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Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcus: Comparison of Diagnosis and Treatment in the Community and at a Specialty Clinic

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Abstract

OBJECTIVES—This study aimed to examine whether pediatric autoimmune neuropsychiatric disorders associated with streptococcus were appropriately diagnosed in the community and to determine subsequent rates of unwarranted use of antibiotic treatment for tics and obsessive-compulsive symptoms without the identification of an infection.

METHODS—The design was a retrospective, cross-sectional, observational study of 176 children and adolescents who were evaluated in a specialty program for tics, Tourette's disorder, and related problems. Previously published diagnostic criteria were used to establish the diagnosis of pediatric autoimmune neuropsychiatric disorders associated with streptococcus in our clinic.

RESULTS—Subjects were significantly less likely to receive a diagnosis of pediatric autoimmune neuropsychiatric disorders associated with streptococcus at the specialty clinic than in the community. In the community, subjects were significantly more likely to be treated with antibiotics or immunosuppressant medication if they received a diagnosis of pediatric autoimmune neuropsychiatric disorders associated with streptococcus. Of the 27 subjects with a community diagnosis of pediatric autoimmune neuropsychiatric disorders associated with streptococcus who were treated with antibiotics, 22 (82%) were treated without laboratory evidence of an infection; 2 were treated with immunomodulatory medications.

CONCLUSIONS—Our results support our hypothesis that pediatric autoimmune neuropsychiatric disorders associated with streptococcus are frequently diagnosed in the community without the application of all working diagnostic criteria. This phenomenon has resulted in unwarranted use of antibiotic treatment for tics/obsessive-compulsive disorder without evidence of laboratory infection.

Keywords

pediatric autoimmune neuropsychiatric disorders associated with streptococcus; group A β -hemolytic streptococcus; obsessive-compulsive disorder; tics; antibiotic treatment

What's Known on This Subject

PANDAS is a term used to describe a subgroup of children with tic and/or obsessive-compulsive disorder symptoms precipitated by a streptococcal infection. The existence of PANDAS as a diagnostic entity is controversial, and treatment guidelines are unclear.

What This Study Adds

Results of the study indicate that the diagnosis of PANDAS without the use of full diagnostic criteria has resulted in the unwarranted use of antibiotics. Evidence has linked excessive antibiotic use to antibiotic resistance, a significant, emerging public health concern.

In 1998, SWEDO et al¹ described the clinical characteristics of 50 children with obsessive-compulsive disorder (OCD) and/or tic disorders in which the onset or exacerbation of symptoms was precipitated by group A β -hemolytic streptococcus (GABHS) infection; the term pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS) was created to describe this theoretical subgroup of cases of OCD and/or tic disorders. Five working criteria for the diagnosis of PANDAS were proposed, that is, (1) presence of lifetime, DSM-IV, diagnostic criteria for OCD and/or tic disorder; (2) onset between age 3 and the beginning of puberty; (3) episodic course of symptom severity; (4) temporal association between symptom onset and/or exacerbation and GABHS infection, as documented with positive throat culture results and/or elevated anti-GABHS antibody titers; and (5) association with neurologic abnormalities during symptom exacerbation, such as tics or choreiform movements but not chorea. Swedo et al¹ speculated that an autoimmune process similar to that in Sydenham chorea and rheumatic fever may play a role in the development of PANDAS.

The hypothesis that there is a subgroup of children with PANDAS has generated much clinical and basic research.²⁻¹⁶ To date, there is still controversy regarding the existence of such a diagnostic entity and its hypothesized pathogenesis.^{17,18} Although questions remain regarding the validity and/or specificity of the diagnostic criteria described by Swedo et al,¹ the risks of medication treatment and the absence of definitive biological markers make it prudent to apply these criteria.

Studies have examined whether specific or different therapeutic approaches, compared with those used for children with OCD and/or tic disorders without PANDAS, such as antibiotic¹⁹⁻²¹ or immunomodulatory²²⁻²³ treatments, should be applied in PANDAS cases. Results of those studies have been mixed. At present, guidelines limit antibiotic use to treatment of acute streptococcal infections diagnosed on the basis of a positive throat culture or rapid streptococcal test results¹⁸ and limit plasma exchange and intravenous immunoglobulin therapy to research protocols only.¹⁷

Given the increase in antibiotic-resistant bacteria in recent years (which is partly the result of unwarranted use of antibiotics) and the high risk of serious adverse events linked to immunomodulatory treatments, investigation of the use of these therapeutic options for patients with OCD and/or tic disorders is of public health significance.²⁴ The aims of this study were to test our hypotheses that PANDAS would be diagnosed in the community without the application of the 5 diagnostic criteria described by Swedo et al¹ and that there would be unwarranted antibiotic treatment for tics and OCD in the community without the identification of an infection source.

