The relationship between group A beta hemolytic streptococcal infection and psychiatric symptoms: a pilot study

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SUMMARY: Çengel-Kültür SE, Çöp E, Kara A, Cengiz AB, Uludağ AK, Ünal F. The relationship between group A beta hemolytic streptococcal infection and psychiatric symptoms: a pilot study. Turk J Pediatr 2009; 51: 317-324.

The aim of this study was to test if children with group A beta hemolytic streptococcal infection (GABHS) are more likely to develop neuropsychiatric symptoms or the syndrome of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection (PANDAS) compared to children with GABHS-negative throat cultures. Children aged 8 to 12 years (n=81) with upper respiratory tract infection were assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children **- Present and Lifetime Version, Children's Yale Brown Obsession Compulsion Scale, Yale Global Tic Severity Scale, Child Behavior Checklist for Ages 4-18, Conners Parent Rating Scale, and State-Trait Anxiety Inventory for Children at baseline and six weeks later. One case of PANDAS was diagnosed and no other differences were observed between groups and time points. It was suggested that GABHS infection may be a triggering factor for PANDAS in some genetically prone individuals.**

Key words: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection (PANDAS), neuropsychiatric disorders, streptococcal infection, autoimmunity, behavioral symptoms.

Following the report of the first 50 cases by Swedo and colleagues[1], neuropsychiatric and behavioral symptoms occurring after streptococcal infection have been identified and named using the acronym PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection)[1-5]. It is proposed that in the molecular pathogenesis of this condition, antibodies developed against the somatic epitopes of group A beta hemolytic streptococci cross-react with some brain structures such as basal ganglia like in post-streptococcal glomerulonephritis, rheumatic fever and Sydenham chorea[2,3,5-9]. Pre-pubertal onset of the neuropsychiatric disorders like obsessive-compulsive disorder (OCD), Tourette syndrome (TS) and tic disorders, acute onset or exacerbation of the symptoms with a full or partial remission, and temporal relation of these disorders with group A beta hemolytic streptococcal (GABHS) infection are listed as the diagnostic criteria for PANDAS[3]. It is reported that along with OCD, TS and tic disorders, psychiatric symptoms such as separation anxiety, hyperactivity, attention deficiency, and emotional liability may also be seen in PANDAS cases[1,10]. Discriminating the PANDAS cases from OCD and/or tic disorders and determining the temporal association of symptoms with GABHS infection are important factors that complicate the clarity of diagnosis. Such difficulties have led to evaluation of the PANDAS hypothesis in many studies; nevertheless, findings of these studies remain controversial[11,12]. While some of them confirm the relationship between GABHS infection and the exacerbation of OCD and tic disorders[13,14], others failed to confirm this relationship[15,16]. The need remains for epidemiological and prospective studies that focus on the nature of PANDAS and on the identification of neuropsychiatric and behavioral symptoms associated with GABHS infections. In this study, it was aimed to investigate the relationship

between GABHS infection and psychiatric diagnoses, attention deficiency-hyperactivity symptoms, behavioral symptoms, anxiety levels, and neuropsychiatric symptom severity, with a prospective cohort study design. To that end, children with GABHS infection were compared to children with GABHS-negative throat culture to evaluate whether the research group was diagnosed more frequently with attention deficiency and hyperactivity disorder (ADHD), OCD, and tic disorder and whether or not they developed higher levels of neuropsychiatric and behavioral symptoms.

Material and Methods

Children aged 8-12 years who admitted to the Pediatric Infectious Disease Outpatients Clinic of Hacettepe University İhsan Doğramacı Children's Hospital with tonsillopharyngitis between December 2003 and December 2004 participated in this study. Based on the throat culture results, those who were GABHS-positive were grouped as the research group (n: 41) and those who were GABHS-negative were grouped as the control group (n: 40). The control group included those who immediately applied after the GABHS-positive child and were matched in terms of age and sex. Children who had cardiac problems compatible with rheumatic fever, severe mental retardation or a major neurological disorder that could interfere with their participation in the study as well as those who had a history of Sydenham chorea, rheumatic fever or any other autoimmune disorders were excluded from the study. All children in the study and their parents provided informed consent.

