Echocardiographic Findings in the PANDAS Subgroup

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ABSTRACT. **Background.** Sydenham’s chorea is the neurologic manifestation of rheumatic fever and is a diagnosis of exclusion requiring only the presence of frank chorea in the absence of another neurologic disorder. Two thirds of children with Sydenham’s chorea also have rheumatic carditis (pathologic mitral valve regurgitation). Although there are similar neuropsychiatric symptoms and preceding group A β-hemolytic streptococcal infection associated with both Sydenham’s chorea and the PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) subgroup, it is unknown whether patients in the PANDAS subgroup have any cardiac involvement.

**Methods.** Sixty children meeting the criteria for PANDAS were entered into protocols at National Institute of Mental Health between 1993 and 2002. Doppler and 2-dimensional echocardiograms were performed on these subjects to assess valvular heart disease.

**Results.** Of these 60 children, no echocardiographic evidence of significant mitral or aortic valve regurgitation was found. One patient was found to have mild mitral regurgitation, and all patients had normal left atrial size and normal left ventricular size and function. Follow-up echocardiograms on 20 children showed no significant valvular regurgitation.

**Conclusion.** The evidence of a clear lack of rheumatic carditis in these children supports the hypothesis that PANDAS is a distinct neuropsychiatric diagnosis separate from Sydenham’s chorea. Pediatrics 2004; 114:e748–e751. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0308; autoimmunity, streptococcal infection, echocardiography, obsessive-compulsive disorder, tics.

**ABBREVIATIONS.** OCD, obsessive-compulsive disorder; GAS, group A β-hemolytic streptococcus; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; SC, Sydenham’s chorea; NIMH, National Institute of Mental Health; LA, left atrium.

Clinical observations and systematic study have demonstrated a subgroup of children with obsessive-compulsive disorder (OCD) and/or tic disorder that experience symptom exacerbations after group A β-hemolytic streptococcal (GAS) infections. This subgroup of children has been designated by the acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections). The recognition of the 5 criteria for PANDAS by Swedo et al1 and colleagues established a homogenous subgroup of children with childhood-onset OCD and/or tic disorders. The 5 clinical characteristics that define the PANDAS subgroup are the presence of OCD and/or tic disorder, prepubertal age of onset, abrupt onset and relapsing-remitting symptom course, association with neurologic abnormalities during exacerbations (adventitious movements or motric hyperactivity), and a temporal association between symptom exacerbations and a GAS infection.

Since the PANDAS subgroup was first proposed in 1998, Sydenham’s chorea (SC) has served as a model of etiology.1 Both SC and PANDAS are neurologic autoimmune disorders resulting from GAS infections, and the high proportion of obsessive-compulsive symptoms among children with SC is well documented.2-4 However, the absence of frank chorea and unique relapsing-remitting symptom pattern in children presenting with sudden-onset OCD and tic disorders suggests that PANDAS has a unique pathology of its own.1,5 The previous diagnosis of SC has remained an exclusionary criterion for the PANDAS subgroup by definition. The Pediatrics and Developmental Neuropsychiatry Branch of the National Institute of Mental Health (NIMH) began screening children for entry into PANDAS treatment protocols in 1992. At the time, no large-scale study of children meeting the criteria for inclusion in the PANDAS subgroup had been conducted, and the extent of the similarities between PANDAS and SC was not well known.

SC is the neurologic manifestation of rheumatic fever and is a diagnosis of exclusion requiring only the presence of frank chorea in the absence of another neurologic diagnosis. Historically, “pure” chorea (SC in the absence of any other major manifestations of rheumatic fever6) has accounted for 5% to 17% of initial attacks of rheumatic fever.7,8 More commonly, SC occurs in conjunction with other manifestations of rheumatic fever. Of patients diagnosed with SC, 30% to 64% also develop significant mitral valve regurgitation or rheumatic carditis, the cardiac...
sequelae of rheumatic fever.\textsuperscript{9,10} Chorea appears 1 to 6 months after an antecedent GAS infection, whereas rheumatic carditis usually occurs only 7 to 21 days after an antecedent GAS infection. However, carditis can occur subsequent to the onset of chorea, or more typically the carditis remains undiagnosed until the onset of their chorea because of the frequent asymptomatic nature of mitral valve regurgitation.\textsuperscript{11}