METHODS

Setting

The study was conducted at the Institute for Tourette and Tic Disorders at the New York University (NYU) Child Study Center (CSC), a specialty program for children and adolescents with tic disorders, Tourette's disorder, and related problems. All subjects were evaluated by a child/adolescent psychiatrist with expertise in the diagnosis and treatment of Tourette's disorder, OCD, and PANDAS.

This was a retrospective, cross-sectional, observational study of all children and adolescents consecutively evaluated at the institute between October 2001 and December 2005. This study also included all subjects who enrolled in 1 of 2 prospective, longitudinal, follow-up studies of PANDAS during this period (PANDAS, $n = 11$; control, $n = 11$). Subjects enrolled in these studies included patients with PANDAS and matched control subjects who had Tourette's disorder and/or OCD but did not have evidence of onset or exacerbation of tics or OCD symptoms in association with GABHS. All youths (from the clinic and the studies) were evaluated by Dr Gabbay or Dr Coffey using the same methods, which included a telephone intake and a comprehensive psychiatric evaluation. The study was approved by the NYU School of Medicine institutional review board.

Patient Selection

All subjects had a diagnosis of a tic disorder and/or OCD and were <21 years of age at the time of assessment. All subjects' psychiatric diagnoses were based on criteria from DSM-IV.²⁵ To meet the diagnostic criteria for PANDAS at the CSC, subjects needed to meet all 5 research diagnostic criteria described by Swedo et al.¹ The same diagnostic criteria were applied to the clinical and research patients who were enrolled in the PANDAS prospective studies.

Chart Review

Medical charts for the patients were reviewed, and standard forms (Institute data forms) were used to record the following: demographic information including ethnicity and gender, age at the time of evaluation, age of onset of OCD and/or tic disorder, referral diagnosis (PANDAS or non-PANDAS), clinical specialty of the physician who treated the child in the community, and type of treatment recommended or received in the community. Treatment information included current or past use of psychotropic (conventional) pharmacotherapy and antibiotic or immunosuppressant treatment. Medical charts also were reviewed for laboratory data documenting GABHS infections, including throat culture reports, anti-streptolysin-O titers, and anti-deoxyribonuclease B titers. If data were not available at the time of the initial evaluation, then laboratory work from the patient's pediatrician or primary care physician was obtained for review of the temporal correlation of the onset or exacerbation of OCD and/or tic symptoms with the index episode. Laboratory data, including throat culture reports, anti-streptolysin-O titers, and anti-deoxyribonuclease B titers, consisted of records obtained from the patients' pediatricians; for patients who participated in the PANDAS longitudinal studies, laboratory data were obtained by the CSC. Subjects who met the 5 diagnostic criteria described by Swedo et al.¹ were considered to have true-positive results, and subjects who did not meet the diagnostic criteria (ie, ≤ 4 criteria) were considered to have false-positive results.

Statistical Analyses

An exact McNemar test was used to compare the proportion of subjects diagnosed as having PANDAS in the community with the proportion diagnosed at the CSC. Fisher's exact test was used to examine whether rates of unwarranted antibiotic treatment were different for subjects with true-positive and false-positive PANDAS diagnoses in the community. Fisher's exact test

also was used to determine whether the proportion of subjects treated with antibiotics or immunotherapy in the community was associated with other cross-tabulated factors, such as comorbid psychiatric disorders and tic severity scores, and to determine whether the proportion treated with conventional psychopharmacotherapy was associated with a diagnosis of PANDAS in the community. All statistical computations were performed by using SAS 9.0 (SAS Institute, Cary, NC), and statistical significance was set at the .05 level.

RESULTS

Participants

The study population consisted of 176 children and adolescents; 124 (70.5%) were male. The mean age at the time of evaluation was 10.6 years (SD: 3.9 years). One hundred forty-one (80.1%) of the subjects were white, 4 (2.3%) were black, 5 (2.8%) were Hispanic, and 26 (14.8%) were of other race/ethnicity. The mean age of onset of Tourette's disorder was 6.1 years (SD: 2.5 years; range: 1–13 years). Comorbid psychiatric diagnoses included OCD ($n = 91$; 51.7%), attention-deficit/hyperactivity disorder ($n = 102$; 58%), mood disorders ($n = 31$; 17.6%), non-OCD anxiety disorders ($n = 61$; 34.7%), and other disorders ($n = 86$; 48.9%), including enuresis, language disorder, impulse-control disorder, learning disorders, oppositional defiant disorder, conduct disorder, pervasive developmental disorder, and trichotillomania.

