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Journal of Psychosomatic Research 55 (2003) 31–39

Journal of Psychosomatic Research

PANDAS
A commentary

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Received 19 December 2001; accepted 17 September 2002

Abstract

PANDAS is an acronym for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection. As defined, the criteria include prepubertal children with either a tic or obsessive-compulsive disorder in whom a Group A β-hemolytic streptococcal infection (GABHS) triggers the abrupt onset or exacerbation of tics/obsessive-compulsive behaviors. Pathophysiologically, it is proposed that antibodies produced against GABHS cross-react with neuronal cells, in a process involving molecular mimicry. Although PANDAS has received widespread notoriety, the existence of this condition has been questioned. This commentary reviews clinical and laboratory issues pertinent to the diagnosis of this entity. We conclude that PANDAS is an intriguing hypothesis that requires further confirmation.

Keywords: Autoimmunity; Neuropsychiatric disorders; OCD; PANDAS; Streptococcal infection; Tics

The word PANDAS typically evokes visions of large, black and white bear-like animals eating bamboo shoots. In medicine, however, the term has been applied to pediatric patients believed to have a poststreptococcal disorder characterized by the presence of neurobehavioral symptoms that include tic disorders and obsessive-compulsive disorder (OCD). More formally, PANDAS represents an acronym for *P*ediatric *A*utoimmune *N*europsychiatric *D*isorders *A*ssociated with *S*treptococcal infection. First formally proposed in 1998 [1], this entity has received widespread notoriety in both scientific and lay publications. This, in turn, has led to frequent calls to physicians from concerned parents seeking a simple explanation for their child's complex behaviors or requesting therapy with prophylactic penicillin and/or immunotherapy. But does PANDAS even exist?

Advocates for the PANDAS disorder emphasize its clinical and laboratory similarities to Sydenham's chorea (SC), a manifestation of rheumatic fever (RF) [2]. In contrast, those who question the existence of this condition cite concerns with its diagnostic criteria and the lack of evidence confirming an association between group A β-hemolytic streptococcal (GABHS) infection and tics/OCD [3]. Other investigators have attempted to validate this disorder through studies of antineuronal antibodies [4]. Clearly, if confirmed, the concept of a postinfectious autoimmune tic disorder would have broad neurobiologic implications and raise issues of prevention and the use of treatments not typically considered in cases of Tourette syndrome (TS).

While we await the results of future research, it is important to understand and critically evaluate the available clinical and laboratory information pertinent to PANDAS. In discussions of this entity, the reader should be aware that: (a) investigators have frequently linked three potentially separate disorders, SC, TS, chronic tic disorder, and PANDAS; and (b) there is an expanding list of proposed post-streptococcal autoimmune disorders, including paroxysmal dyskinesias [5], acute disseminated encephalomyelitis [6], dystonia [7], myoclonus [8], and anorexia nervosa [9]. Although some overlaps may exist between TS and PANDAS, the authors believe it is essential that each of these entities be characterized by its own specific criteria. Blurred distinctions should not be

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doi:10.1016/S0022-3999(02)00582-2

permitted. For example, findings in unselected cases of TS have often been used as supporting evidence for the concept of PANDAS. We have organized this manuscript to provide a brief description of each of these three major diagnoses and a review of the clinical and investigative evidence that both support and challenge the diagnosis of PANDAS. In brief, we conclude that PANDAS is an intriguing hypothesis that requires further confirmation.

Sydenham's chorea

SC is considered the prototype for an infectious agent (i.e., GABHS) triggering an autoimmune disorder that, in turn, causes a variety of neuropsychiatric symptoms. SC has a clearly defined association with RF [10] and with a preceding GABHS infection [11]. The distinguishing clinical feature of this disorder is the presence of chorea that typically involves the face and extremities. Motor and vocal tics have been reported in patients with SC [12,13]. Affected individuals may present with behavioral or emotional difficulties that predate the motor abnormalities by weeks to months and there is an increased incidence of obsessive compulsive symptoms [2,14]. Carditis is reported in 30–60%, with higher percentages in subjects evaluated by echocardiograms. Onset is usually between the ages of 5–15 years, a female predominance has been observed in all large studies, and the diagnosis is made strictly by clinical observation. No confirmatory test is available, but elevated antistreptococcal titers are demonstrated in about 80% of patients. Most symptoms resolve in 1–6 months although mild to moderate chorea may persist [12]. About 20–60% of cases have recurrent episodes of chorea, usually within 1–2 years after the original event.

D8/17 is a monoclonal antibody, directed against a polymorphic protein on the surface of B lymphocytes. This marker has been found to have an expanded expression in individuals with RF or rheumatic heart disease as compared to controls [15]. Although its precise role is unknown, D8/17 was originally considered a putative susceptibility marker for RF [16].

An autoimmune process has been confirmed in RF based on the identification of antimyocardial antibodies that cross-react with streptococcal antigens [17]. In SC, it is hypothesized that antibodies against GABHS also cross-react against CNS neurons through the process molecular mimicry. The concept of autoimmunity is supported by several studies. Husby et al. [18], the first to describe antineuronal antibodies in SC, used an immunofluorescent antibody staining technique to show specific cross-reactivity of IgG to neuronal cytoplasmic antigens in human caudate and subthalamic nuclei in 47% (14/30) of acutely ill SC patients as compared to 14% (7/50) with rheumatic carditis, 0% in child controls (0/24) and 3.2% (1/31) in adult controls. Subsequent studies have provided confirmatory data using similar techniques [2,19], direct immunofluorescence on unfixed frozen sections from rat striatum [20], and enzyme-linked immunosorbent assays (ELISA) on human postmortem basal ganglia [21]. Additional support for the hypothesis of molecular mimicry comes from the finding that antibodies to streptococcal M protein can cross-react with human brain tissue [22]. Despite the seemingly strong supportive evidence for autoimmunity in SC, the reader should recognize that levels of autoantibodies against brain are present in healthy subjects [2,20,23,24] and that the presence of an antibody does not necessarily imply a functional effect.

