The evaluation of relationship between group A streptococcal infection with tic disorders in children

Soroor Arman, MD, *Javad Golmirzaei,* MD, *Alireza E. Naeini,* MD, *Mohammad M. Azhar,* MD.

ABSTRACT

الأهداف: تقييم العلاقة بين المجموعة أ بيتا العدوى بالمكورات العنقودية (GABHS) واضطرابات (tic) لدى الأطفال.

الطريقة: أجريت هذه الدراسة على مجموعة التحكم بعيادة الطفل والمراهق النفسية –مدينة اصفهان –إيران خلال الفترة مابين مايو 2008م إلى فبراير 2009م. تم فحص عدد 36 طفل (15–5 عام) والذين يعانون من (tic) و36 مريض لا يعانون من (tic) ويعانون من اضطراب الوسواس القهري (OCD) من الناحية السريرية والمخبرية لوجود علامات (GABHS). تمت مراجعة المعدات والأدوات المستخدمة في هذه التجربة وفقاً ل (DSM IV–TR) و الفحوصات المخبرية (مزرعة الحنجرة، فحص اكتشاف المستضدات السريع). (RADT)، ومضادات الحالة العقدية [ASO] O ونقاط يالي العالمية (YGTSS). كانت مجموعة التحكم وهم نفس نوع الجنس والعمر وفقاً للمجموعة التي تعاني (tic) الذين قدموا إلى العيادة من أجل أمراض أخرى والذين احتاجوا إلى فحص الدم. لم يكن أحد من مجموعة الحالة أو مجموعة التحكم يعانون من تاريخ للإصابة مؤخراً (GABHS).

النتائج: العلاقة بين اضطراب (tic) والتهاب (GABHS) إذا تم أخذي أي من الفحوصات المخبرية: مزرعة بكتريا الحنجرة، (ASO≥250)، (RADT). وفي مجموعة (tic) كانت 16 (44.4%) وبلغ في مجموعة التحكم 9 (25%)، لم يكن هنالك فروقاً ملحوظة (p<0.05). لم يتبين وجود علاقة ملحوظة بين (ASO) ونقاط (YGTSS) بلغت نسبة تحديد RADT 100%.

خاتمة: أظهرت النتيجة علاقة بين التهاب (GABHS) واضطراب (tic) ولكن لا يعني ذلك أن التهاب (GABHS) يسبب اضطراب (tic).

Objectives: To evaluate the relationship between group A beta hemolytic streptococcus infection (GABHS) and tic disorders in children.

Methods: This is a case-control study that was conducted in Child and Adolescent Psychiatric Clinic, Isfahan, Iran, between May 2008 and February 2009. Thirty-six children (aged 5-15) with tic and 36 children without tic and obsessive-compulsive disorder (OCD) were investigated for clinical and laboratory signs of GABHS. The tools utilized in this research were clinical interview according to the DSM IV-TR and laboratory tests (throat culture, rapid antigen detection test [RADT], anti streptolysin O [ASO] and yale global tics severity scale [YGTSS]). The control group was of the same gender and age as the tic group who had come to the clinic for other illnesses and was in need of blood test. None of the subjects in the case and control groups had a clinical history of GABHS infection.

Results: 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%), there were significant differences (p<0.05). No significant correlation was found between ASO titer and YGTSS scores. The specificity of RADT was 100%.

Conclusion: The result showed correlation between GABHS infection and tic disorder, but it does not mean that GABHS infection caused tic disorder.

Saudi Med J 2009; Vol. 30 (9): 1180-1185

From the Departments of Child and Adolescent Psychiatry (Arman, Azhar, Golmirzaei), and Infectious Disease (Naeini), School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

Received 16th May 2009. Accepted 25th July 2009.

