Identification of Children With Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections by a Marker Associated With Rheumatic Fever

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Objective: *The authors' goal was to determine whether a trait marker of rheumatic fever susceptibility (labeled D8/17) could identify children with pediatric autoimmune neuropsychiatric disorders (obsessive-compulsive disorder and tic disorders) associated with streptococcal infections (PANDAS).* *Method:* *Blood samples obtained from 27 children with PANDAS, nine children with Sydenham's chorea, and 24 healthy children were evaluated for D8/17 reactivity. Individuals were defined as D8/17 positive if they had 12% or more D8/17+ cells.* *Results:* *The frequency of D8/17-positive individuals was significantly higher in both patient groups than it was among the healthy volunteers: 85% of the children with PANDAS and 89% of the children with Sydenham's chorea, compared with 17% of the healthy children, were D8/17 positive. Further, the mean number of D8/17+ cells was similar in the two patient groups and was significantly higher in these groups than in the group of healthy children.* *Conclusions:* *These results suggest that there may be a subgroup of D8/17-positive children who present with clinical symptoms of obsessive-compulsive disorder and Tourette's syndrome, rather than Sydenham's chorea, but who have similar poststreptococcal autoimmunity.*
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Childhood-onset obsessive-compulsive disorder, once considered a psychological disorder or neurosis, is now known to be a neurobiological disorder with a variety of etiologic factors, including genetic susceptibility, neurophysiological aberrations, and regional brain dysfunction (1). Poststreptococcal autoimmunity has been postulated as another etiologic factor (2, 3). This hypothesis is supported by data from two parallel lines of research: studies of Sydenham's chorea (a variant of rheumatic fever characterized by neurological dysfunction) and investigations of childhood-onset obsessive-compulsive disorder and Tourette's syndrome (2–7). Results of these studies led to the identification of a subgroup of children with obsessive-compulsive disorder or Tourette's syndrome in whom symptom exacerbations were abrupt, dramatic, and temporally related to group A β-hemolytic streptococcal infections (4, 8). Further research has revealed a distinct subgroup of neuropsychiatrically ill children whose tics and obsessive-compulsive symptoms appear to arise in response to an exogenous pathogen (usually β-hemolytic streptococcal infections) and for whom targeted therapeutic and preventive strategies can be developed. This subgroup is designated by the acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections).

In this paper, we describe the association of a known marker for susceptibility to rheumatic fever with PANDAS. This marker is found on a subset of DR+ cells in the peripheral circulation (B cells are included in this group). The relative frequency of cells bearing this marker is an inherited characteristic. Susceptibility to rheumatic fever also appears to be genetically determined: familial rates of rheumatic fever are dramatically high, and large family studies have suggested

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TABLE 1. D8/17 Status in Children With Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS) or Sydenham's Chorea and Healthy Volunteers

	Percent D8/17+ Cells[a]				D8/17-Positive Individuals[b]		Odds Analysis	
Subjects	Mean	SD	Median	Range	N	%	Odds Ratio[c]	p
Children with PANDAS (N=27)	29	20	25	0–77	23	85	28.8	<0.0001
Children with Sydenham's chorea (N=9)	35	22	29	5–76	8	89	40.0	<0.0001
Healthy children (N=24)	8	9	5	0–34	4	17		

[a]Means were compared by analysis of variance and Duncan's multiple range post hoc test. PANDAS patients and patients with Sydenham's chorea differed significantly from the healthy children ($F=12.4$, $df=2, 57$, $p<0.001$).
[b]Individuals were defined as D8/17 positive if they had ≥12% D8/17+ cells.
[c]Odds ratios were calculated in comparison with healthy children.

either an autosomal recessive or autosomal dominant (with limited penetrance) pattern of inheritance (9, 10). Individuals at risk for the development of rheumatic fever can be identified on the basis of a DR+ cell surface marker recognized by a monoclonal antibody designated D8/17. This marker has been tested in a wide variety of study groups and has been found to be both highly specific (only 5%–15% of healthy volunteers are D8/17 positive) and highly sensitive in identifying individuals with rheumatic fever, 90%–100% of whom are D8/17 positive regardless of disease status (i.e., D8/17 appears to function as a trait marker) (11, 12).

METHOD

Twenty-seven children met the following diagnostic criteria and were included in the PANDAS group: 1) presence of obsessive-compulsive disorder (diagnosed according to DSM-III-R or DSM-IV) or tic disorder, 2) symptom onset between 3 years of age and puberty, 3) episodic course of symptom severity characterized by the abrupt onset of symptoms or frequent, dramatic symptom exacerbations, 4) symptom exacerbations associated with β-hemolytic streptococcal infection, and 5) presence of neurological abnormalities, such as motoric hyperactivity or adventitious movements, including choreiform movements or tics (note: choreiform movements are not chorea).

