Group A β-hemolytic Streptococcal Infection in Children and the Resultant Neuro-psychiatric Disorder; A Cross Sectional Study; Tehran, Iran

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ABSTRACT

Introduction: Group A Beta-Hemolytic Streptococcus (GABHS) can induce PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection). GABHS is the most important and common bacterial cause of acute pharyngitis in Iranian children. We studied the role of GABHS (anti-streptococcal antibodies) in suspected cases of PANDAS in a cross sectional studies.

Methods: Across sectional study was done in 2 pediatric psychiatric /and neurologic clinics in Tehran (Rasul Akram and Aliasghar Hospital) during 2008-2010. We studied serum anti-streptococcal antibodies (anti streptolysin O, anti Deoxyribonuclease B, and anti-streptokinase (ABcam-ELISA, USA) in 76 cases with psychiatric manifestation (OCD, ADHD) in compare with 39 healthy controls. These antibodies were studied in 53 cases with movement disorders (Tic/ Tourette syndrome) in compare with 76 healthy controls. Sensitivity, specificity and positive predictive value of tests were calculated.

Results: In movement disorders ASOT, Anti-DNase and Anti streptokinase was significantly higher than controls (P<0.0001, P=0.000, P<0.00001). ASOT (cut off level> 200IU/ml) had 75% sensitivity; 84% specificity and 80% PPV; Anti- streptokinase (cut off level> 332 IU/ml) had 34% sensitivity; 85% specificity, and 72% PPV; Anti-DNase (cut off level> 140IU/ml) had 70% sensitivity; 99% specificity and PPV 90% for differentiating the group. ASOT, Anti-DNase and Anti streptokinase titer was significantly higher than controls (P<0.0001, P=0.000, P<0.0001). ASOT had 90% sensitivity; 82% specificity, PPV 92%; Anti streptokinase: 82% sensitivity; 82% specificity, PPV 95%; Anti DNase: 92% sensitivity; 82% specificity, PPV 92% for differentiation the cases from normal controls.

Discussion: These findings support that a post infectious immune mechanism to GABHS may play a role in the pathogenesis of PANDAS in our children. A combination of throat culture, rapid antigen detection test, and serologic testing for GABHS is required to achieve maximum sensitivity and specificity for diagnosis. We prefer to use antibiotic prophylaxis in PANDAS cases for preventing recurrent streptococcal infections. Ongoing research is needed for identifying optimum diagnostic, prevention and therapeutic approach especially, aggressive treatment (intravenous immunoglobulin, plasmaphresis).

Key Words:
Group A ß-hemolytic streptococcus (GABHS), PANDAS (pediatric autoimmune neuropsychiatric disorders), OCD (obsessive-compulsive disorder), ADHD syndrome (attention deficient hyperactive disorders), Tic, Tourette syndrome

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1. Introduction

The etiology of some neuropsychiatric disorders in children is unknown. According to the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; five inclusionary criteria explained for PANDAS: presence of OCD and/or tic disorder, pre-pubertal symptom onset, sudden onset or episodic course of symptoms, temporal association between streptococcal infections and neuropsychiatric symptom exacerbations, and associated neurological abnormalities. (Bloch et al., 2007: 569-582).

Muller et al., (2000) reported the increased anti-streptococcal antibodies in patients with Tourette's syndrome. Luo et al., (2004) suggested that there was no clear relationship between new GABHS infections and symptom exacerbations in an unselected group of patients with TS and/or OCD. In the last decade a condition reported PANDAS associated with streptococcal infection (Michel & Gereber, 2004; Danchin et al., 2005; Brynska & Wolanczyk, 2004). In some children with PANDAS, new GABHS infections are temporally associated with exacerbations of tic or obsessive-compulsive (OCD) symptoms (Danchin et al., 2005; Brynska & Wolanczyk, 2004), Post-streptococcal autoimmunity investigated by some authors. (Leung et al., 2006; Bloch & Leckman et al., 2007:569-582; Tanz et al., 2009). Blyth & Robertson (2006) study determined the sensitivity and specificity of a single antibody titer in post streptococcal disease ranged from 70.5 to 72.7% and 86.4 to 93.2%, respectively. The combination of ASO and ADNaseB was the most sensitive and specific combination for identifying post streptococcal disease (sensitivity 95.5%, specificity 88.6%). Other study provides no evidence for a temporal association between GABHS infections and tic/OC symptom exacerbations in children who meet the published PANDAS diagnostic criteria (Leckman, King, Gilbert, & Dure, 2011). The immunomodulatory therapies, including plasma exchange and intravenous immunoglobulin for controlling the post-streptococcal neuropsychiatric symptoms in PANDAS were recommended by some authors (Snider & Swedo, 2003; Swedo, Garvey, Snider & Hamilton, 2001; Leonard & Swedo, 2001). Routine microbiologic or serologic testing for GABHS in children who present with PANDS was recommended by some authors (Loiselle, Wendlandt, Rohde and Singer, 2003; Mabrouk & Eapen, 2009; Shulman, 2009; Tanya et al., 2004).