Address correspondence and reprint request to: Dr. Javad Golmirzaei, Department of Child and Adolescent Psychiatry, Alzahra Hospital, Sofeh Ave., Isfahan, Iran. Tel. +98 (913) 3132535. Fax: +98 (311) 6691491. E-mail: GolmirzaeiJavad@yahoo.com

Tic disorders are a common group of neuropsychiatry disorders that begin in childhood.[1] Tics are sudden, repetitive movements, gestures or phonic productions that are stereotypic and purposeless and typically mimic some aspect of normal behavior.[2,3] Tics can either be phonic or be displaced with motor movement (or both) and range from simple to complex.[4] According to the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), tics disorders can be divided into 4 groups: 1) Transient tic disorder 2) Chronic motor or vocal tic disorder 3) Tourette's syndrome and 4) Tic disorder not otherwise specified (NOS).[2,5] Tic disorders are very common, and their clinical impact on the affected patient is often more significant than the impact of the tics themselves.[6] The etiology of tic disorders is unknown, but a mixed genetic-environmental model has been suggested.[7] Previous reports have suggested that an autoimmune mechanism after streptococcal infection may be etiologically related to Pediatric Autoimmune Neuropsychiatry Disorders Associated with Streptococcal Infection (PANDAS).[8,9] Swedo et al[10] published the first description of PANDAS in 1998. Five criteria were established for inclusion in the PANDAS subgroup: 1) presence of Obsessive-compulsive disorder (OCD) and/or a tic disorder, 2) childhood onset, 3) acute onset and episodic course of symptom severity, 4) association with GABHS infection, and 5) association with neurological abnormalities.[10] A temporal relationship between GABHS and neuropsychiatry disorders are controversial.[11] The confusion with regards to the role of GABHS may be promoted further, because clinically, it is assumed that tic disorders worsen during times of stress or illness of any kind.[11,12] Individuals reporting more psychosocial stress have both a higher incidence and a greater severity of certain infectious illnesses.[4] Molecular mimicry is just one possible mechanism by which post-infectious autoimmune disorders can occur.[13] Strong evidence implicates the basal ganglia and corticostriatal thalamocortical (CSTC) abnormalities as central to the pathogenesis of tics.[2,14] The M protein is the major surface and virulence surface protein of GABHS. M6 and M19 proteins may share common epitopes with brain structures.[15,16] Exacerbations of neuropsychiatry symptoms begin within 7-14 days after the streptococcal infection and usually occur simultaneously. If there is a recent onset of tics, the throat culture results will be positive.[14] There are specific tests for intercurrent (throat culture or rapid antigen detection test [RADT]) or antecedent (measurement of anti-streptolysin O [ASO]) GAS infections. The use of throat culture and RADT increase the precision of our diagnosis.[7,16,17] A high level of ASO indicates an antecedent infection.[18,19] The aim of this research is to evaluate the relationship between streptococcal infection and tic disorder in children.

Methods. This case-control study was conducted in the Child and Adolescent Psychiatric Consultation Center, Isfahan University, Isfahan, Iran, between May 2008 and February 2009. Patients were selected from those who had a sudden onset or recent exacerbation of their tic disorders. The study was approved by the Human Ethics Committee, Isfahan University of Medical Sciences, Isfahan, Iran. All participants and their families received a full explanation of the nature of the study and we asked them to signed the consent form. After providing written informed consent, each subject underwent a diagnostic evaluation managed by the child and adolescent psychiatrist using the structured clinical interview of the DSM-IV-TR. We used the Yale Global Tic Severity Scale (YGTSS) to assess tic severity showed to be excellent in terms of validity and reliability.[20,21] This scale was also used in Iranian children in the previous studies.[22,23]

Thirty-six patients were included in the study once the following criteria have been met: agreed to participate in the study, sign the informed consent form, and must be between 5-15 years old. Exclusion criteria were: movement disorder with organic cause, use of stimulant, positive history of rheumatic fever, prophylactic treatment with antibiotics and OCD. A control group of 36 children without OCD and tic disorders were matched for gender and age with the patients group. Seventy-two children were referred to the reference laboratory. Specific tests were performed for intercurrent (culture of throat and RADT) and antecedent (measurement of antistreptolysin o titter) infection. The staff performing the laboratory tests were unaware of the clinical diagnosis, and the psychiatrists who assessed the YGTSS were blinded to the results of the laboratory tests.