Auscultation has been the traditional method for diagnosing pathologic mitral valve regurgitation in rheumatic fever patients, because severe regurgitation is audible in the form of an apical holosystolic murmur.\textsuperscript{11} The sensitivity of Doppler echocardiography allows the detection of lesser degrees of valvular regurgitation that are not audible by auscultation.\textsuperscript{9,12,13} Thus, mitral and aortic insufficiency can be detected in patients with no clinical evidence of carditis. A study of rheumatic fever patients with no auscultatory evidence of rheumatic carditis found that 68\% of those subjects had pathologic mitral valve regurgitation detectable by Doppler echocardiography.\textsuperscript{12} These findings hold true for patients presenting with SC; a 1999 study using Doppler echocardiography to detect inaudible valvular dysfunction found that 64\% of patients with SC have significant mitral valve regurgitation.\textsuperscript{9} There is also evidence that silent mitral valve regurgitation is no less serious or lasting than audible regurgitation.\textsuperscript{11} In 1 recent study of 35 patients with acute rheumatic fever, 50\% of patients had acute valvular lesions detected by Doppler echocardiography despite no auscultatory evidence of rheumatic carditis, and 30\% of those lesions were still present after 5 years.\textsuperscript{13}

In patients with rheumatic fever and SC, there are significant echocardiographic findings in many patients who have no auscultatory evidence of cardiac involvement. It is unknown whether children suffering from another poststreptococcal autoimmune neuropsychiatric disorder, namely PANDAS, might also have evidence of rheumatic carditis.\textsuperscript{9,14} Accordingly, children entered into PANDAS protocols at the NIMH were assessed by physical examination and echocardiography to facilitate both the potential diagnosis and treatment of valvular disease. The primary purpose of this investigation was to determine the incidence and severity of pathologic valvular regurgitation identified by 2-dimensional and color Doppler echocardiography in children with PANDAS.

\textbf{METHODS}

Sixty subjects meeting the diagnostic criteria for the PANDAS subgroup were evaluated at the NIMH. All 60 subjects met the 5 PANDAS criteria.\textsuperscript{1} Children with a history of SC or rheumatic fever, significant autoimmune disorders or neurologic disorders other than tics or evidence of autism, schizophrenia, or other psychotic disorders were excluded. Twenty-six subjects (43.3\%) were included in a yearlong double-blind study comparing azithromycin and penicillin antibiotic prophylaxis. Twenty-nine subjects (48.3\%) with severe symptoms were included in a prospective study of plasma exchange.

At baseline presentation, all subjects underwent transthoracic 2-dimensional and Doppler echocardiography using the Acuson Sequoia (Siemens, Mountainview, CA) or the Sonos 5500 (Philips, Inc, Andover, MA) echocardiography machines. Standard parasternal, apical, and subcostal views were acquired with the patients in the left lateral recumbent position and were stored on VHS videotape for later analysis. Videotape studies were subsequently digitized, and all measurements were performed on digital loops using a Digisonics off-line analysis station (version 3.2 software, Digisonics, Inc, Houston, TX). Cardiac measurements were performed according to the American Society of Echocardiography guidelines.\textsuperscript{15} Chamber sizes were indexed to body-surface area and compared with reference values for age-matched normal subjects.\textsuperscript{16} Fractional shortening (FS) of the left ventricle was determined from the internal dimensions of the left ventricle in diastole (LVIDD) and systole (LVIDS) and was defined as \(\text{FS} = (\text{LVIDD} - \text{LVIDS})/\text{LVIDD} \times 100\).

Valves were examined for the presence of focal or diffuse thickening of the leaflets or subvalvular apparatus (for the mitral valve). Color Doppler flow mapping of the mitral and aortic valves was performed in multiple views to detect the presence or absence of regurgitant flow. Valvular regurgitation was evaluated by previously described criteria\textsuperscript{12,17,18} which include: (1) jet duration of >100 millisecond, (2) presence of a high-velocity turbulent jet in at least 2 imaging planes, and (3) extension of the jet beyond the paravalvular region (>1 cm). In addition, mitral regurgitation was quantitated by color Doppler velocity mapping as the ratio of the area of the color jet divided by the maximum left atrium (LA) area such that a small noneccentric jet with an area of <20\% of the LA area was considered mild mitral regurgitation.\textsuperscript{16} Aortic regurgitation was further quantitated in the parasternal long-axis views using the ratio of the maximal proximal jet width to the LA outflow tract diameter such that an aortic regurgitation jet with a ratio of <25\% was considered mild aortic regurgitation.\textsuperscript{19}