GABHS is the most important and common bacterial cause of acute pharyngitis in children. Diagnoses of streptococcal pharyngitis only based on clinical findings are misleading in most times. Adding the rapid strip test in pharyngeal swab is helpful for rapid diagnosis and treatment of streptococcal pharyngitis. Anti-streptococcal antibodies are used for diagnosis of acute and post streptococcal disease (Leung, Newman, Kumar & Davies, 2006; Tanz, Gerber, Kabat, Rippe, Seshadri & Shulman, 2009). A combination of ASO and ADNaseB is required in post streptococcal disease to achieve maximum sensitivity and specificity. The upper limit of normal values of the Anti-streptococcal antibodies (ASO, AntiDNase B) varied between countries (Danchin, Carlin, & Devenish, 2005).

GABS infection and its sequels are common in Iranian children (18-20). In spite of widespread resistance to antibiotics, penicillin is still the first drug of choice for treatment of GABHS pharyngitis in Iran (Sadeghi & Obodi, 2006; Kohan, Panjeshahin & Sadeghi, 2006: 66-68; Nourouzi & Naderi Nasab, 2009). Suppurative and of GABHS were reported by some Iranian authors. (24-26) (2009) At least 2 studies reported the correlation between GABHS infection and tic disorder in Iranian children (Saadat et al., 2003:609-13; Noorbakhsh et al., 2010). In spite of previous studies, there seems to be insufficient evidence to follow routine microbiologic or serologic testing for group A streptococcus in Iranian children who were present with neuropsychiatric symptoms. Prescribing the antibiotic or immune-modifying therapies in PANDAS cases is undefined.

Here, we studied the role of GABHS (serum anti-streptococcal antibodies) in suspected cases of PANDAS in 2 cases with control studies.

2. Methods

We carried out this cross sectional study in the pediatric psychiatric and pediatric neurologic clinics in two referral hospitals (Rasul and Aaliasghar) in Tehran (2008-2010). This study was approved by the Ethical Committee in the Research Center of Pediatric Infectious Diseases in Rasul Hospital, Tehran University of Medical Sciences.

It was performed according to the Declaration of Helsinki Principles. All of the participants were fully informed about the study and they signed the informed consent forms.

Initially a questionnaire was completed by an authorized physician for each case, and then complete clinical and laboratory /imaging exams were carried out.

2.1. Case definition

Cases with neurologic manifestations: 53 pre pubertal children with movement disorders (Tic+/- Tourette syndrome) with unknown causes for their disorder. All cases were studied and were referred by pediatric neurologist after clinical and complete laboratory, imaging studies for excluding the organic and other known pathologic etiologies for movement disorders.

Cases with psychiatric manifestation: 76 cases with psychiatric manifestations (OCD +/- ADHD) according DSM-IV-TR criteria (Bloch & Leckman, 2007: 569-582) were referred by pediatric psychiatrist after clinical and complete laboratory or imaging studies.

Control group: children who were hospitalized for elective general surgery in the general surgery ward (i.e. appendicitis, hernia, etc.). These cases were age-matched with cases. They were visited by pediatrician before surgery. They would have been selected as controls only if they had not any abnormal finding after appropriate physical exams. We used their extra blood (which was taken for their routine blood tests before their respective surgery) for the serologic tests.

Exclusion Criteria: All cases with proven etiology for neuropsychiatric manifestations (e.g.; tumor, vasculitis, brain anomalies, metabolic disorders, encephalopathy, encephalitis, post infectious encephalitis and etc.) were excluded by pediatric neuropsychiatric clinician before enrolled to study.

The 2 ml Blood samples (2 ml) obtained and centrifuged in all cases and controls. It was transferred and kept frozen at -20°C in our research laboratory. ELISA assay (ABcam, USA) for specific antistreptococcal antibodies (antistreptolysin O, anti Deoxy ribonuclease B, and anti-streptokinase) was done. Results were interpreted by cut-off control as suggested by the manufacturer. The antibody titers (IU/ml) in several of cases and controls were compared and analyzed statistically.