Serologic evaluation. Anti-streptolysin O titters were assessed in 2 ways using the omega diagnostic kit (Paris, France). First, we used the qualitative method wherein the patient's serum and latex was laid on a slide and after 2 minutes, the ASO in the serum was checked for agglutination. After that, ASO titters were checked by serum dilution using Ben Mary (Fater Rizpardaz Noavar, Tehran, Iran) and centrifuge at 37^0C and ASO titters were found. The positive ASO titter determined ASO ≥250 Todd's unit.[24,25]

Bacteriological evaluation. A sample swabbed from the throat was taken. The swab was then streaked in sheeps blood agar. Discs of bacitracin and co-trimoxazole were laid on the area of the plate that had more colonies. For the appropriate humidity and CO_2 (10%), the plates were placed in the incubator for 18-24 hours at 37^0C, and the probable hemolysis was checked.[16,24]

Rapid antigen detection test. A quantitative and rapid test was used for detecting the antigen of GABHS using throat swab sampling. It is a rapid chromatography

immunoassay method (ACON Laboratories, Inc. USA). After sampling, the swab was immediately applied in the reactive substances from the kit and was checked within 5 minutes. If a red line appears in both the test and control areas, we considered it positive for GABHS infection.[16,24]

The data was analyzed using the Statistical Package for Social sciences (SPSS) Version 15. The statistical significance was determined as $p<0.05$. The quantitative data was analyzed by Chi-square or the Fisher's exact test and the qualitative data was analyzed using the Man-Whitney test. Spearman-correlation test was applied when necessary.

Results. The patient group affected by tic disorders consisted of 36 children (26 [72.2%] boys and 10 [27.8%] girls), aged between 5 and 15 years (mean age 10.1±2.7 years). Significant differences were found between the gender of patients using the Chi-square test ($p<0.05$). The control group without OCD and tic disorders consisted of 36 children (26 [72.2%] boys and 10 [27.8%] girls), aged between 5 and 15 years (mean age 9.9±3.2 years), that matched the patient group for gender and age. No significant differences were found between the patients and control subjects using t-test ($p=0.75$). The mean ASO titter was greater in patients with tic than in control subjects, but the difference was not significant. We used the Man-whitney test. Positive ASO titter in the tic group was 14 (38.9%) and in the control group was 8 (22.2%), but the Chi-square test did not show significant differences ($p=0.06$). The range of ASO titter in the tic group was 125-500 todd units (125 todd units [n=22 (61.1%)], 250 todd units [n=12 (33.3%)], 333 todd units [n=1 (2.8%)], and 500 todd units [n=1 (2.8%)]). The range of ASO titter in the control group was 125-250 todd units, (125 todd units [n=22 (77.8%)] and [250 todd units [n=8 (22.2%)]. The YGTSS scores of patients ranged from 10-34 (mean=16.58 ±6.4). In the control group, YGTSS scores were zero. No significant correlation was found between ASO titter and YGTSS scores ($p=0.751$, r=-0.05). Throat swab cultures were positive for GABHS in children with tic 2(5.6%), in control subjects 2(5.6%) (**Table 1**). Positive rapid antigen detection test for GABHS in the tics group was 5(13.9%)and in the control group was 4 (11.1%) but there was no significant difference by using Fisher's exact test ($p=0.5$) (**Table 1**).

