Clinical Presentation of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections in Research and Community Settings

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Abstract

Background: The first cases of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) were described > 15 years ago. Since that time, the literature has been divided between studies that successfully demonstrate an etiologic relationship between Group A streptococcal (GAS) infections and childhood-onset obsessive-compulsive disorder (OCD), and those that fail to find an association. One possible explanation for the conflicting reports is that the diagnostic criteria proposed for PANDAS are not specific enough to describe a unique and homogeneous cohort of patients. To evaluate the validity of the PANDAS criteria, we compared clinical characteristics of PANDAS patients identified in two community practices with a sample of children meeting full research criteria for PANDAS.

Methods: A systematic review of clinical records was used to identify the presence or absence of selected symptoms in children evaluated for PANDAS by physicians in Hinsdale, Illinois ($n=52$) and Bethesda, Maryland ($n=40$). Results were compared against data from participants in National Institute of Mental Health (NIMH) research investigations of PANDAS ($n=48$).

Results: As described in the original PANDAS cohort, males outnumbered females (95:45) by $\sim 2:1$, and symptoms began in early childhood (7.3 ± 2.7 years). Clinical presentations were remarkably similar across sites, with all children reporting acute onset of OCD symptoms and multiple comorbidities, including separation anxiety (86–92%), school issues (75–81%), sleep disruptions (71%), tics (60–65%), urinary symptoms (42–81%), and others. Twenty of the community cases (22%) failed to meet PANDAS criteria because of an absence of documentation of GAS infections.

Conclusions: The diagnostic criteria for PANDAS can be used by clinicians to accurately identify patients with common clinical features and shared etiology of symptoms. Although difficulties in documenting an association between GAS infection and symptom onset/exacerbations may preclude a diagnosis of PANDAS in some children with acute-onset OCD, they do appear to meet criteria for pediatric acute-onset neuropsychiatric syndrome (PANS).

Introduction

THE FIRST 50 CASES OF pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) were described in 1998. (Swedo et al. 1998). The PANDAS subgroup was distinguished from other cases of childhood-onset obsessive-compulsive disorder (OCD) by five clinical criteria: Presence of OCD or tic disorder, prepubertal onset, acute symptom onset and episodic (relapsing-remitting) course, presence of associated neurological abnormalities (particularly choreiform move-

ments), and temporal association with Group A streptococcal (GAS) infection (Swedo et al. 1998, 2004). Early reports demonstrated that the unique clinical presentation of the PANDAS subgroup was useful in determining which children would benefit from treatment with antibiotics (Murphy and Pichichero 2002) or immunomodulatory therapies (Garvey et al. 1999; Perlmutter et al. 1999; Snider et al 2005), such as intravenous immunoglobulin (IVIG) and plasmapheresis (interventions that are not helpful for non-PANDAS tic disorders and OCD, respectively) (Hoekstra 2004; Nicolson et al. 2000). In addition, cross-reactive autoantibodies were

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found in sera of acutely ill PANDAS patients (Kirvan et al. 2006, 2007; Swedo 1994); these autoantibodies were not present in convalescent samples or in samples obtained from patients with non-PANDAS OCD or tic disorders (Singer et al. 2008).

Although the early literature provided strong support for the distinctive clinical and laboratory presentation of the PANDAS subgroup, a series of editorials labeled the diagnosis “controversial” and questioned the nature, postulated etiology, and even the existence of PANDAS (Kurlan 1998; Kurlan and Kaplan 2004; Gilbert and Kurlan 2009; Singer et al. 2012). Particular criticism was leveled against the requirement that symptoms have an acute onset/episodic course and be temporally related to GAS infections, as these were reported to be difficult to operationalize in community settings (Gabbay et al. 2008). However, investigators who systematically applied the PANDAS criteria have reported samples of patients with remarkable similarity to the initial cohort (e.g., Murphy et al. 2012). To determine if the criteria could be successfully applied in clinical settings, we compared characteristics of patients evaluated by two pediatric practitioners (M.E.L., M.K.) with those of children meeting full research criteria for PANDAS (National Institute of Mental Health [NIMH]). We hypothesized that the clinical characteristics of the three patient samples would be comparable, and, therefore, that the PANDAS diagnostic criteria defined a clinically distinct patient group.

