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Association of Common Cold with Exacerbations in Pediatric but not Adult Patients with Tic Disorder: A Prospective Longitudinal Study

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ABSTRACT

Cross-sectional data and case studies suggest a temporal relationship between fluctuations in tic severity and preceding infections. In this study, we aimed to examine this possible relationship in a prospective longitudinal design. Two groups of tic disorder patients were included, a pediatric group between 7 and 15 years of age ($n = 20$), and an adult group over 15 years of age ($n = 41$). During a 24-week period, participants were asked to fill out weekly self-questionnaires regarding the presence of tic exacerbations and the experience of the common cold. In addition, 6 throat swabs were taken at monthly intervals and cultured for streptococci; also, 3 serial serum assessments of streptococcal antibodies were performed at 8-week intervals. In the pediatric group, our results indicated a strong association between the self-report of a common cold and a symptom exacerbation 4 weeks later (Odds ratio = 4.685; $p = 0.001$). In the adult group, we found no association between reports of common cold and tic exacerbations. Association with streptococcal infections could not be determined owing to the limited number of observed streptococcal infections. Thus, this study points to a hitherto unknown association of common viral infections with tic exacerbations in children, which may support the involvement of immune dysregulation in tic disorders.

INTRODUCTION

ALTHOUGH THE PRECISE MECHANISM at a molecular level is unknown, a growing number of studies suggest the involvement of autoimmunity in the pathogenesis of tic disorders (recently reviewed in Hoekstra et al. 2002). A common feature of autoimmune disorders, in general, is their relapsing course over time. Infections have been suggested to induce or reinforce autoimmune reactions in genetically

predisposed individuals and may, thus, be associated with exacerbations and remissions in autoimmune conditions (Luppi et al. 1995).

A pattern of fluctuations in symptom severity is also common in tic disorders (Lin et al. 2002). Fluctuations in tic severity may only partially be explained by psychosocial factors, such as stress, anxiety, and fatigue (Hoekstra et al. 2004). Some authors have suggested an association between infections with group A β hemolytic streptococci and changes in tic severity in

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at least a subgroup of patients, so-called pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) (Swedo et al. 1998). The possible relationship of tic disorders with streptococcal infections has been largely based on cross-sectional data (Muller et al. 2000, 2001; Cardona and Orefici 2001) and some case studies (Murphy and Pichichero 2002; Perlmutter et al. 1998; Tucker et al. 1996). Only one small prospective study demonstrated that in patients meeting criteria for PANDAS, marked obsessive-compulsive severity symptom changes over time were positively correlated with streptococcal titer elevations (Murphy et al. 2004). On the other hand, infections other than streptococcal have also been described in association with tic disorders, including viral infections (Allen et al. 1995). Therefore, in this prospective longitudinal study, we aimed to examine the possible temporal relationship between symptom exacerbations and preceding streptococcal throat infections or virally induced upper respiratory infections in an unselected cohort of pediatric and adult patients with a tic disorder.

METHODS

Subjects

Participants were required to be at least 7 years of age. Given the large range in age of participating subjects, and given the possibility that pediatric patients may be differently affected by infections than adult patients, we decided to separately analyze patients below and above 16 years of age; that is, a pediatric group of patients between 7 and 15 years of age, and an adult group of 16 years of age and older. All patients with a tic disorder could only enter the study if they fulfilled the criteria for a definite tic disorder, according to the Tourette Syndrome Classification Study Group (1993). These criteria require observable tics to be present during the clinical interview to allow for study entry. Subjects were not selected or excluded based on PANDAS criteria (Swedo et al. 1998). PANDAS criteria require the presence of obsessive-compulsive disorder and/or tic disorder,

prepubertal symptom onset, sudden onset or episodic course of symptoms, temporal association between streptococcal infections and neuropsychiatric symptom exacerbations, and associated neurological abnormalities. We did not specifically assess whether subjects did or did not meet these criteria.