Following the assessments in the infectious diseases clinic and laboratory tests for GABHS, the patients were referred to the child and adolescent psychiatry clinic, were interviewed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL)[17,18]. To evaluate the neuropsychiatric and behavioral symptoms, Children's Yale Brown Obsession Compulsion Scale (CY-BOCS)[19,20], Yale Global Tic Severity Scale (YGTSS)[21,22], Child Behavior Checklist for Ages 4-18 (CBCL/4-18)[23,24], Conners Parent Rating Scale (CPRS)[25,26] and State-Trait Anxiety Inventory for Children (STAIC)[27,28] were used. The researchers who made the psychiatric assessments (EÇK, FÜ) were blinded to the throat culture results and the file records during the evaluations. Similarly, those who conducted the laboratory tests and those in the pediatrics department were also unaware of the psychiatric assessments. Only one of the researchers (EÇ) was aware of the throat culture results due to her role during the composition of the control group. When there were more than two missing or invalidly marked items (missing values or multiple markings or scratching), the scale was accepted as invalid. All patients were given appropriate treatments according to the protocols of the infectious diseases clinic for their upper respiratory tract infection (URTI).

In total, 81 children (28 girls, 53 boys) were included in the study. Patients were evaluated at two time points: initial interview and six months later using the same psychiatric tools. Seventy-five (92.6%) of the initial sample could be interviewed at the second time point.

Measures

Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL) is a Diagnostic and Statistical Manual of Mental Disorders (4th ed) (DSM-IV)-compatible, semi-structured diagnostic interview designed to assess past and current episodes of Axis I disorders in children aged 6-17 years[17]. Parents are interviewed regarding their children and children are interviewed directly. Diagnosis is based on summary ratings according to information from both informants. The validity and reliability study of the Turkish version of this interview has been conducted by Gökler et al.[18].

Children's Yale Brown Obsession Compulsion Scale (CY-BOC) is a semi-structured tool to measure the severity of OCD signs within the past week[19]. There are five major sections: (1) instructions, (2) obsession screening list, (3) items to determine the severity of obsessions, (4) compulsion screening list, and (5) items to determine the severity of compulsions. Information is gathered from the child and his/her parents. The obsession and compulsion subtotal scores are the sums of items 1-5 and 6-10, respectively. The validity and reliability study of the *Turkish* version of this scale was carried out by Erkal et al.[20].

Yale Global Tic Severity Scale (YGTSS) provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and vocal

symptoms with a semi-structured interview[21]. The reliability study of the *Turkish* version of this scale was made by Zaimoğlu et al.[22].

Child Behavior Checklist for Ages 4-18 (CBCL/4-18) is a parent report scale used to evaluate maladaptive behavioral and emotional problems[23]. With this scale, behaviors were scored in two dimensions as internalizing (i.e., anxious, depressive, and overcontrolled) and externalizing (i.e., aggressive, hyperactive, noncompliant, and undercontrolled) behaviors. The sum of these subscales forms the Total Problem score. Test-retest reliability of the *Turkish* version of this scale was found as.70 and.84 and internal consistency was found as.39 and.86[24].

Conners Parent Rating Scale (CPRS) is a 48-item scale that includes hyperactivity, behavior disorder, attention deficiency, and oppositional defiant disorder subscales self-rated by parents[25]. It is evaluated with a 4-point Likert-type scale. Higher scores from the scale indicate the level of symptoms specific to disruptive behavior disorders. The *Turkish* adaptation study of this scale was made by *Dereboy et al.*[26].

State-Trait Anxiety Inventory for Children (STAIC) was used to determine the subjective anxiety levels and consists of two separate, self-report scales containing 20 items each[27]. One of the sections of this scale, state anxiety inventory (SAI), is used to measure temporary anxiety states. The second section, trait anxiety inventory (TAI), aims to measure the individual differences in anxiety tendency. The *validity* and *reliability study* of the *Turkish* version of this scale was conducted by Özusta[28].