Methods

A systematic records review was conducted at each of the sites (NIMH, Hinsdale, and Bethesda). Data were culled from all available sources, including documentation of phone conversations, emails, and physician notes, as well as clinical and research records. In addition to evaluating clinical presentations and documenting evidence that cases met criteria for PANDAS, we also

examined whether cases met criteria for pediatric acute-onset neuropsychiatric syndrome (PANS) (Swedo et al. 2012). NIMH records were reviewed by a child psychiatrist (R.H., P.G.), who also accessed the research databases for archived information. Hinsdale and Bethesda records were reviewed by a bachelor’s level research assistant with oversight from the attending clinicians (M.E.L., M.K.). All of the outside information was de-identified prior to analysis at NIMH.

The cases presented here include 48 participants in clinical investigations at NIMH, and 92 children receiving clinical evaluations and treatment in the community. The community cases were evaluated by a pediatric neurologist (M.E.L.) in Bethesda ($n=40$), or a pediatrician (M.K.) in Hinsdale ($n=52$). Both community physicians have extensive experience in the diagnosis and treatment of PANDAS, and children were referred to these clinics specifically for evaluation of symptoms consistent with a PANDAS diagnosis.

The NIMH sample included children evaluated for participation in a study ($n=42$) of IVIG for the treatment of PANDAS (Protocol 11-M-0058; NCT 01281969) or a natural history investigation ($n=6$) of childhood neuropsychiatric disorders (Protocol 13-M-0028; NCT 01778504). Both studies were approved by the Central Nervous System Institutional Review Board (CNS IRB) at the National Institutes of Health. Parents provided informed consent and children assented for participation. More than 200 potential subjects were screened for participation through telephone interviews with parents and referring clinicians and review of comprehensive medical records, and 58 were evaluated in person. Of these, two children refused study participation (prohibiting collection of necessary clinical information) and eight did not meet criteria for inclusion in the PANDAS research cohort: Three did not have acute symptom onset, two did not have a primary diagnosis of OCD/tics (one had generalized anxiety disorder, one had

TABLE 1. PANDAS CRITERIA BY SITE

	NIMH (n=48)		Hinsdale (n=52)		Bethesda (n=40)	
	Mean	SD	Mean	SD	Mean	SD
1. Prepubertal symptom onset						
Age at PANDAS first episode	8.22	2.39	6.66	2.62	6.98	3.09
Age at site evaluation	8.58	2.38	9.19	2.96	8.48	2.43
	#	%	#	%	#	%
Males	29	60%	37	71%	29	73%
Females	19	40%	15	29%	11	27%
2. Presence of OCD and/or a tic disorder	48	100%	52	100%	40	100%
3. Acute symptom onset and episodic (relapsing-remitting) course						
Acute symptom onset	48	100%	52	100%	40	100%
4. Association with neurological abnormalities	48	100%	52	100%	40	100%
5. Temporal association between GABHS infection and symptom onset/exacerbations						
Documented evidence of exposure	48	100%	42	81%	30	76%
a. Positive GAS culture	20	42%	6	12%	7	18%
b. High ASO and/or DNase-B titer	22	46%	28	54%	16	40%
c. Other evidence of exposure	6	12%	8	15%	7	18%
No evidence of GABHS	-	-	4	8%	5	12%
Data not found in chart	-	-	6	11%	5	12%

PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; NIMH, National Institute of Mental Health; OCD, obsessive-compulsive disorder; GABHS, Group A beta-hemolytic streptococcus; GAS, Group A streptococcus; ASO, antistreptolysin O; DNase-B, deoxyribonuclease-B.