Also, the presence of comorbid psychiatric diagnoses, which we did not record systematically, was no ground for exclusion. However, patients with a history of schizophrenia or pervasive developmental disorders were not included. Excluded from the study were subjects with a history, or family history, of an autoimmune disorder. None of the subjects who were willing to participate in the study fulfilled any of these exclusion criteria. The tic-disorder patients were recruited from the outpatient clinic of the Child and Adolescent Psychiatry Center, Groningen, the Netherlands, or from the Dutch Tourette's Syndrome patients association. The aim and procedure of this study were fully explained to the subjects before written consent was requested. If the subjects were under 18 years of age, the parents were informed as well, and the written, informed consent of the parents and the subjects' assent were obtained. Patients and parents were informed that we intended to study the relationship between infections and changes in tic severity over time, without revealing clues to an expected possible time frame. The study was approved by the Dutch Central Review Board. To assess tic severity at study entry, we used the motor and vocal scores of the Yale Global Tic Severity Scale (Leckman et al. 1989). The sum of both scores was used as a measure of total tic severity.

Twenty tic-disorder patients entered the pediatric study group (14 boys, 6 girls), ranging in age from 7 to 15 years (mean = 12.3; SD = 2.5). The adult group of tic-disorder patients consisted of 41 patients (25 men, 16 women) and ranged in age between 16 and 64 years (mean = 34.1; SD = 15.3). The mean total tic severity score for the pediatric tic-disorder patients at study entry was 18.6 (SD = 10.0; range = 8–50), with a mean motor score of 12.5 (SD = 5.2; range = 6–25) and a mean vocal score of 6.1 (SD = 6.4; range = 0–25). For the adult tic-disorder group, the mean total tic severity score

at study entry was 23.5 (SD = 8.9; range = 10–50), with a mean motor score of 14.6 (SD = 4.4; range = 7–25) and a mean vocal score of 8.9 (SD = 6.5; range = 0–25). The mean total, motor, and vocal tic severity of the adult and pediatric study group did not differ significantly (*t* test). At study entry, 13 of the 20 (i.e., 65%) pediatric tic-disorder patients were taking psychotropic medication, such as an antipsychotic agent (*n* = 8; either haloperidol, pimozide, or risperidone), clonidine (*n* = 3), or a combination of an antipsychotic agent and clonidine (*n* = 2). In addition, 14 of the 41 (34%) of the adult patients were on medication, such as an antipsychotic agent (*n* = 11) or an antidepressive agent (*n* = 3).

Procedure

During 24 consecutive weeks, each week, on a chosen fixed day of the week, participants were asked to fill out a questionnaire. When participants were children, parents were allowed to assist the children in filling out the questionnaire. On this questionnaire, participants had to state whether or not they had experienced a common cold over the past 7 days, as well as whether they had experienced symptoms suggestive of a pharyngitis (i.e., a sore throat). Because common cold is such a universal experience, we did not ask for specific symptoms suggestive of a common cold, but simply asked for the presence or absence of a common cold according to the patient's opinion. In addition, again according to the participants' subjective experience, they had to fill out whether the tic severity over the past 7 days had stayed about the same, had decreased or increased slightly, or had increased or decreased much, compared to the preceding period of 7 days. Finally, they were asked to record any change in psychotropic medication regime. All questionnaires were to be mailed to us in stamped envelopes on a weekly base. During this 24-week study period, every 4 weeks, that is, at study entry (week 0), and, subsequently, at weeks 4, 8, 12, 16, and 20, throat specimens were taken, which were cultured for streptococci. In addition, at 3 time points, at weeks 4, 12, and 20, blood was drawn for assessing antistreptolysine O (ASO) titer and antideoxyribonuclease (anti-DNAse B) titer.

Either an ASO titer above 200 IU/mL, or an anti-DNAse B titer above 200 E/mL, or both, was considered as elevated antistreptococcal titer. To avoid inter-assay variability, these laboratory assessments were done concurrently for all samples. The whole study was performed in the period between September 2001 and May 2002.