Statistical analysis: All analyses were conducted using SPSS 13 software. Chi square values were calculated for all categorical variables. $P<0.05$ was considered significant. Mann-Whitney test and Student's t-test were used. Sensitivity, specificity and positive predictive value of tests were calculated.

3. Results

Movement disorders: 53 cases with movement disorders (tic and/or Tourret) with mean age=7.9+ 2.9 years were compared with and 76 healthy controls with mean age=9+2.7 years (Table 1).

Positive ASO Titer (>200 IU/ml) was observed in 40/53 cases; and 10/76 controls ($P<0.0001$).

Positive anti streptokinase titers (>332 IU/ml) were found in 18/53 cases; and 7/76 controls ($P=0.0001$).

Anti-DNase titer (>140 IU/ml) was observed in 41/53 cases and 5/76 controls ($P<0.00001$).

ASOT (cut off level> 200 IU/ml) had 75% sensitivity; 84% specificity and 80% PPV; Anti- streptokinase (cut off level> 332 IU/ml) had 34% sensitivity; 85% specificity, and 72% PPV; Anti-DNase (cut off level> 140 IU/ml) had 70% sensitivity; 99% specificity and PPV 90% for differentiating the groups.

Psychiatric disorders: 76 cases with psychiatric manifestations (OCD /ADHD disorder) with mean age=8.9+ 2.4 years were compared with 39 healthy controls with mean age=9+2.7 years (Table 1).

Positive ASO Titer (> 200IU/ml) was observed in 69 /76 cases; and 6/34 controls ($P<0.0001$).

Positive anti streptokinase titer (>332 IU/ml) was found in 65/76 cases; and 3/34 controls ($P=0.0000$).

Anti-DNase titer (>140 IU/ml) was observed in 70/76 cases and 6/34 controls ($P<0.0001$).

ASOT (cut off level=200) had 90% sensitivity; 82% specificity, 'PPV 92%; Anti streptokinase (cut off level=332) had 82% sensitivity; 82% specificity, PPV 95%; Anti-DNase (cut off level=140) had 92% sensitivity; 82% specificity, PPV 92% for differentiating the cases from normal controls.

4. Discussion

As expected, increased anti-streptococcal antibodies were observed in PANDS cases, which presented with neuropsychiatric symptoms as a ADHD/OCD, and movement disorders (TIC). All 3 types of antibodies (ASOT, Anti- DNase and Anti streptokinase) were significantly higher in PANDAS cases in compare with normal children. 75% sensitivity; 84% specificity and 80%

Table 1. Movement & Psychiatric Disorders.

	Variables	ASOT	Anti-DNase	Anti streptokinase
Movement Disorder	Specificity	84%	99%	85%
	Sensitivity	75%	70%	34%
	Positive Predict Value	80%	90%	72%
Psychiatric Disorders	Specificity	82%	82%	82%
	Sensitivity	90%	92%	82%
	Positive Predict Value	92%	95%	95%

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PPV for ASOT titer (> 200 IU/ml); 34% sensitivity; 85% specificity, and 72% PPV for Anti- streptokinase (>332 IU/ml); 70% sensitivity; 99% specificity and 90% PPV for Anti-DNase (> 140 IU/ml) were determined in cases with movement disorders (Tic/ Tourette syndrome). Also, 90% sensitivity, 82% specificity, 92% PPV for ASOT titer (>195); 82% sensitivity; 82% specificity, 95% PPV for Anti streptokinase (> 223); 92% sensitivity; 82% specificity, 92% PPV for Anti-DNase B (>140) were observed in cases with psychiatric manifestation (OCD/ADHD disorder). All of above findings support the theory that a post infectious immune mechanism to GABHS may play a role in the pathogenesis of PANDAS in Iran. Like here, Danchin, et al., reported the higher cut-off levels for ASO (120, 480 and 320); and Anti-DNase B (100, 400 and 380) in normal age matched children living in Melbourne Australia (Danchin et al., 2005).

Our results are much close to Muller et al., study (11) in which the cut-off levels of ASOT and anti-DNase B was >250 U/ml and >400 U/ml respectively. TS patients exhibited higher antistreptococcal titers than age-matched comparison groups of both children/adolescents and adults using different types of calculation (Muller, Riedel, Straube, Gunther & Wilske, 2000).