There would be a positive correlation with GABHS infection if any of the following 3 laboratory test had a positive result: throat culture, RADT, and ASO ≥250 todd units. In the patients group, the result was 16 (44.4%) and in the control group 9 (25%), there were significant differences using the Chi-square test. ($p=0.04$) (**Table 1**). The rate of family history of tic was significantly higher in the patient group as compared with the control group ($p=0.002$) (**Table 1**). Patients with tic were classified as follows: transient tic 5 (13.9%), chronic motor or vocal tic 13 (36.1%), Tourette's syndrome 18 (50%), and no tic disorder NOS (0%). In the tics group, the age of 18 patients was<10 years, 18 patients were ≥10 years. Premonitory urge in former was 5 (27.8%) and in latter was 11 (61.1%) ($p=0.02$). Specificity of RADT in the tic group and the control group were 100%. In other words, all those who had negative RADT, had a negative throat culture. Sensitivity of RADT was 40% in the tic group and 42% in the control group. Thus, only 40-42 percent of those who had positive RADT had a positive throat culture.

Discussion. In this case-control study, the rate of positive throat culture between the 2 groups was equal, and the rate of positive RADT in the tic group was more than the control group, but no significant differences were found. We have rheumatogenic strains of GABHS and it would be a possibility for the existence of PANDAS-Genic strains of GABHS.[26] The sampling of our study was performed in the winter and had a bias caused by climatic factors or epidemic factors of GABHS infection. Therefore, it would be better if the sampling was carried out in all 4 seasons to avoid

Table 1 - Mean ± standard deviation of ASO* titter and prevalence of different variables according to tic disorder.

Parameters	Tic group	The control group	P-value
Mean ASO titter (Todd units) (mean ±SD)	182.8 ± 84.6	152.7 ± 52.7	>0.05
Mean rank	39.72	33.28	0.103
Throat culture (%)			
Positive	2 (5.6)	2 (5.6)	
Negative	34 (94.4)	34 (94.4)	1
RADT			
Positive	5 (13.9)	4 (11.1)	0.5
Negative	31 (86.1)	32 (88.9)	
Correlation with GABHS (if any of laboratory-tests takes place) (%)*			
Positive	16 (44.4)	9 (25)	0.04
Negative	20 (55.6)	27 (75)	
Family history of tics			
Positive	16 (44.4)	4 (11.1)	0.002
Negative	20 (55.6)	32 (88.9)	

ASO - anti streptolysin O, RADT - rapid antigen detection test, GABHS - group A beta hemolytic Streptococcal