Statistical Methods

Statistical analyses were conducted using SPSS 10.0, 1999 package program. While McNemar test was used for qualitative data, depending on their compliance with the quantitative data, t-test (Student's or paired) and Mann-Whitney or Wilcoxon tests were used. For the variables that complied with the assumptions, two-way ANOVA was also used; therefore, it was determined sufficient to give only the related p values.

Results

Eighty-one children (28 girls, 53 boys [age: 8.97±1.76 years]) were included in the study. However, only 75 (92.6%) of the initial cases could be interviewed at the second time point. When the related parameters were assessed according to the throat culture results (positive-negative), CPRS attention deficiency score, hyperactivity score, oppositional defiant disorder score and conduct disorder score, CBCL internalizing and total problem scores, SAI score, YGTSS motor tic total score, vocal tic total score, total score and overall impairment score, and CY-BOCS compulsion and obsession scores and total score were not statistically different between the children with positive throat culture and those with negative throat culture (Table I). In addition, the values and percentages of change between the interviews for the children with positive and negative throat culture results were also calculated, and also failed to yield any statistically significant differences (Table I).

On the other hand, when CBCL externalizing score was assessed, a statistically significant increase between the first (time 1) and second (time 2) interviews was seen and this increase was similar for both throat culture diagnoses groups (Table I). TAI score was also assessed in a similar way, but this score did not reveal any significant change across interviews or over time for both throat culture diagnoses groups (Table I). However, for both groups, the decrease in TAI score over time approached statistical significance (Table I).

The analyses were repeated in line with the existence of problem in CPRS sub-tests and no statistically significant difference was found (Table II). In order to evaluate a possible interview-throat culture interaction in the CPRS results, total percentages of change were calculated. The rates of children who changed status between the two interviews were similar in both throat culture groups (Table II).

When DSM-IV diagnoses were evaluated, the negative throat culture group did not significantly differ from the positive throat culture group in terms of receiving a psychiatric diagnosis (Table III). One patient in the negative throat culture group who w as taken to follow-up was initially diagnosed with PANDAS in accordance with an acute emergence of OCD symptoms following a new tonsillopharyngitis (GABHS+) during the follow-up. This case is presented below:

Case Report

An 8.5-year-old girl who admitted to the emergency room with complaints of sore throat, fever, and swelling on the neck for one week

Table I. Descriptive Statistics (median-IQR) of Continuous Variables and Related Test Results