Definitions of infections and tic exacerbations

A 2-titerstep rise in either ASO or anti-DNAse B, or both, was regarded as evidence of an experienced streptococcal infection. To determine the precise time of the actual infection, in case of such a 2-titerstep rise, we used information from the questionnaires regarding symptoms suggestive of a pharyngitis (i.e., a sore throat). A newly acquired positive throat culture (i.e., a positive throat culture that had not been present in the preceding assessment) was considered a streptococcal colonization, provided we did not detect a subsequent 2-titerstep rise in the levels of the antistreptococcal antibodies. Positive throat cultures that were present at the first, as well as subsequent, throat swabs were considered carrier states.

Only those reports of common colds which had not been reported in the preceding week were considered a common cold in the analyses. When a common cold had already been reported in the preceding week, a subsequent report of a common cold was relabeled as "not a common cold." This was done to ensure that each common cold only once have entered the analyses: A cold may be present across 2 subsequent periods of 7 days, but this is extremely unlikely to represent two separate infections. When no information was available regarding the preceding week (this was the case with regard to all first questionnaires, as well as when participants had failed to return the questionnaire in the preceding week), reports of a common cold on the questionnaires were removed from the analyses (i.e., treated as missing values). Thus, only reports of newly acquired common colds during the observation period were used in the statistical analyses.

When participants filled out that their tic severity over the past 7 days had increased much,

compared to the preceding period of 7 days, this was considered a tic exacerbation. All other answers to this topic were classified as "no tic exacerbation."

Statistical analysis

In both patient groups, we intended to determine a possible association of the self-report of a common cold, and a streptococcal pharyngitis or colonization, respectively, with an exacerbation of tic severity during the same week, as well as 1, 2, 3, 4, 5, and 6 weeks later. For this purpose, odds ratios were computed, including 95% confidence intervals, by using chi-square analysis. Odds ratios were also computed with regard to a possible association between a change in medication and tic exacerbations. Patients who did not complete the whole study remained part of all statistical analyses. Frequencies of both common colds and tic exacerbations were computed for the entire 24 weeks, assuming that missing weeks would have the same chance of either event as in nonmissing weeks. Given the number of statistical comparisons (seven for each patient group), we considered two-tailed p values less than 0.007 significant. This p value was based on a Bonferroni adjustment (0.05/7).

RESULTS

Response rate

The pediatric group returned a total number of 412 questionnaires, a response rate of 85.8% returned questionnaires. The adult patient group returned a total number of 731 questionnaires, an overall response rate of 74.3%. In contrast to the pediatric group, in which all patients participated throughout the whole study period, 6 of 41 adult patients decided to withdraw from the study, all within the first 4 weeks, thus lowering the overall response rate. Without these 6 patients, the response rate in the adult group was 84.5%. In addition, we collected a total number of 53 pediatric serial sera for assessment of streptococcal antibodies (88.3% of planned assessments; 2 of the children refused blood draws), as well as 111 serial adult sera (90.2%

of planned sera). Finally, we collected 116 serial pediatric throat swabs (96.7% of planned swabs), as well as 217 serial throat swabs in the adult patient group (88.2% of planned swabs).

Frequency of tic exacerbations

The pediatric patient group reported 55 tic exacerbations; this is 13.3% of all 413 weekly questionnaires, or a computed mean number of 3.2 (median = 3.4; range = 0–7; SD = 2.4) exacerbations per child per 24 weeks. All in all, 15 of the 20 children (75%) reported at least one tic exacerbation during the study period. The adult patient group reported 99 tic exacerbations, being 13.5% of 731 questionnaires, or a computed mean number of 3.2 (median = 2.3; range = 0–12; SD = 3.3) exacerbations per adult participant per 24 weeks. Of the 35 adult patients, who participated for longer than 4 weeks, 27 (77.1%) experienced at least one tic exacerbation during the study period.