Rates of Community Diagnosis

Of the 176 subjects in our sample, 31 (17.6%) received diagnoses of PANDAS in the community. Nineteen subjects had false-positive diagnoses of PANDAS (ie, did not meet the full criteria described by Swedo et al¹) in the community; those 19 subjects represented 61.3% of the 31 subjects who received PANDAS diagnoses in the community. Notably, the diagnosis was made for some children in the community with OCD and/or tic symptoms who had only a single documented elevation in anti-streptolysin-O titer, which provides no useful information without evidence of acute infection; in some cases, the diagnosis was made without any documented laboratory evidence. Although there may be slight variations in anti-streptolysin-O titer measurements among medical laboratories, a single documented elevation indicates only previous exposure to streptococcal bacteria and is not sufficient for a PANDAS diagnosis unless it is accompanied by evidence of acute infection.

Table 1 provides a cross-tabulation of subjects with respect to whether the PANDAS diagnosis was received in the community or at the CSC. Subjects were significantly less likely ($P < .03$) to receive a PANDAS diagnosis at the CSC (19 subjects; 10.8%) than in the community (31 subjects; 17.6%).

Antibiotic and Immunologic Treatments

Of the 31 subjects with community diagnoses of PANDAS, 27 (87%) were treated with antibiotics for either acute treatment of the index episode or prophylaxis. The duration of treatment ranged from brief courses (1 week) to long-term prophylaxis for up to 4 years. Antibiotics prescribed for these subjects included penicillin, amoxicillin, clarithromycin, erythromycin/sulfisoxazole, amoxicillin/clavulanate, azithromycin, clindamycin, and cefadroxil. Subjects were significantly more likely ($P < .0001$) to be treated with antibiotics if they received a diagnosis of PANDAS in the community (27 of 31 subjects treated; 87%), compared with those who did not receive a diagnosis of PANDAS in the community (5 of 143 subjects treated; 3.5%).

Of the 27 subjects with community diagnoses of PANDAS who were treated with antibiotics, 22 (82%) were treated without laboratory evidence of an infection. Of those 22 subjects, 17

(77%) were treated with antibiotics for an index episode (ie, short-term antibiotic treatment of 10–30 days). Antibiotic treatment ranged from 1 to 5 courses. Twelve subjects (55%) received prophylactic treatment for up to 4 years. Seven subjects (32%) received both acute and prophylactic treatment.

Twelve subjects in the community were diagnosed as having PANDAS according to strict criteria (true-positive cases); all 12 were treated with antibiotics, but 8 (67%) of 12 were treated without identification of an infection source. Nineteen subjects had unconfirmed diagnoses of PANDAS in the community (false-positive cases); of those subjects, 15 were treated with antibiotics, and 14 (93%) of 15 were treated without laboratory documentation of an infection. There were no significant differences with respect to unwarranted antibiotic treatment in the community between subjects who were diagnosed with PANDAS on the basis of all criteria described by Swedo et al¹ (true-positive cases) and subjects who were diagnosed without meeting the full criteria (false-positive cases) ($P > .1$).

Two subjects (7%) were treated with steroids and intravenously administered immunoglobulin for tics. When only data for the 31 subjects who received PANDAS diagnoses in the community were examined, antibiotic and/or immunosuppressant treatment was not statistically significantly associated with tic severity ($P > .99$), comorbid attention-deficit/hyperactivity disorder ($P > .99$), comorbid mood disorders ($P > .99$), comorbid OCD ($P = .495$), or comorbid anxiety disorders ($P = .615$).

Conventional Treatment of Tics/OCD

Treatment information was available for all 31 subjects with community diagnoses of PANDAS. Of those 31 subjects, 19 (63.3%) received conventional psychopharmacological treatment for tics/OCD (ie, α -adrenergic agonists or neuroleptic agents for tics and selective serotonin reuptake inhibitors for OCD). When proportions of patients in the false-positive ($n = 19$) and true-positive ($n = 12$) PANDAS groups who received conventional treatment were compared, subjects with false-positive diagnoses were less likely to be treated with conventional treatment (42.1%) than were those with true-positive diagnoses (91.67%; $P < .008$). In contrast, of the 143 subjects without community diagnoses of PANDAS, 83 (58.5%) received conventional psychopharmacological treatment. There was no significant difference in the proportions of subjects with and without community diagnoses of PANDAS who received conventional psychopharmacological treatment ($P = .77$).