missing of the PANDAS-Genic strains of GABHS.[26] In this study, the mean ASO titter and the rate of positive ASO ≥250 todd units was higher in the tic group as compared with the control group, but we must consider the seasonal bias. The investigators found that the incidence of motor tic was significantly higher during the winter months of November through February when compared with the spring months of March to June.[13] Although no direct streptococcal infection rates were determined, the period overlaps with the high seasonal prevalence of streptococcal infection seen in this age group.[27] Other factors were obviously at play, such as other upper respiratory tract infections and stress associated with school.[27] Group C and group G streptococcal infections may lead to similar mechanisms of immune activation but remain undetected during standard cultures or rapid strep tests designed to report only GABHS infection.[27] Group C and group G streptococcal infections may lead to false-positive evaluations in strep titters but conclude minimal risk of neuropsychiatric sequelae.[27] In this study, the majority of tic patients did not have an ASO ≥250 and some subjects in the control group had positive ASO ≥250 but did not have tic disorder. It may be related to the type of the pathogen and host susceptibility, as has been developed by the model of pathogenesis of PANDAS: GABHS + susceptible host → abnormal immune response → PANDAS. D8/17, which is a monoclonal antibody that identifies a specific B lymphocyte cell-surface marker, is one possible susceptibility factor for PANDAS.[13] Significantly, elevated levels of this marker have been found in individuals with rheumatic fever and, to a lesser extent, in their family members when compared with controls.[9] It is considered a possible trait marker, indicating genetic susceptibility to rheumatic fever.[9] Elevated levels of antibodies that recognize the D8/17 marker have been demonstrated in children with PANDAS, and more generally in subjects with early onset OCD and tic disorders.[9] Although some authors mentioned that D8/17 have not been able to correlate reliably and consistently with suspected PANDAS cases and recent studies that used more accurate methods (flow cytometry), they nevertheless failed to replicate these results.[15] Tourette's syndrome (TS) and other closely related disorders clearly have a strong genetic components,[2] and GABHS can trigger neuropsychiatry disorders in some of the susceptible hosts. On the other hand, host factors are also of critical importance. Males appear to be at higher risk factor, as three-quarters of the PANDAS subjects are male, but the mechanism of this increased vulnerability is unknown. In any case, our study population was similar to those reported in the literature for age and male/female ratio (higher in boys), and frequency of positive family history of tics.[2,7] Data on the relationship between tic disorders and streptococcal infection have been published. Our results are in close accordance with those of themes: Swedo et al,[10] describing the first 50 cases of PANDAS, reported that in 42% of children, symptom onset was associated with GABHS infection. Kiessling et al,[28] have reported that after an outbreak of streptococcal infections in Rhode Island, a strong increase in the number of children with tics and elevated ASO titters, were found. Cardona and Orefici,[7] found a strong relation of ASO titters not only with the presence of tics, but also with its severity as measured by YGTSS scores, but in our study, no significant correlation was found between ASO titter and YGTSS scores. However, there is a possible explanation; although ASO titter is an objective measure; YGTSS scoring has a subjective component. Cardona et al,[29] found that the higher rate of echocardiographic abnormalities observed in patients with tic disorder and exposure to GABHS, suggest a post-streptococcal pathogenesis. Murphy et al,[27] found that patients with marked tic symptom changes may be characterized by streptococcal titter elevations and exhibit evidence of seasonal tic exacerbations in the fall and winter months. Mell et al,[30] found that patients with tic disorder were more likely than controls to have had a prior streptococcal infection in the 3 months before the onset date. The risk was higher among children with multiple streptococcal infections within 12 months. On the other hand, other studies were found to be in disagreement with our findings. Singer et al[31] found that 41 subjects affected by TS had a risk ratio for ASO titter >166 units similar to that of control subjects. Luo et al,[32] showed that no clear relationship between new GABHS infections and symptom exacerbations in an unselected group of patients with TS exists. Perrin et al[26] found no differences in the frequencies of the neuropsychiatric symptoms between the group who was ill and GABHS-positive and those ill and GABHS-negative. Kurlan et al,[33] believed that additional intensive studies are needed to determine whether there is clinical or scientific evidence to support the relationship between GABHS infection and neuropsychiatric disorders. Moretti et al,[15] mentioned that the validity of the PANDAS is still questionable. Investigators at the Johns Hopkins Children's Centre said that there was no evidence of streptococcal antibodies binding to or interacting with brain tissue. This finding makes an immune origin of PANDAS unlikely.[34]

Limitations in this study were that a small sample size was used and that sampling was only carried out in one season. Therefore, we suggest that more epidemiologic studies be done for the evaluation of interference between genetics and GABHS.

In conclusion, this study was conceived as a case-control study and the result showed correlation between GABHS infection and tic disorder but it does not mean that GABHS infection caused tic disorder. To validate our observations and to examine whether subsequent exacerbation of tics is associated with concurrent increase in ASO titters, a longitudinal study of our patient population is currently proceeding.