		n	Time 1	Time 2	Difference	p-value
CPRS attention deficiency	Positive	28	2 (3.75)	2 (3.00)	0 (0.75)	0.586
	Negative	34	3 (4.00)	3 (4.00)	0 (0.00)	0.523
p-value			0.169	0.252	0.649	
CPRS hyperactivity	Positive	28	3 (4.75)	3 (4.00)	0 (2.00)	0.059
	Negative	34	5 (4.00)	4.5 (3.25)	0 (1.25)	0.583
p-value			0.141	0.033	0.517	
CPRS oppositional defiant disorder	Positive	28	2 (3.25)	2 (3.75)	0 (0.00)	0.797
	Negative	34	3 (3.25)	3 (4.5)	0 (1.25)	0.848
p-value			0.886	0.406	0.913	
CPRS conduct disorder	Positive	28	3.5 (6.75)	3 (6.5)	0 (1.00)	0.456
	Negative	34	3 (7.25)	3 (8.25)	0 (0.5)	0.711
p-value			0.943	0.904	0.772	
CBCL total problem score*	Positive	13	60.61 (14.06)	62.15 (9.79)	-1.54 (7.24)	0.469
	Negative	14	61.57 (15.27)	62.57 (13.16)	-1.00 (10.30)	
p-value					0.877	
CBCL internalizing score	Positive	13	60.00 (13.52)	56.77 (10.22)	3.23 (9.96)	0.149
	Negative	14	59.07 (14.69)	56.14 (12.79)	2.93 (11.41)	
p-value					0.942	
CBCL externalizing score	Positive	13	57.15 (13.46)	59.92 (10.36)	-2.77 (7.08)	0.007
	Negative	14	55.50 (16.07)	61.64 (12.29)	-6.14 (8.63)	
p-value					0.280	
SAI	Positive	9	28.00 (5.50)	28.00 (6.50)	-1.00 (7.00)	0.733
	Negative	11	28.00 (5.00)	28.00 (2.00)	0.00 (7.00)	0.918
p-value			0.396	0.644	0.760	
TAI	Positive	10	35.50 (6.25)	31.00 (10.25)	3.00 (7.00)	0.067
	Negative	11	34.00 (5.00)	27.00 (13.00)	5.00 (12.00)	0.050
p-value			0.804	0.359	0.415	
Motor tics total score	Positive	11	0.54 (1.57)	0.41 (1.39)	0.52	0.581
	Negative	10	0.98 (3.35)	0.29 (1.13)	-1.06	0.285
p-value			0.480	0.690	0.392	
Vocal tics total score	Positive	11	0.11 (0.67)	0	-1.0	0.317
	Negative	10	1.11 (3.39)	1.07±3.17	-2.07	0.062
p-value			0.058	0.057	0.355	
Overall impairment score	Positive	11	1.57±3.98	1.18±4.09	-0.84	0.705
	Negative	10	3.37±6.83	2.68±5.92	-1.06	0.285
p-value			0.142	0.312	0.712	
YGTSS total score	Positive	11	2.23±5.61	1.59±5.46	-0.81	0.588
	Negative	10	4.98±10.01	4.04±9.08	-1.13	0.258
p-value			0.096	0.234	0.645	
Compulsion total score	Positive	11	0.57 (2.2)	0	-1.63	0.102
	Negative	10	1.11 (2.99)	0.41 (2.35)	-1.54	0.123
p-value			0.375	0.266	0.983	
Obsession total score	Positive	11	0.20±0.90	0.17±1.02	0	1.0
	Negative	10	0.63±2.09	0.39±1.86	-1.15	0.249
p-value			0.215	0.533	0.626	
CY-BOCS total score	Positive	11	0.77 (2.42)	0.17±1.02	-1.08	0.279
	Negative	10	1.73 (4.77)	0.87±4.41	-1.54	0.123
p-value			0.239	0.368	0.796	

IQR: Interquartile range. CPRS: Conners Parent Rating Scale. CBCL: Child Behavior Checklist. SAI: State Anxiety Index. TAI: Trait Anxiety Index. YGTSS: Yale Global Tic Severity Scale. CY-BOCS: Children's Yale Brown Obsession Compulsion Scale.

Table II. Distribution of CPRS Subtest Scores According to Time in Throat Culture-Negative and -Positive Groups

CPRS subtests		Throat culture		Time 2 A	Time 2 B	p-value	Percentage of change (%)	p-value
Attention deficiency	Time1	Positive	A	25	2	0.500	7.14	0.841
			B	0	1			
		Negative	A	29	2	0.500	5.88	
			B	0	3			
Hyperactivity	Time1	Positive	A	21	1	0.625	14.28	0.721
			B	3	3			
		Negative	A	22	2	0.687	17.65	
			B	4	6			
Oppositional defiance	Time1	Positive	A	27	0	1.000	0.00	0.197
			B	0	1			
		Negative	A	31	0	0.5	5.88	
			B	2	1			
Conduct disorder	Time1	Positive	A	28	0	–	0.00	–
			B	0	0			
		Negative	A	34	0	–	0.00	
			B	0	0			

A: Score under cut off-point.
B: Score above cut off-point.