DISCUSSION

Diagnosis and Treatment Rates

To the best of our knowledge, this is the first study to examine several important public health implications with regard to the diagnosis of PANDAS in a large metropolitan community, specifically, the application of the 5 working diagnostic criteria described by Swedo et al¹ in the diagnosis of PANDAS and consequent antibiotic treatment for tics/OCD symptoms with or without evidence of infection. This study also examined the use of conventional, evidence-based treatment for tics and OCD. The results of our study supported our hypotheses; when strict diagnostic criteria were applied, most children who received PANDAS diagnoses in the community did not meet the full criteria for PANDAS. Rates of community diagnosis of PANDAS were significantly higher ($P < .043$) than rates of CSC diagnosis (for which all of the 5 working diagnostic criteria described by Swedo et al¹ were required). In addition, rates of use of antibiotic and/or immunomodulatory treatment for tics/OCD in the community were statistically significantly higher ($P < .0001$) than those recommended in the specialty program; 82% of patients who received PANDAS diagnoses in the community were treated with antibiotics without documentation of an infection source.

Antibiotic and Immunologic Treatments in PANDAS and Public Health Implications

To date, there is insufficient scientific evidence to support recommendations for antibiotic prophylaxis in PANDAS. In one 8-month, placebo-controlled, crossover trial of prophylactic penicillin treatment for children who met strict diagnostic criteria for PANDAS, no group differences in numbers of infections or neuropsychiatric symptom exacerbations were found between the 2 groups.¹⁹ One report that suggested therapeutic benefit for such children used open-trial methods and was not placebo-controlled or blinded, which limited the study's informativeness.² In a later study, randomized prophylactic treatment with penicillin or azithromycin for 12 months for children with PANDAS was examined. Results indicated significant decreases in both streptococcal infections and neuropsychiatric exacerbations in both treatment groups over the course of the treatment year, compared with the previous baseline year.²⁰ However, methodologic difficulties, such as small sample size, retrospective reports for the baseline year, and lack of an adequate placebo treatment, were noted.²¹

There also is insufficient evidence to support immunologic treatment, such as plasma exchange and intravenously administered immunoglobulin treatment, in PANDAS.^{22,23} Because these immunomodulatory treatments are highly invasive, with significant risks such as allergic responses, infections, and bleeding, only the most severely affected children would currently be considered eligible. The potential risks associated with these procedures have prompted the National Institute of Mental Health to restrict their use solely to research trials, until their efficacy and safety have been firmly established.²⁰

Conventional treatment for tic disorders and OCD in children with putative PANDAS is still indicated, as it would be for children without PANDAS.¹⁸ Conventional, evidence-based, pharmacological treatment of chronic tics and Tourette's disorder includes α -adrenergic agonists (such as clonidine and guanfacine), atypical neuroleptic agents (such as risperidone), or typical neuroleptic agents (such as haloperidol or pimozide). Evidence-based treatment for OCD includes both pharmacological and nonpharmacological interventions; selective serotonin reuptake inhibitor treatment is considered first-line pharmacological treatment, and cognitive behavioral therapy (ie, exposure and response prevention) is considered first-line nonpharmacological treatment.⁴

Concern has been raised that incorrect diagnosis of PANDAS, with currently incomplete scientific understanding of the disorder, has led to unwarranted use of antibiotics, plasmapheresis, and intravenously administered immunoglobulin, at the cost of withholding conventional, evidence-based treatment. Our findings support the relevance of this concern; although rates of conventional treatment for tics and OCD did not differ between the community and specialty clinic patients ($P = .54$), patients who received false-positive PANDAS diagnoses in the community were less likely to receive evidence-based, appropriate, conventional treatment ($P < .02$).