TABLE 2. COMORBID SYMPTOMATOLOGY

	<i>NIMH</i> (n=48)		<i>Hinsdale</i> (n=42)		<i>Bethesda</i> (n=30)	
	#	%	#	%	#	%
1. Anxiety	44	92%	40	95%	22	73%
2. Emotional lability and/or depression	45	94%	28	66%	21	70%
3. Irritability, aggression, and/or severely oppositional behaviors	18	38%	11	26%	15	50%
4. Behavioral (developmental) regression	30	63%	29	69%	18	60%
5. Deterioration in school performance	36	75%	37	88%	24	80%
6. Sensory or motor abnormalities	37	77%	40	95%	29	97%
7. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency	43	90%	41	98%	25	83%
Average number of categories present per patient	5.65		4.86		4.97	

NIMH, National Institute of Mental Health.

psychosis), and three had no evidence of streptococcus infection or exposure prior to symptom onset (but would have met criteria for PANS). Therefore, 48 children were included in the NIMH PANDAS sample.

Chi square analyses (Yates) were conducted to assess for significant differences between the community and research samples.

Results

Table 1 shows the PANDAS criteria by site. All subjects in Bethesda, Hinsdale, and at NIMH met at least four of the five PANDAS criteria: Presence of OCD and/or tics, pre-pubertal onset, acute onset and episodic course, and presence of motor abnormalities (Swedo et al. 1998). All 48 patients in the NIMH research group showed evidence of a GAS infection or exposure within 3 months prior to the onset of symptoms. In Bethesda, 5 of the 40

records showed no evidence of preceding GAS infection, and the information was incomplete in another 5, leaving 30 patients (75%) who met all five PANDAS criteria in Bethesda. Ten potential subjects similarly were excluded in the Hinsdale practice (4 had no documented GAS infections, and 6 were missing key clinical data); therefore, 42 patients (82%) fully met PANDAS criteria in Hinsdale.

Although the medical records did not contain sufficient information to determine if the PANDAS diagnosis was based on a primary tic disorder or primary OCD, it was clear that all of the children had a history of abrupt onset of obsessions and/or compulsions accompanied by a variety of comorbid neuropsychiatric symptoms. As shown in Table 2, on average, children had comorbid symptoms in five different domains, indicating that they would easily meet the PANS requirement for co-occurring symptoms in at least 2 of 7 domains (Swedo et al. 2012).

TABLE 3. COMPARISON OF CLINICAL CHARACTERISTICS OF PANDAS PATIENTS IN COMMUNITY AND RESEARCH SETTINGS

	<i>NIMH</i> (n=48)		<i>Community</i> (n=72)		χ^2
	#	%	#	%	
Separation anxiety	44	92%	62	86%	NS
Behavioral regression (tantrum, baby talk)	30	63%	47	65%	NS
OCD symptoms	48	100%	72	100%	NS
Intrusive thoughts	19	40%	53	74%	NS
Phobias/contamination fears	40	83%	40	56%	NS
Unfounded fears	24	50%	48	67%	NS
Repetitive behaviors	36	75%	39	54%	NS
Aggressiveness	20	42%	26	36%	NS
Hyperactivity or inattentiveness	44	92%	34	47%	4.5 ($p=0.03$)
Violent images or hallucinations	13	27%	10	14%	NS
Dysgraphia	21	44%	46	64%	NS
Mydriasis	16	33%	45	63%	NS
Tics	32	67%	43	60%	NS
Urinary symptoms	25	52%	58	81%	NS
Frequency and/or urgency	14	29%	40	56%	NS
Daytime or night-time enuresis	9	19%	33	46%	NS
Increased sensory sensitivity	21	44%	31	43%	NS
School issues	39	81%	54	75%	NS
Inability to concentrate	38	79%	47	65%	NS
Trouble in math	16	33%	30	42%	NS
Sleep problems	34	71%	51	71%	NS
Restricted food intake	23	48%	17	24%	NS

PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; NIMH, National Institute of Mental Health; OCD, obsessive-compulsive disorder.