Frequency of reports of infections

In the pediatric group, 37 common colds were reported; this is 9.6% of valid cases, or a computed mean number of 2.3 (median = 2.1; range = 0–4; SD = 1.6) common colds per child per 24 weeks. All in all, 18 of the 20 children (90%) reported at least one common cold during the study period. In addition, in the pediatric group, only one streptococcal infection, as well as one single newly acquired streptococcal colonization, was detected. Two additional subjects in the pediatric group turned out to be streptococcal carriers. At the 1st of 3 serum assessments, 9 of the 18 children (50%) of whom sera were available demonstrated at least one elevated antistreptococcal titer. Apart from the 1 child who experienced a subsequent 2-titerstep rise, none of the remaining children demonstrated any relevant titer rises thereafter.

In the adult group, 58 common colds were reported; this is 8.4% of valid cases, or a computed mean number of 2.0 (median = 2.1; range = 0–4; SD = 1.4) common colds per adult participant per 24 weeks. Of the 35 adult patients, who participated for longer than 4 weeks, 29 patients (82.9%) experienced at least one common cold during the study period. In the adult

group, no evidence of a streptococcal infection was detected. A new streptococcal colonization during the study period happened in 2 adult patients, whereas we found 1 adult streptococcal carrier state. At the 1st of 3 serum assessments, 10 of the 35 adult patients (28.6%) of whom sera were available demonstrated at least one elevated antistreptococcal titer. None of the patients demonstrated any subsequent relevant titer rises.

Changes in medication

In the pediatric group, participants reported 35 times a change in use of psychotropic medication, or in 8.8% of valid cases. In the adult group, this was reported 75 times, or in 10.6% of valid cases. In both the pediatric and the adult patient group, no statistically significant relationship was found between change in medication use and report of a tic exacerbation during the same week, or 1, 2, 3, 4, 5, or 6 weeks later.

Association between tic exacerbations and infections

In the pediatric group, self-report of a common cold was strongly associated with an exacerbation in tic severity 4 weeks later (Table 1). When no common cold was reported, tic severity 4 weeks later was reported as "much increased" in 11.2% of cases, whereas the report of a newly acquired common cold led to a "much increased" tic severity 4 weeks later in 37.0% of cases, yielding an odds ratio of 4.685. No statistically significant associations were found between common cold and tic exacerba-

tions in the same week or 1, 2, 3, 5, or 6 weeks later (Table 1). In the adult patient group, no statistically significant associations were observed between reports of a common cold and tic exacerbations in the same week or subsequent weeks (Table 2). Given the low number of observed streptococcal infections ($n = 1$ in the pediatric group versus $n = 0$ in the adult group) or colonizations ($n = 1$ in the pediatric group versus $n = 2$ in the adult group), we were not able to determine associations between streptococcal pharyngitis or colonization and subsequent tic exacerbations.

DISCUSSION

Although the first notion of a possible link between infection and tic disorders dates back to 1929 (Selling), this is one of the first studies that examined the association between exacerbations in tic severity and preceding infections in a prospective longitudinal design. In the pediatric patients, we found a strong association between self-reports of a common cold and a subsequent exacerbation in tic severity 4 weeks later. It is improbable that this resulted from a nonspecific stress reaction, as we did not find an association with tic exacerbations in other weeks, including the week in which the common cold was newly reported. The usual duration of cold symptoms in children is 10–14 days (Owen Hendley 2000); thus, the cold has already entirely disappeared by the time of the tic exacerbation 4 weeks later. In contrast, we did not encounter this association in the adult patients. Only a trend regarding the occurrence of tic exacerbations 3 weeks after the cold may be no-

TABLE 1. ODDS RATIOS, INCLUDING 95% CONFIDENCE INTERVALS AND SIGNIFICANCE LEVELS REGARDING THE ASSOCIATION BETWEEN THE SELF-REPORT OF A COMMON COLD AND TIC EXACERBATIONS IN THE SAME WEEK AS WELL AS IN THE FOLLOWING 6 WEEKS IN THE PEDIATRIC PATIENT GROUP