The eight girls and 19 boys in the PANDAS group had a mean age of 9.9 years (SD=2.3, range=5.3–14.6). Three children met diagnostic criteria for obsessive-compulsive disorder alone, five for obsessive-compulsive disorder and Tourette's syndrome, five for obsessive-compulsive disorder and tics, six for subclinical obsessive-compulsive disorder and Tourette's syndrome and tics, two for tics alone, and six for Tourette's syndrome alone. None of the children had ever had chorea, arthritis, carditis, or any other major criterion of rheumatic fever; therefore, there were no "missed" cases of Sydenham's chorea (13).

Nine children with Sydenham's chorea (five boys and four girls whose mean age was 9.8 years, SD=1.6) served as a positive comparison group (3, 4). All met the revised Jones criteria for rheumatic fever (13). Twenty-four healthy children (seven boys and 17 girls whose mean age was 10.3 years, SD=2.2) served as the negative comparison group. All subjects and their parents gave written informed assent and consent, respectively, for participation in this study.

The method of D8/17 staining and assessment has been described in detail elsewhere (11, 12). The ratio of DR+ cells to D8/17+ cells divided by the number of DR+ cells was multiplied by 100 to yield the percentage of D8/17+ cells. Individuals were defined as D8/17 positive if they had 12% or more D8/17+ cells and D8/17 negative if they had 10% or less D8/17+ cells. These cutoffs were established from previous work that has demonstrated a bimodal curve of distribution for this marker (10–12).

SAS was used for the statistical analysis, and comparisons among the PANDAS patients, the patients with Sydenham's chorea, and the healthy children were analyzed by using chi-square (odds ratio) with the dichotomous variable of D8/17 positive versus D8/17 negative. The percentages of D8/17+ cells in each group were compared by using analysis of variance and Duncan's multiple range post hoc test.

RESULTS

Twenty-three of the 27 PANDAS patients and eight of the nine patients with Sydenham's chorea were found to be D8/17 positive; in contrast, only four of the 24 healthy children were D8/17 positive (table 1). The frequency of D8/17 positive children among the healthy children was significantly smaller than the frequency among both patients with Sydenham's chorea ($\chi^2=14.7$, $df=1$, odds ratio=40, confidence interval=10–166, $p<0.0001$) and patients with PANDAS ($\chi^2=23.9$, $df=1$, odds ratio=29, confidence interval=9–95, $p<0.0001$) (table 1). The mean and median values of the percentages of D8/17+ cells by group are also given in table 1. The mean percentage of D8/17+ cells was significantly smaller in the group of healthy children than in the PANDAS group and in the Sydenham's chorea group (table 1). The patient groups did not differ significantly from one another in their mean values. Nonparametric analysis of these data provided the same results.

DISCUSSION

These data demonstrate that a trait marker associated with rheumatic fever can be used to identify children with PANDAS. The results raise questions about the nature of the relationship between PANDAS and Sydenham's chorea. Both disorders are triggered by β-hemolytic streptococcal infections, both have neuropsychiatric symptoms, and both have dramatically high rates of D8/17 positivity. However, the disorders are distinct and separable—it is clear that PANDAS does not merely represent "missed" cases of rheumatic fever (as Sydenham's chorea) because each of the children was carefully screened by a pediatrician and a pediatric neurologist and none of the major Jones criteria (including chorea) was found in the PANDAS patients.

Several factors could account for the differential response to β-hemolytic streptococcal infection seen in

PANDAS and Sydenham's chorea. These include differences in genetic vulnerability, neurodevelopmental maturation at the time of exposure, and the specificity of the host-microbe interaction. For example, in Sydenham's chorea, cross-reactive antibodies might recognize a different population of cells from those which cause obsessive-compulsive symptoms or tics (14, 15).

Although the findings of this study require amplification and replication, they raise intriguing possibilities. If the D8/17 marker is able to identify PANDAS-susceptible individuals, not only would it be the first such marker for a psychiatric disorder, but it would have both immediate and long-term benefits. In the short-term, it would improve research into the etiology and pathophysiology of obsessive-compulsive disorder and Tourette's syndrome by allowing us to define a more homogeneous subgroup of patients for study; it would provide patients and their families with more accurate descriptive and prognostic information; and it would promote the development of treatments designed to address the underlying pathophysiology of the disorder, rather than mere symptom palliation. Studies of the effectiveness of immunomodulatory therapies for reducing symptom relapses are underway for children who have already been identified as having PANDAS, and preliminary results are encouraging (8). The long-term benefit of an effective trait marker of PANDAS susceptibility would be the ability to screen at-risk individuals and prevent symptom onset. If the D8/17 marker proves reliable in identifying PANDAS-susceptible individuals, then it may be possible to provide prophylaxis to at-risk individuals and prevent the onset of some cases of obsessive-compulsive disorder and Tourette's syndrome. Such possibilities provide the impetus for further investigations.

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