Table III. Psychiatric Diagnoses According to DSM-IV

		Positive throat culture		Negative throat culture	
		Time 1 n (%)	Time 2 n (%)	Time 1 n (%)	Time 2 n (%)
No diagnosis		29 (85.3)	29 (85.3)	30 (80.4)	29 (78.3)
Diagnosed		5 (14.7%)	5 (14.7%)	11 (19.6)	12 (21.7)
Distribution of diagnoses*	Anxiety disorders	3 (8.8)	3 (8.8)	4 (9.6)	4 (9.6)
	Attention deficit hyperactivity disorder	0	0	2 (4.9)	2 (4.9)
	Elimination disorders	3 (8.8)	3 (8.8)	3 (7.3)	3 (7.3)
	Obsessive-compulsive disorder	0	0	2 (4.9)	3 (7.3)**
	Tic disorder	0	0	1 (2.4)	1 (2.4)
	Oppositional defiant disorder	1 (2.9)	1 (2.9)	1 (2.4)	1 (2.4)
	Major depressive disorder	0	0	1 (2.4)	1 (2.4)

*Total number of diagnoses seems to be higher than the total number of cases due to comorbid diseases.
**PANDAS case.
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders - 4th edition.

was diagnosed as URTI; throat culture was taken and she was given antibiotic treatment. After five days of antibiotic treatment, because of ongoing fever and increased swelling on the neck, she was re-admitted to the infectious diseases clinic and hospitalized with diagnosis of deep neck infection.

On laboratory tests, throat culture revealed normal throat flora and urine, and blood bacterial cultures were negative. Complete blood count and routine biochemistry were normal. Chlamydia-mycoplasma-toxoplasma and cytomegalovirus (CMV) serology as IgM and IgG were negative, and ASO and C-reactive protein (CRP) levels

were within normal range. Neck surface ultrasonography (USG) revealed multiple reactive lymphadenopathies.

The patient was treated with intravenous sulbactam-ampicillin and was discharged at the end of three days with oral antibiotic treatment. One week later, follow-up examination showed complete resolution of symptoms. Evaluation at the child and adolescent psychiatry outpatient clinic on the same day revealed no psychopathology.

Two weeks later, she was re-admitted to the pediatric infectious disease outpatient clinic with complaints of sore throat and fever. White blood cell count was 13100/mm^3 and throat culture was positive for GABHS. She was given oral antibiotics for 10 days. A week after completion of therapy she presented with obsessive-compulsive behaviors at the child and adolescent psychiatry outpatient clinic. Obsessions included microbes and disease contamination and uncertainty about whether or not doors and windows were locked. Compulsions involved repetitive checking of doors and windows and hand washing. The symptoms were uncontrollable, causing anxiety and interfering seriously with daily life. The compulsion subtotal score on the CY-BOCS scale was 15/20 and the obsession subtotal score was 11/20, consistent with obsessive-compulsive behavior. The patient was diagnosed as OCD using the K-SADS-PL. Her medical and psychiatric history was unremarkable except for premature birth (34 weeks, 1800 g) and history of URTI two or three times per year. Her elder sister had a history of subclinical marginal cleanliness when she was 5-6 years old. Six weeks after the obsessive-compulsive symptoms started, 60-70% of symptoms improved without any treatment and at the end of the two months she completely recovered.

Discussion

In this study, patients (8-12 years old) who were diagnosed as URTI in the outpatient clinics of Hacettepe University İhsan Doğramacı Children's Hospital infectious disease unit over a one-year period were compared based on their GABHS positivity with regard to anxiety levels, problem behaviors, attention deficiency, hyperactivity, neuropsychiatric symptoms, and DSM-IV diagnoses. Although an increase in the neuropsychiatric and behavioral symptoms was expected in the GABHS-positive group, after six weeks of follow-up, no salient differences between GABHS-positive and -negative groups were identified. Some studies testing the PANDAS hypothesis noted no associations between GABHS infections and tic exacerbations and behavioral problems[15,29,30]. Most of them evaluated patients who already had the diagnoses of OCD or tic disorders for the instant exacerbations in relation to GABHS. In the literature, one study searched for subclinical PANDAS symptoms in a prospective design. In this largest prospective study of PANDAS symptoms to date, in which the patients with GABHS infection were compared to those with viral infection and healthy controls, no significant relationship between GABHS infection and clinical or subclinical level PANDAS symptoms was revealed[16]. Our findings are consistent with the result of this study in regard to psychiatric symptoms. On the other hand, in some recent community-based case control studies, an increase in the risk of neuropsychiatric disorders after GABHS infection in genetically susceptible individuals has been reported[31,32]. In one of these studies, even though no relation was determined with a streptococcal infection within the last three months, a streptococcal infection within the last 12 months was shown to be related to a three-fold increase in the risk of tic disorders, OCD, ADHD and major depressive disorder[32]. In this study, a similar increase in the risk of developing neuropsychiatric disorders was also found in relation to the diagnosis of sinusitis. In accordance with these results, it is meaningful to suggest for future prospective studies to increase the follow- up period to at least one year and to include the patients with recurrent GABHS infections in comparison with a healthy control group and with other infectious diseases.