\textbf{RESULTS}

The 60 subjects included in this study consisted of 33 boys and 27 girls as shown in Table 1. GAS infections were documented in all 60 subjects by 1 of 3 methods. A positive GAS culture or scarlet fever was diagnosed during the 2 months preceding the onset or exacerbation of the neuropsychiatric symptoms in 41 of the subjects. Five of the subjects were treated with 10 days of antibiotics by their primary physician for a “presumed” GAS infection with symptoms of pharyngitis, fever, and tonsillar exudates during the 2 months preceding onset or exacerbation. In 14 of the subjects, there were no documented symptoms of a GAS infection during the 2 months preceding onset or exacerbation, but there was an elevated antistreptococcal antibody titer documented 3 weeks to 3 months after onset or exacerbation. Antistreptococcal antibody titers have peak elevation 3 to 8 weeks after a GAS infection and can remain elevated for several months (Table 2.)

Fifty-five percent of the subjects (\(n = 33\)) had baseline Doppler echocardiograms performed <6 months after symptom onset (average of 2.79 months [SD: 1.3]), 15\% of the subjects (\(n = 9\)) were evaluated between 6 and 12 months after symptom onset (av-

\begin{table}[h]
\centering
\caption{Characteristics of Study Population}
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Gender} & \textbf{Number} & \textbf{Percent} & \textbf{Age at Onset (SD)} \\
\hline
Male & 37 & 62 & 7.9 (2.4) \\
Female & 23 & 38 & 7.4 (2.0) \\
\hline
\textbf{Diagnosis} & & & \\
OCD only & 24 & 40 & 7.8 (2.4) \\
Tic disorder only & 16 & 27 & 7.0 (1.6) \\
OCD and Tic disorder & 30 & 50 & 7.7 (2.2) \\
\hline
\end{tabular}
\end{table}
Average of 8.9 months [SD:1.9]), and 30% of the subjects (n = 18) were evaluated >12 months after symptom onset (average of 2.7 years [SD: 1.8]). Among baseline studies from all 60 patients, 32 were found to have trace or physiologic mitral regurgitation, 1 patient had mild mitral regurgitation, and 1 patient had trace aortic regurgitation. One subject was noted to have thickened mitral valve leaflets but had only trace mitral regurgitation and a normal aortic valve. Another subject had normal mitral and aortic leaflet morphology, but had mild mitral regurgitation. Both of these patients had normal left atrial dimensions, left ventricular dimensions, and left ventricular fractional shortening, as did the entire group (Table 3.).

Twenty subjects who were more severely psychiatrically ill at baseline had long-term follow-up in a treatment protocol and had Doppler echocardiograms performed an average of 3.8 years (SD: 0.7) after baseline evaluation. Among long-term follow-up studies from 20 patients, 11 were found to have trace or physiologic mitral regurgitation. No subjects in this group were found to have pathologic mitral valve regurgitation, abnormal leaflet pathology, or aortic regurgitation.

**DISCUSSION**

This evidence suggests that children in the PANDAS subgroup are distinct from those with SC with respect to cardiovascular complications. Of 60 subjects meeting the criteria for the PANDAS subgroup, none showed any evidence of significant pathologic mitral valve regurgitation. This is markedly lower than the 30% to 64% of the SC population with pathologic mitral valve regurgitation.9,10 In addition, one study of SC patients noted that for patients whose symptoms lasted >2 years, the rate of carditis was 31.2%, which increased to 50% among patients whose symptoms lasted for >2 years.14 The finding that none of these 60 subjects had pathologic mitral valve regurgitation was not secondary to the exclusion of children with pathologic mitral valve regurgitation before study entry. Subjects were placed in the PANDAS subgroup at screening and then entered into an NIMH study before their evaluation by echocardiography. Thus, although SC and rheumatic fever are exclusionary criteria for the PANDAS subgroup, evidence of pathologic mitral valve regurgitation was not an exclusionary criterion. In our study, 45% of patients had their baseline echocardiograms performed >6 months after symptom onset. It is possible that in this group, pathologic mitral valve regurgitation may have resolved completely or to the point of physiologic regurgitation.