<i>Week in which exacerbation was reported</i>	<i>Odds ratio (95% confidence interval)</i>	<i>p value</i>
Same week	0.550 (0.162–1.860)	0.301
1 week later	2.219 (0.886–5.554)	0.107
2 weeks later	0.876 (0.248–3.092)	0.835
3 weeks later	1.684 (0.593–4.783)	0.348
4 weeks later	4.685 (1.954–11.231)	0.001
5 weeks later	0.402 (0.092–1.765)	0.176
6 weeks later	0.768 (0.218–2.708)	0.673

TABLE 2. ODDS RATIOS, INCLUDING 95% CONFIDENCE INTERVALS AND SIGNIFICANCE LEVELS REGARDING THE ASSOCIATION BETWEEN THE SELF-REPORT OF A COMMON COLD AND TIC EXACERBATIONS IN THE SAME WEEK AS WELL AS IN THE FOLLOWING 6 WEEKS IN THE ADULT PATIENT GROUP

<i>Week in which exacerbation was reported</i>	<i>Odds ratio (95% confidence interval)</i>	<i>p value</i>
Same week	1.964 (0.995–3.876)	0.065
1 week later	1.267 (0.571–2.808)	0.569
2 weeks later	1.406 (0.599–3.304)	0.448
3 weeks later	1.989 (0.936–4.229)	0.089
4 weeks later	0.934 (0.352–2.477)	0.890
5 weeks later	0.983 (0.369–2.623)	0.973
6 weeks later	1.491 (0.624–3.563)	0.385

ticeable in adults. Apparently, children and adults differ with regard to the impact of infections on changes in tic severity. While differences between children and adults are well known with regard to both the immunological response to infections and the maturity of the nervous system, we currently do not have a plausible explanation for the different impact of upper respiratory infections on children and adults with a tic disorder. Future studies should focus on the immunological pathways that may be involved. Also, speculations about why the time frame between the upper respiratory infection and the subsequent exacerbation in tic severity appears to be 4 weeks will have to await for such studies to be done. Although the association between the pediatric patients' report of a common cold and a tic exacerbation 4 weeks later was highly significant, it is somewhat unexpected that no such significant or nearly significant associations were found after 3 or 5 weeks. Thus, our finding clearly needs independent replication to rule out the possibility that the finding may have occurred by chance. Currently, we know of one additional study that pointed to the relevance of common colds in obsessive-compulsive and tic disorders (Giulino et al. 2002). In that study, the presence of the common cold at the time of onset of obsessive-compulsive disorder and tic symptoms appeared to be associated with sudden, rather than insidious, onset of symptoms.

Prior studies pointed to a possible association between tic disorders and streptococcal infections, as was suggested by increased serum levels of antistreptococcal antibodies in unselected patients with a tic disorder (Muller et al. 2000, 2001; Cardona and Orefici 2001). Although

that approach bears the risk of circular reasoning, other authors preferred to preselect patients based on working criteria for PANDAS (Garvey et al. 1998). Indeed, a number of prospectively identified PANDAS cases have recently been presented (Murphy and Pichichero 2002; Murphy et al. 2004). Thus, there is some indication that streptococcal infections may be associated with tics. We intended to address this issue in our study, using unselected tic disorder patients, in order to preclude a priori selected cases that, by definition, demonstrate a temporal relationship with streptococcal infections but identified only one streptococcal infection in the pediatric cohort versus none in the adult patient group over a period of 16 weeks. Thus, this study does not resolve the issue of whether or not streptococcal infections are associated with subsequent exacerbations in tic severity. The low frequency of streptococcal infections found in this study could be partially because the average age of the pediatric group was in the older range, as these infections are more common in those younger than 10 years. However, given both the relatively low incidence of streptococcal infections and the probability that only a subgroup of tic-disorder patients may have an immune-mediated pathogenesis, future longitudinal studies will demand a large number of patients and a much longer time frame if a true association in at least this subgroup between tic exacerbations and streptococcal infections is to be demonstrated.