Comparisons of the community cases meeting PANDAS criteria ($n=72$) with the NIMH PANDAS research subjects ($n=48$) revealed similarities in demographics including: Sex distribution (approximately two boys: one girl), age of first PANDAS episode (7.6 ± 2.7 ; range, 1–14), and age at first evaluation (8.9 ± 2.6 ; range, 3–17). These results were also comparable to those reported in the first cohort of PANDAS patients (Swedo et al. 1998). Further, the frequency of co-occurring symptoms was strikingly similar across samples, as is shown in Table 3. Differences were noted for only 1 of the 14 symptom categories, hyperactivity/inattentiveness. Separation anxiety was the most common comorbid symptom in both the NIMH and community samples (92% and 86%, respectively), followed closely by school issues (81% and 75%), and sleep problems (71% for both). It is also noteworthy that restricted food intake was observed in nearly one half of the NIMH sample and one quarter of the patients evaluated by the community clinicians. Further, as noted, all patients had sufficient comorbidity to fulfill the PANS diagnostic criteria.

Discussion

This report summarizes the clinical characteristics of three groups of children evaluated and treated for PANDAS. The samples included 92 patients in two community practices (a pediatrician's and a pediatric neurologist's) and 48 children participating in research studies at the NIMH. The mean duration of illness at NIMH was only 6 months, whereas that of the community samples was >2 years. Further, and not unexpectedly, diagnostic and data collection procedures at NIMH were quite different from those employed in Bethesda or Hinsdale. Despite these differences, the community and research samples had remarkably similar clinical presentations, with differences noted only in the frequency of co-occurring hyperactivity/inattentiveness. The lower rate recorded for the community sample may reflect the methodologic limitations of this retrospective chart review, as motoric hyperactivity appeared to have been included in the "associated neurologic symptoms" required for the PANDAS diagnosis. Similarly, it was not possible to separate cases with primary OCD from those with a primary tic disorder because the PANDAS criteria require only one of the disorders. Our study was further limited by lack of documentation of GAS infections in 22% of the community cohort. Often, this was because a history of exposure and/or throat culture had not been obtained by the child's primary healthcare provider. These omissions are particularly concerning in light of a report from Murphy and Pichichero (2002) documenting that OCD symptoms completely abated in 8 of 12 PANDAS children who received antibiotics within a few days of symptom onset.

The results of this study confirm the utility of the PANDAS diagnostic criteria in identifying a unique, clinically homogeneous group of patients (Swedo et al. 1998). The distinctive clinical presentations described in this report are not only similar to those described in the initial PANDAS cohort (Swedo et al. 1998), but also are comparable to more recent samples acquired in research settings (e.g., Murphy et al. 2012). Acuity of onset appears to be particularly important in the diagnosis of PANDAS, as demonstrated by a comparison of cases diagnosed in community and research settings (Gabbay et al. 2008) and by investigations that fail to find clinical and laboratory differences between PANDAS and non-PANDAS cases when PANDAS is defined by an "episodic course," rather than "an acute onset and relapsing-remitting symptom course" (e.g., Singer et al 2008; Leckman et al. 2011). The importance of acute symptom onset is further highlighted by its

prominence in the nomenclature and diagnostic criteria of PANS, which requires that OCD (or eating restrictions) and comorbid symptoms reach peak severity within 24–48 hours of onset. PANS is conceptualized as an "umbrella" diagnosis that includes not only PANDAS and other infection-triggered cases (Allen et al. 1995), but also those without infectious precipitants (Swedo et al. 2012). The relative distribution of these various subgroups is presently unknown, and can be determined only with prospectively collected information about premorbid infections and exposures. It is interesting that $>80\%$ of our cases who met PANS criteria also had evidence of a "temporal association between GAS infection and symptom onset/exacerbation." Therefore, in this case series, four of five children with PANS also met diagnostic criteria for PANDAS.

The comparability of clinical presentations across community and research settings confirms the utility of the PANDAS criteria in defining a unique, clinically distinctive patient group. The results also highlight the importance of assessing acuity of symptom onset in both PANDAS and PANS. Establishing a more clearly delineated and universally available framework for evaluating children with acute-onset neuropsychiatric symptoms is an important next step in confirming these findings and informing future research.

Disclosures

No competing financial interests exist. Drs. Swedo, Hommer, and Grant and Mr. Seidlitz and Ms. Lougee are employees of the Intramural Research Program of the National Institute of Mental Health (NIMH).

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