current study, Pathologic Anti Dnase B antibody titer was discovered in 40.8% of PANDAS patients, 35.5% had pathologic ASO antibody titer, and GABHS was found in 18.4% of patients in throat swab culture. Pathologic ASO antibody titer was substantially higher in patients with tics and OCD, whereas pathologic Anti Dnase

B antibody titer was higher in individuals with tics, OCD, Tourette syndrome, and ADH. Patients with tics, ADH, and OCD had considerably higher ASO antibody titers. Furthermore, patients with combined tics, ADH, OCD, and Tourette syndrome had considerably higher Anti Dnase B antibody titers.

These results suggest that GABHS infection is related to PANDAS clinical findings. Consistent with our study results, some previous studies strongly support this association [21-26] but they contradict other studies that firmly deny it [19, 27, 29, 30]. All of these studies agree that further study is needed to understand whether or not this association occurs, as well as the cellular and immunological systems involved.

Moreover, there was a strong association between OCD, tics, and Tourette syndrome and GABHS infection in a US National Health Insurance study [20]. In a study by **Geller et al.** [33] the mean ASO antibody titer, GABHS throat cultures, and anti-basal ganglia antibodies (ABGA) were significantly higher in Tourette syndrome patients than in controls, however there was no difference in ASO antibody titer between children with and without ABGA. According to Church et al. [28], children with Tourette syndrome had a significantly higher ASO antibody titer than normal children with recent GABHS pharyngitis.

Remarkably, Participants who tested positive for streptococcal infection were found to be more likely to have both OCD and tics (51%), compared to those who tested negative for streptococcal infection (30%). As a result, patients who have both OCD and tics may be more likely to have GABHS infections [36]. Recurrent GABHS infections in the preceding year significantly raised the likelihood of Tourette syndrome, implying that antibodies must reach a certain level before the disease manifests itself. Only such alteration of Anti Dnase B and ASO antibody titers is commonly deemed in PANDAS studies and many patients with PANDAS experienced symptoms only after multiple GABHS infections [31, 37,38].

Similarly, children and adolescents with Tourette syndrome may be more likely to have GABHS infections and exhibit more antibacterial and antineuronal antibodies with a stronger immune response to GABHS [24, 39]. Notably, **Snider et al.** [38] concluded that antibiotic therapy with azithromycin and penicillin in children with PANDAS is effective in preventing GABHS infections and GABHS-related psychiatric exacerbations.

Although presence of many studies consistent with our results yet **Schrag et al.** [15] could not prove an association between neuropsychiatric symptoms and GABHS infection by database analysis. Also, **Leckman et al.** [22] found no rise in GABHS exacerbations in the PANDAS group, but a greater exacerbation in the control group, and found that there is no evidence of an association between GABHS infections and exacerbations of tic/OCD symptoms in children who fulfil the established PANDAS diagnostic criteria.

The differences in the results of these studies can be explained by evaluating different patient populations with underlying patient characteristics and inclusion criteria, which may include differences in an upper limit of normality of antibody detections for GABHS. When a true GABHS infection occurs, Anti Dnase B and ASO levels rise somewhat but stay below the upper limit of normal titers, which is overlooked in the absence of intentional monitoring. The opposite is also true: choosing an antibody titer that is too low can lead to unidentifiable discrepancies between PANDAS patients and healthy controls [34,35].

PANDAS is a diagnosis of exclusion, so patients referred for testing may have seen multiple physicians and tried various therapies before the correct diagnosis was made. In patients with these disorders, prolonged illness before proper diagnosis and treatment may affect the outcome of a therapy course and the length of time to observe improvement in their symptoms [19, 40]. A full medical and psychiatric history, a thorough physical examination, a comprehensive cognitive assessment, and a series of laboratory testing are required to identify PANDAS and associated disorders. Further targeted blood tests should also be carried out if there is a suspicion of a medical explanation for the neuropsychiatric symptoms [19].

The current study has many strengths, including identifying the clinical spectrum of patients with PANDAS and helping in tracking these patients to reduce the disease burden. In addition, it may assist healthcare providers in providing an appropriate diagnosis to this group of patients. There is a need to improve PANDAS diagnosis for better estimation of PANDAS patients to decrease morbidity.

The main limitations of this study are its retrospective nature and absence of both control

group and long-term monitoring of the bacteriological and antibody titers parameters of PANDAS patients and controls to verify any newly discovered GABHS infections that weren't present before. Studies that follow patients from the initiation of tics provide more useful information, but they are considerably more challenging to conduct and can only follow a reduced number of patients. Future prospective multicenter studies including clinical trials are warranted to prove the association of GABHS infections and neuropsychiatric manifestations and efficacy of antibiotics therapy of GABHS to reduce PANDAS manifestations.

Conclusion

PANDAS is not an uncommon neuropsychiatric disorder that can be manifested by OCD, tics, Tourette syndrome, and ADH. The diagnosis of PANDAS requires careful assessment, including documentation of neuropsychiatric symptoms associated with evidence of GABHS infection. There is a need to improve PANDAS diagnosis for better estimation and earlier detection of PANDAS patients to decrease morbidity.

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