In our study, it was possible to overlook neuropsychiatric and behavioral problems due to improvement of symptoms with antibiotic treatment. PANDAS could only be determined in one patient, as could be expected due to the rarity of PANDAS as a clinical entity. Murphy and Pichichero[13] observed 12 children with PANDAS in a three-year follow-up study among approximately 4,000 patients infected with GABHS, suggesting the rarity of PANDAS

in its classical manifestation. In that study, they also observed that the OCD symptoms developed after GABHS infection disappeared rapidly after antibiotic treatment.

Our PANDAS case shows clinical similarities to PANDAS cases in the literature[3,10,33] as it was characterized by disease anxiety, contamination obsession with hand-washing compulsion, symptoms that were so acute as to be dated specifically, possible OCD history in the family, and rapid recovery from the symptoms. Due to the high frequency of GABHS infections and high frequency (5-10%) of GABHS positivity in the upper respiratory tract in asymptomatic children, it has been thought that when PANDAS is considered, especially if the child is asymptomatic, throat culture result alone is not sufficient to reach a diagnosis[34,35]. Another fact is that acute exacerbations in the patients with tic disorders and OCD are common and it is possible to accept exacerbations as PANDAS cases by chance[29]. Recent studies show that GABHS history and the relapsing – remitting symptom course or "saw-toothed" pattern are not highly reliable for the diagnosis[35]. Therefore, for a PANDAS diagnosis, it has been reported that at least two neuropsychiatric exacerbations related to GABHS should occur or follow-up throat culture should be negative for a definite diagnosis[12]. In our case, throat culture was shown to be GABHS-positive prior to OCD symptoms, supporting the PANDAS diagnosis. Following an efficient antibiotic treatment, the patient's symptoms recovered rapidly as emphasized in the literature[13]. Nevertheless, it does not mean her recovery was completely accomplished by antibiotic usage.

Although there were no differences in terms of temporal changes between the two groups, there was a significant increase in the externalizing score of the CBCL between evaluations at baseline and at the end of the six-week follow-up. This may be related to the time of the first evaluation when all groups were sick due to the URTI. This result is also consistent with the findings of Perrin and colleagues[16]. They observed increased symptoms of inattentiveness and fidgetiness at baseline among sick children who were both GAS-positive and GAS- negative compared to healthy children.

Our study has important limitations that should be mentioned. Firstly, the narrow age range, and secondly, the inclusion period limited to one year caused a small sample size and short follow-up period. Thus, it was not possible to observe the differences that could be related to recurrent or asymptomatic GABHS infection or carrier status. Another factor that is interpreted as a limitation is the lack of narrow-band instruments to evaluate neuropsychiatric and behavioral symptoms that could be specific to the clinical picture of PANDAS. With such a tool, it could have been possible to identify low severity or temporary neuropsychiatric symptoms that did not lead to functional impairment. One further limitation is that the study lacked a healthy control group to control for the stressor effect of the infection.

As a result, the findings of our study suggest that children infected with and treated for GABHS do not appear to be at increased risk over children with presumed viral syndrome for development of psychiatric symptoms. Although there was no increase in the symptoms, PANDAS was identified in one of the cases; the fact that the family history of the patient was positive in terms of neuropsychiatric disorders indicates that GABHS infection may be a triggering factor for PANDAS in some genetically prone individuals. Future epidemiologic or prospective studies will be revealing in better understanding PANDAS and its pathogenesis.

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