In contrast to the low incidence of streptococcal infections, common colds are fairly frequent, with an annual incidence of around four colds per year in teenagers and adults, which center around the winter season in temperate

climates (Owen Hendley 2000). Thus, our study's reported frequency of slightly more than two colds per individual during the 24-week study period in the fall and winter period fits well with established epidemiological figures (Owen Hendley 2000). The common cold is almost exclusively a viral disease (Makela et al. 1998). Viral infections are well known to trigger autoimmune conditions (Hill and Rose 2001; Mason 2001; Cooke et al. 1998; Panoutsakopoulou and Cantor 2001), though the precise mechanism of induction of autoimmunity by viral infections is largely unknown. One possibility would be molecular mimicry, in which antibodies or T-cells generated in the response to a virus crossreact with self-antigens. Because common colds can be caused by a plethora of viral species, future studies should try to identify which viruses may be associated with tic exacerbations in children and how these may influence antineuronal antibody levels (Laurino et al. 1997). Also, it would be of interest to prospectively study the role of infections regarding the onset of tic disorders (e.g., in young children with one or both parents and/or siblings affected by tics).

In this study, we relied exclusively on subjective self-questionnaires for both detecting tic exacerbations and common colds. Moreover, we only looked at a possible association between preceding infections and the report of a "much increased" tic severity and did not specifically analyze minor tic-symptom fluctuations or major improvements in tic severity, which we all categorized under "no tic exacerbation." This was done because symptom severity in tic disorders may naturally fluctuate in relation to a host of possible factors (Hoekstra et al. 2004), but, in contrast, infections have been described to be associated with "abrupt symptom exacerbations," one of the original PANDAS criteria (Swedo et al. 1998). We also thought such "abrupt symptom exacerbations" to be most reliably identified if patients were asked to always compare a possible worsening in tics with the situation in the preceding week and not with a baseline tic-severity level. However, as a disadvantage of this approach, occasionally, an "exacerbation" may have been merely the result of a temporary tic improvement during the previous week. Obviously, future studies should try

to objectively determine exacerbations in tic severity, using established rating instruments (Lin et al. 2002), preferably with at least weekly assessments of tic severity. In addition, such studies may want to objectively document symptoms of the common cold. However, the excellent response rates in our study over a period of 24 weeks is surely an indicator of the high motivation of participants and, thus, of the reliability of the present data.

CONCLUSION

In conclusion, our finding that the common cold appears to be associated with children's exacerbations in tic severity 4 weeks later adds to the growing literature that indicates the possible involvement of the immune system in tic disorders (Hoekstra et al. 2002). In addition, this finding underlines the unique possibilities of tic disorders to study the complex interplay between immune factors, brain functioning, and behavior.

REFERENCES

- Allen AJ, Leonard HL, Swedo SE: Case study: A new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry* 34:307–311, 1995.
- Cardona F, Orefici G: Group A streptococcal infections and tic disorders in an Italian pediatric population. *J Pediatr* 138:71–75, 2001.
- Cooke SP, Rigby SP, Griffiths DJ, Venables PJ: Viral studies in rheumatic disease. *Ann Med Interne (Paris)* 149:30–33, 1998.
- Garvey MA, Giedd J, Swedo SE: PANDAS: The search for environmental triggers of pediatric neuropsychiatric disorders. Lessons from rheumatic fever. *J Child Neurol* 13:413–423, 1998.
- Giulino L, Gammon P, Sullivan K, Franklin M, Foa E, Maid R, March JS: Is parental report of upper respiratory infection at the onset of obsessive-compulsive disorder suggestive of pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection? *J Child Adolesc Psychopharmacol* 12:157–164, 2002.
- Hill SL, Rose NR: The transition from viral to autoimmune myocarditis. *Autoimmunity* 34:169–176, 2001.
- Hoekstra PJ, Kallenberg CG, Korf J, Minderaa RB: Is Tourette's syndrome an autoimmune disease? *Mol Psychiatry* 7:437–445, 2002.