Our results also indicated that the diagnosis of PANDAS without use of full diagnostic criteria in a large metropolitan community resulted in unwarranted use of antibiotics, which substantiates an existing, major, public health concern. Our findings should be taken within the context that the highest prevalence rates of antibiotic use are found among children, as are the highest rates of infection with antibiotic resistance.^{26–28} It is estimated that up to 110 million antimicrobial courses are prescribed each year in the United States, with the highest rate in children.²⁹ For example, a study from 1992 showed that up to 44% of children were given antibiotics because of symptoms of the common cold.²⁹ Evidence has linked excessive antibiotic use to antibiotic resistance.^{30,31} Importantly, the development of antibiotic resistance can be reversed through careful, judicious, antibiotic use.³² Although several studies indicated decreases in antibiotic use among children over the past decade, antibiotic resistance still

represents a significant emerging compromise to public health.^{29,33} Our findings emphasize the risk of unwarranted antibiotic use for treatment of tics and/or OCD in a subset of children.

Limitations

Several limitations must be taken into consideration in interpretation of our study results. The number of patients was small; therefore, it is difficult to draw firm conclusions. With regard to our sample, although we drew patients from a large metropolitan area, our clinic requires self-payment. Therefore, our demographic distribution (largely white and mostly middle-class) may not reflect the demographic features of the entire metropolitan area. However, subjects who were enrolled in the PANDAS cohort studies were evaluated and treated at no cost, which fostered a broader demographic distribution.

Because our study design was retrospective, based on cross-sectional, systematic, chart review, our findings may be subject to informants' recall bias. Furthermore, the clinical raters were not blinded to treatment status. The study did not have enough statistical power to examine whether incorrect or incomplete PANDAS diagnosis in the community resulted in unwarranted treatment with antibiotics. Despite these limitations, our sample size was relatively large and our distribution of psychiatric comorbid disorders was typical of findings from other specialty and general child and adolescent psychiatry clinics.³⁴ Therefore, it is likely that our findings can be generalized to other settings. Our clinician raters, although not blinded to treatment status, had established expertise in the evaluation of tic disorders. Therefore, ratings were consistent throughout the study and reflected extensive expertise in this area.

CONCLUSIONS

To our knowledge, this is the first study to examine the prevalence and clinical consequences of PANDAS diagnosis and treatment in a large metropolitan area. Our results support our hypothesis that PANDAS is frequently diagnosed in the community without application of the full diagnostic criteria. This phenomenon has resulted in unwarranted use of antibiotic treatment for tics/OCD without evidence of laboratory infection, at least in some cases. Our findings have important public health implications. All clinicians who evaluate and treat children with tic disorders and/or OCD should have up-to-date information regarding treatment guidelines. We think that resolution of the controversy surrounding PANDAS requires prospective studies that determine potential biological markers, specific phenomenologic features, and the clinical course of the PANDAS subgroup.

PHYSICISTS IN CONGRESS CALCULATE THEIR INFLUENCE

“Washington—According to the Congressional Research Service, there are only about 30 scientists among the 535 senators and representatives in the 110th Congress, and that is counting the psychologist, the psychiatrist, a dozen other MD's, three nurses, an engineer, two veterinarians, a pharmacist and an optometrist. But physics is on a roll. ‘Go back 15 years, and there weren't any physicists,’ said Vernon J. Ehlers, a Republican who taught the subject at Calvin College in Grand Rapids, MI, until he was elected to Congress in 1993. His was a lone voice until 1998, when Rush Holt, assistant director of the Princeton Plasma Physics laboratory won election from New Jersey as a Democrat. And today there are three, adding Bill Foster, a physicist at Fermi-lab and another Democrat, who won a special election in March in Illinois. ‘If we continue to reproduce in this manner,’ Mr Foster began, and Mr Ehlers finished the thought, ‘the entire Congress would consist of physicists!’ They were joking—probably. But a Congress full of physicists might solve some worrisome problems, the three-member physics caucus argued one afternoon when they met for a joint interview in the Capitol. There are 435 people in the House, Mr Holt said, and 420 don't know much about science and choose not to.”

Dean C. *New York Times*. June 10, 2008

Noted by JFL, MD

Abbreviations

PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcus; GABHS, group A β -hemolytic streptococcus; CSC, Child Study Center; OCD, obsessive-compulsive disorder; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

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TABLE 1

Cross-tabulation Between Community and CSC PANDAS Diagnoses

Diagnosis in Community	<i>n (%)</i> ^a		
	Positive Diagnosis at CSC	Negative Diagnosis at CSC	Total
Positive	12 (6.8)	19 (10.8)	31 (17.6)
Negative	7 (3.9)	138 (78.4)	145 (82.4)
Total	19 (10.8)	157 (89.2)	176 (100)

^aPercentages are of all patients (*N* = 176).