Acknowledgment. *I would like to express my special thanks to Hodgat Golpayegani, abnd Golnar Golpaygani for helping us in editing the article.*

References

1. Leckman JF, Coben DJ. Tic Disorders. In: Rutter M, Taylor E, editors. Child and Adolescent psychiatry. 4th ed. Massachusetts: Blackwell Science, Inc; 2002. p. 593-611.
2. Bloch MH, Leckman JF. Tic disorders. In: Martin A, Volkmar FR, editors. Lewis's child and adolescent psychiatry: A comprehensive textbook. 4th ed. Philadelphia (PA): Lippincott Williams & Willkins; 2007. p. 569-582.
3. King RA, Leckman JF. Tic Disorders. In: Wiener JM, Dulcan MK,editors. Textbook of child and Adolescent psychiatry, 3rd ed. Washington (DC): American Psychiatric Publishing, Inc; 2004. p. 709-726.
4. Scahill L, Leckman JF. Tic disorders. In: Sadock BJ, Sadock VA, editors. Kaplan & Sadock's comprehensive textbook of psychiatry. Philadelphia (PA): Lippincott Williams & Willkins; 2005. p. 3228-3236.
5. First MB, Frances A, Pincus HA. Dignostic and Statistical Manual of Mental Disorder: American Psychiatric Association, Washington (DC): American Psychiatric Publishing; 2000. p. 108-111.
6. Singer HS. Tourette syndrome and Its Associated Neurobehavioural problems. In: Swaiman KF, Ashwal S, Ferriero DM, editors. Pediatric Neurology principles and practice. 4th ed. Philadelphia (PA): Mosby; 2006. p. 887-903.
7. Cardona F, Orefici G. Group A streptococcal infections and tic disorders in an Italian pediatric population. ***J Pediatr*** 2001; 138: 71-75.
8. Dale RC, Heyman I. Post-streptococcal autoimmune psychiatric. Post-streptococcal autoimmune psychiatric and movement disorders in children and movement disorders in children. ***British Journal of Psychiatry*** 2002; 181: 188-190.
9. Arnold PD, Richter MA. Is obsessive-compulsive disorder an autoimmune disease? ***CMAJ*** 2001; 165: 1353-1358.
10. Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. ***Am J Psychiatry*** 1998; 155: 264-271.
11. Kurlan R, Kaplan EL. The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) etiology for tics and obsessive-compulsive symptoms: hypothesis or entity? Practical considerations for the clinician. ***Pediatrics*** 2004; 113: 883-886.
12. Leslie DL, Kozma L, Martin A, Landeros A, Katsovich L, King RA, et al. Neuropsychiatric Disorders Associated With Streptococcal Infection: A Case-Control Study Among Privately Insured Children. ***J Am Acad Child Adolesc Psychiatry*** 2008: 21. [Epub ahead of print]
13. Snider LA, Swedo SE. Post-streptococcal autoimmune disorders of the central nervous system. ***Curr Opin Neurol*** 2003; 16: 359-365.
14. Swedo SE,Leonard HL, Rapoport JL.The pediatric Autoimmune Neuropsychiatric Disorders Associated With streptococcal lnfection (PANDAS) Subgroup: Separating Fact From Fiction. ***Pediatrics*** 2004; 113: 907-911.
15. Moretti G, Pasquini M, Mandarelli G, Tarsitani L, Binio M. What every psychiatrist should know about PANDAS: a review. (updated 2008; accessed 2008 May 21). Avaialable from URL: http://www.cpementalhealth.com/content/4/1/13. May 21st 2008.
16- Bisno A, Stevens SD. Streptococcus pyogenes. In: Mandell G, Bennett J, Dolin R. Principles and Practice of Infectious Disease. Philadelphia (PA): Elsevier; 2005. p. 2362- 2379.
17. Gerber MA. Group A streptococcus. In: Kliegman R, Behrman E, Jenson HB, Stanton B, editors. Nelson textbook of Pediatrics. Philadelphia (PA): Saunders; 2007. p. 1135-1145.
18. Brooks G, Carrol K. The streptococci. In: Brooks G, Carrol K, Butel J, Morse S. Jawetz Melnick Adelberg's Medical Microbiology. New York (NY): MC Graw-Hill; 2007. p. 233-248.
19. Wessels MR. Streptococcal and Enterococcal infections. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al. Harrisons Internal Medicine. 17th ed. USA: McGraw Hill Companies, Inc; 2008. p. 881-890.
20. Mohammadi M, Mesgarpour B, Sahimi Izadian E, Mohammadi M. Psychology and Psychopharmacology Tests in Children and Adolescent. 1st ed. Tehran: Teimourzadeh Publication 2007. p. 147-150.
21. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The Yale Global Tics Severity scale: initial testing of a clinician-rated scale of Tic severity. ***Journal of the American Academy of Child and Adolescent Psychiatry*** 1989; 28: 566-730.
22. Karahmadi M, Shahrivar Z. The Evaluation of Executive function in patient's with Tourrett's Syndrome with and without Attention Deficit Hyperactive Disorder. ***Journal of Isfahan Medical University*** 2006; 82: 61-66.
23. Ghanizadeh A, Mosallaei S. Psychiatric disorders and behavioral problems in children and adolescent with Tourrett's Syndrome. ***Brain and Development*** 2008; 10: 1-5.
24. Sagah HR, Soroushnia M. Comprehensive Textbook of laboratory equipment and diagnostic products, Tehran(TR): Mir Publication; 2004: 2498: 2611-2612.
25. Ghaemi EO, Mansourian AR, Ahmadi AR, Saeidi M, Moradi A, Behnampour N.Seroprevalence of streptococcus, Brucella and salmonella Infection in Mental Retarded children in Iran. ***Research Journal of Microbiology*** 2006; 1: 371-374.
26. Perrin EM, Murphy ML, Casey JR, Pichichero ME, Runyan DK, Miller WC, et al. Does group A beta-hemolytic streptococcal infection increase risk for behavioral and neuropsychiatric symptoms in children? ***Arch Pediatr Adolesc Med*** 2004; 158: 848-856.
27. Murphy TK, Sajid M, Soto O, Shapira N, Edge P, Yang M, et al. Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcus in children with obsessive-compulsive disorder and tics. ***Biol Psychiatry*** 2004; 55: 61-68.