Like us, Blyth and Robertson (2006) reported that the combination of ASO and Anti-DNase B was the most sensitive and specific combination for identifying post streptococcal disease (sensitivity 95.5%, specificity 88.6%), but adding Anti streptokinase does not increase the sensitivity or specificity of serological testing in acute and post streptococcal disease. Some authors reviewed the subgroup of children with early and abrupt onset of OCD and/or tic disorders subsequent to streptococcal infections (PANDAS) (Blyth and Robertson, 2006; Leonard & Swedo, 2001). For the latter study group, long-term (2–5 yr.) follow-up revealed continued symptom improvement for the majority of patients, particularly when antibiotic prophylaxis had been effective in preventing recurrent streptococcal infections. In addition, the episodic nature of the subgroup's illness provides opportunities to study brain structure and function during health and disease, as well as allowing for investigations of the etiologic role of anti-neuronal antibodies and neuroimmune dysfunction in both OCD and tic disorders (Leonard & Swedo, 2001). Arman et al. (2009) evaluated the relationship between group A streptococcal infection with tic disorders in Child and Adolescent in Isfahan (Center of Iran) during 2008-2009.

The throat cultures, rapid antigen detection test, anti streptolysin O (≥250) were compared between cases and controls. None of the subjects in the case and control groups had a clinical history of GABHS infection. The relationship between tic disorder and GABHS infection (if any of these laboratory tests takes place: throat culture, RADT, ASO ≥250) in the tic group was 16 (44.4%) and in the control group was 9 (25%, P<0.05). The specificity of RADT was 100%. No significant correlation was found between ASO titer and Tic scores. They concluded that correlation between GABHS infection and tic disorder exist but it does not mean that GABHS infection caused tic disorder (Noorbakhsh, Tabatabaei, Farhadi & Ebrahimi Taj, 2011).

In contrast, Leckman et al., (2011) study provides no evidence for a temporal association between GABHS infections and tic/OCD exacerbations in children who meet the published PANDAS diagnostic criteria (Luo et al., 2004).

The overall rate of acute exacerbations of neuropsychiatric symptoms was 0.56 exacerbations per patient per year. The association between symptom exacerbations and new GABHS infections among patients was not greater than the expected rate on the basis of chance (Luo et al., 2004).

Snider et al., (2004) revealed that both intravenous immunoglobulin and plasma exchange were effective (40 and 55%) in reducing neuropsychiatric symptom severity in the PANDAS subgroup. A recently completed placebo-controlled trial revealed that both IVIG and plasma exchange were effective in reducing neuropsychiatric symptom severity (40% to 55% reductions, respectively) for a group of severely ill children with OCD and/or tic disorders (Swedo et al., 2001).

Leonard et al., (2001) study described that antibiotic prophylaxis had been effective in preventing recurrent streptococcal infections in PANDAS. In addition to the use of anti-tic and antiobsessional agents, the use of Penicillin during the acute phase and for prophylaxis, tonsillectomy, immunemodulatory therapies such as plasma exchange and intravenous immunoglobulin, etc. have all been reported to improve the symptoms (Leonard & Swedo, 2001; Muller et al., 2000; Blyth & Robertson, 2006; Leckman & et al., 2011; Loiselle et al., 2003; Mabrouk & Eapen, 2009).

In spite of widespread resistance to antibiotics, penicillin is still the first choice for treatment and prevention of GABHS pharyngitis in Iran. Erythromycin is the best alternative drug for patients sensitive to penicillin (Sadegh & Obodi 2006: 57-65; Kohan et al., 2006: 66-68; Nourouzi & Naderi Nasab, 2009).

Based on the definition of PANDAS, there should be pre-pubertal symptom onset, a history of a sudden onset of symptoms and/or an episodic course with abrupt symptom exacerbation and temporal association between streptococcal infections and neuropsychiatric symptom exacerbation. The existence of these three criteria in a cross sectional study has not been verified. At the time of study, all of cases were in prepubertal age and had the sign and symptom of neuro-psychiatric disorder. The progression or stopping or exacerbation is not achievable from the present study. A longitudinal study in cases presented with neuro-psychiatric disorder would be helpful.

Our findings support the theory that a post infectious immune mechanism to GABHS may play a role in the pathogenesis of PANDAS. A combination of throat culture, rapid antigen detection test, and ASO and ADNaseB, Anti streptokinase present with PANDS is required to achieve the maximum sensitivity and specificity. We prefer to use antibiotic prophylaxis in PANDAS cases for preventing recurrent streptococcal infections. Ongoing research is needed for identifying the optimum diagnostic, prevention and therapeutic approach especially, aggressive treatment (intravenous immunoglobulin, plasmaphresis).

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