Although the echocardiograms were collected prospectively to determine if there were findings of pathologic valvular regurgitation in the PANDAS subgroup, there was not a control group examined, and the echocardiograms were performed over a 9-year period from December 1993 to September 2002. Over the last decade, there have been marked technologic improvements in echocardiography machines, and Doppler sensitivity has improved significantly resulting in the visualization of trace amounts of mitral regurgitation in a larger number of normal, healthy subjects. At the time that most of these echocardiograms were performed, quantitative measurements such as regurgitant volume and regurgitant orifice area were not routinely performed, and the mitral regurgitation jets were not confirmed with continuous Doppler spectral analysis.

Several studies have attempted to distinguish

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**TABLE 2. GAS Association**

<table>
<thead>
<tr>
<th>Evidence of Infection</th>
<th>Timing</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive throat culture or Scarlet fever</td>
<td>During 2 mo preceding onset or exacerbation</td>
<td>41</td>
<td>68</td>
</tr>
<tr>
<td>Elevated antistreptococcal antibody titer</td>
<td>3 wk to 3 mo after onset or exacerbation</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>Pharyngitis, fever, tonsillar exudates, treated with antibiotics without culture</td>
<td>During 2 mo preceding onset or exacerbation</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

**TABLE 3. Baseline 2-Dimensional Echocardiographic Findings in PANDAS**

<table>
<thead>
<tr>
<th>Echocardiogram Parameter</th>
<th>Findings (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mitral valve</td>
<td></td>
</tr>
<tr>
<td>Normal leaflet morphology</td>
<td>59</td>
</tr>
<tr>
<td>Abnormal mitral valve thickening</td>
<td>1</td>
</tr>
<tr>
<td>Trace mitral valve regurgitation</td>
<td>32</td>
</tr>
<tr>
<td>Mild mitral valve regurgitation</td>
<td>1</td>
</tr>
<tr>
<td>2. Aortic valve</td>
<td></td>
</tr>
<tr>
<td>Normal leaflet morphology</td>
<td>60</td>
</tr>
<tr>
<td>Trace aortic valve regurgitation</td>
<td>1</td>
</tr>
<tr>
<td>3. Left atrial dimension/BSA</td>
<td>2.5 ± 0.6 cm² (normal 2.5 ± 0.3) *</td>
</tr>
<tr>
<td>4. Left ventricle end-diastolic dimension/BSA</td>
<td>3.7 ± 0.9 cm² (normal 3.9 ± 0.4) *</td>
</tr>
<tr>
<td>5. Left ventricle end-systolic dimension/BSA</td>
<td>2.4 ± 0.6 cm² (normal 2.5 ± 0.3) *</td>
</tr>
<tr>
<td>6. Fractional shortening</td>
<td>33 ± 5%</td>
</tr>
</tbody>
</table>

* Normal mean and SD are based on average body surface area (BSA) of 1.1 m².22
pathologic from physiologic valvular regurgitation in rheumatic fever patients and controls.\textsuperscript{12,17,20} Improvements in echocardiography over the last 2 decades have resulted in increased numbers of children found to have physiologic valvular regurgitation. This regurgitation is of a nonpathologic nature and has been observed in up to 45\% of healthy volunteers between ages 6 and 19 years.\textsuperscript{17} Consequently, the definitions of pathologic valvular regurgitation that were used in earlier studies would not be considered pathologic by today’s echocardiographers. Despite this, the current guidelines for grading severity of valvular lesions recommend evaluation of valvular morphology and cardiac chamber sizes in addition to the size of the color Doppler jet.\textsuperscript{21} Using these criteria, our study found that only 1 of 60 subjects had mild mitral regurgitation that would be considered physiologic by current standards, and 1 subject had abnormal leaflet pathology (thickened mitral leaflets) with only a trace amount of mitral regurgitation.

The lack of evidence of significant pathologic mitral valve regurgitation at baseline or in long-term follow-up in the PANDAS subgroup indicates that although these children may share a similar clinical course with SC patients, this most likely represents a poststreptococcal condition with a very low risk of significant early or late cardiac involvement.

\textbf{REFERENCES}

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