28. Kiessling LS, Marcotte AC, Culpepper L. Antineuronal antibodies: tics and obsessive-compulsive symptoms. ***J Dev Behav Pediatr*** 1994; 15: 421-425.
29. Cardona F, Ventriglia F, Cipolla O, Romano A, Creti R, Orefici G.A Post-streptococcal pathogenesis in children with Tic disorders is suggested by a color doppler echo-cardiographic study. Rome (IT): University La Sapienza; 2007. p. 1-18.
30. Mell LK, Davis RL, Owens D. Association between Streptococcal Infection and obsessive-compulsive disorder, Tourettes syndrome, and Tic Disorder. ***Pediatrics*** 2005; 116: 56-60.
31. Singer HS, Giuliano JD, Hansen BH, Hallett JJ, Laurino JP, Benson M, et al. Antibodies against human puttamen in children with Tourette syndrome. ***Neurology*** 1998; 50: 1618-16124.
32. Luo F, Leckman JF, Katsovich L, Findley D, Grantz H, Tucker DM, et al. Prospective longitudinal study of children with tic disorders and/or obsessive-compulsive disorder: relationship of symptom exacerbations to newly acquired streptococcal infections. ***Pediatrics*** 2004; 113: e578-e585.
33. Kurlan R, Johnson D, Kaplan EL; and the Tourette Syndrome Study Group. Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: a prospective blinded cohort study. ***Pediatrics*** 2008; 121: 1188-1197.
34. Gause C, Morris C, Lopez P. Strep Throat Unlikely Cause of Neuropsychiatric Disorder (updated 2008 June 4; accessed 2008 June 4). Available from URL: http://www.hopkinschildrens.org/strep-throat-unlikely-cause-of-neuropsychiatric-disorder.aspx

Ethical Consent

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.