- Hoekstra PJ, Steenhuis MP, Kallenberg CG, Minderaa RB: Association of small life events with self-reports of tic severity in pediatric and adult tic disorder patients: A prospective longitudinal study. *J Clin Psychiatry* 65:426–431, 2004.
- Laurino JP, Hallett J, Kiessling LS, Benson M, Pelletier T, Kuhn C: An immunoassay for anti-neuronal antibodies associated with involuntary repetitive movement disorders. *Ann Clin Lab Sci* 27:230–235, 1997.
- Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, Cohen DJ: The Yale Global Tic Severity Scale: Initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry* 28:566–573, 1989.
- Lin H, Yeh CB, Peterson BS, Scahill L, Grantz H, Findley DB, Katsovich L, Otko J, Lombroso PJ, King RA, Leckman JF: Assessment of symptom exacerbations in a longitudinal study of children with Tourettes' syndrome or obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry* 41:1070–1077, 2002.
- Luppi P, Rossiello MR, Faas S, Trucco M: Genetic background and environment contribute synergistically to the onset of autoimmune diseases. *J Mol Med* 73:381–393, 1995.
- Makela MJ, Puhakka T, Ruuskanen O, Leinonen M, Saikku P, Kimpimäki M, Blomqvist S, Hyypia T, Arstila P: Viruses and bacteria in the etiology of the common cold. *J Clin Microbiol* 36:539–542, 1998.
- Mason A: Viral induction of type 2 diabetes and autoimmune liver disease. *J Nutr* 131:2805S–2808S, 2001.
- Muller N, Kroll B, Schwarz MJ, Riedel M, Straube A, Lutticken R, Reinert RR, Reineke T: Increased titers of antibodies against streptococcal M12 and M19 proteins in patients with Tourettes' syndrome. *Psychiatry Res* 101:187–193, 2001.
- Muller N, Riedel M, Straube A, Gunther W, Wilske B: Increased antistreptococcal antibodies in patients with Tourettes' syndrome. *Psychiatry Res* 94:43–49, 2000.
- Murphy ML, Pichichero ME: Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Arch Pediatr Adolesc Med* 156:356–361, 2002.
- Murphy TK, Sajid M, Soto O, Shapira N, Edge P, Yang M, Lewis MH, Goodman WK: Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcus in children with obsessive-compulsive disorder and tics. *Biol Psychiatry* 55:61–68, 2004.
- Owen Hendley J: The Common Cold. In: *Cecil Textbook of Medicine*. Edited by Goldman L, Claude Bennett J. Philadelphia, W.B. Saunders Company, 2000, pp 1790–1792.
- Panoutsakopoulou V, Cantor H: On the relationship between viral infection and autoimmunity. *J Autoimmun* 16:341–345, 2001.
- Perlmutter SJ, Garvey MA, Castellanos X, Mittleman BB, Giedd J, Rapoport JL, Swedo SE: A case of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *Am J Psychiatry* 155:1592–1598, 1998.
- Selling L: The role of infection in the etiology of tics. *Arch Neurol Psychiatry* 22:1163–1171, 1929.
- Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, Lougee L, Dow S, Zamkoff J, Dubbert JK: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: Clinical description of the first 50 cases. *Am J Psychiatry* 155:264–271, 1998.
- The Tourette Syndrome Classification Study Group. Definitions and classification of tic disorders. *Arch Neurol* 50:1013–1016, 1993.
- Tucker DM, Leckman JF, Scahill L, Wilf GE, LaCamera R, Cardona L, Cohen P, Heidmann S, Goldstein J, Judge J, Snyder E, Bult A, Peterson BS, King R, Lombroso P: A putative poststreptococcal case of OCD with chronic tic disorder, not otherwise specified. *J Am Acad Child Adolesc Psychiatry* 35:1684–1691, 1996.

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