Tourette syndrome

The Gilles de la Tourette syndrome is characterized clinically by the presence of involuntary chronic motor and vocal tics that wax and wane [25]. Tics are exacerbated by stress, anxiety, and fatigue and may improve during activities that require concentration. In addition, individuals have a variety of comorbid neurobehavioral problems including OCD, attention-deficit hyperactivity disorder, anxiety, mood disorders, and episodic behavior disorder. TS typically begins in childhood, usually between ages 6–7 years. Although TS was originally proposed to be a lifelong disorder, its course may be quite variable, and some patients may have a spontaneous remission or marked improvement independent of the use of tic-suppressing medications [26,27]. The reported prevalence of TS is now estimated at about 3% of school-aged children [28,29].

Although the precise pattern of transmission and identification of the gene remains elusive, most experts concur that TS is an inherited disorder. For example, studies of monozygotic twins show an 86% concordance rate for chronic tic disorders compared with a rate of 20% in dizygotic twins [30,31]. Additional evaluation of twins, however, illustrates that genotype does not predict phenotype; monozygotic twins show great variability in the frequency and severity of tic symptoms. Other studies have further supported the concept that factors such as genetic heterogeneity, epigenetic factors, and gene-environment interactions play an important role in determining tic severity in TS [32,33]. The expanding list of proposed environmental factors that may alter the presentation or exacerbation of tics includes low birth weight, nonspecific maternal emotional stress, severity of maternal nausea and vomiting during pregnancy, pre- or postnatal exposure to drugs or toxins, hyperthermia, allergens, and infections [34]. The recognition that infection, fever, and medications can exacerbate tics has important implications for establishing strict definitional criteria for PANDAS. More specifically, we contend that, until other clinical or laboratory markers are available to distinguish tic disorders from PANDAS, the presence of tics before any infection-related exacerbation should exclude the diagnosis of a primary post-infectious etiology, i.e., PANDAS.

GABHS infection as a primary trigger for tics: PANDAS

A hypothesized role for infections, especially streptococcal infections, as the primary etiology for tics is not new. Several early case reports described children with tic disorders and associated acute sinusitis [35,36]. Kondo et al. [37] reported on an 11-year-old who, 10 days after a streptococcal infection, developed tics that responded to prednisolone but not neuroleptics. Two similar cases, with tic onset associated with GABHS infection and tic suppression requiring ACTH and prednisone, were reported by Matarazzo [38]. In one case, tics recurred in association with other bacterial infections and required repeated courses of corticosteroids. Kiessling [39], in an outpatient clinic setting, identified current or recent GABHS infections in 8 out of 14 children with initial or recurrent tics. Proposals of relationships between tics and infectious agents are not limited to GABHS. Typical symptoms of TS have also been reported in isolated cases following acute infections with *Streptococcus pyogenes*, *Lyme borreliosis*, and *Mycoplasma pneumoniae* [40–42].

In 1998, Swedo et al. [1] proposed that SC was not the only immune-mediated CNS manifestation of GABHS and described their diagnostic criteria for PANDAS, a subset of patient with tic disorders and OCD. More specifically, they suggested that a systematic clinical evaluation of children with OCD and tic disorders, including TS, would define a homogeneous subgroup. Hence, based on 50 cases recruited from a nationwide search, they established the working criteria shown in Table 1.

The majority of children with PANDAS had normal premorbid personalities, with few signs of hidden dysfunction. Symptom onset was acute and dramatic and often occurred at an early age, tics 6.3 + 2.7 years, OCD 7.4 + 2.7 years (mean ± S.D.). Patients often presented with severe tics involving the head, limb, or whole body without a prior history of more typical eye blinking or facial movements [43]. The disorder has a relapsing-remitting pattern with dramatic and acute symptom exacerbations interspersed with periods of relative quiescence. Psychiatric comorbidity, including emotional lability, separation anxiety, night-time fears, cognitive deficits, oppositional behaviors, and motor hyperactivity, is common. Comorbid symptoms, especially ADHD, also worsened after the GABHS infection, but this was not assessed systematically. Boys outnumbered girls by a ratio of 2.6:1. Of the 50 patients, only a maximum of 72% had their symptom onset documented to be associated with a GABHS infection (42% had a definite infection, 28% had a history of pharyngitis, and 2% had only GABHS exposure). In all subjects, however, recurrence of at least one symptom was preceded by a documented GABHS infection within the prior 6 weeks. In some patients who had multiple recurrences of symptoms, exacerbations occurred without any sign of a streptococcal infection in the preceding month.

Table 1
Clinical diagnostic criteria for PANDAS

1. Presence of OCD or a tic disorder.
2. Onset between age 3 years and the beginning of puberty.
3. Abrupt onset of symptoms or a course characterized by dramatic exacerbations of symptoms.
4. The onset or the exacerbations of symptoms is temporally related to infection with Group A β hemolytic streptococcus.
5. Abnormal results of neurologic examination (hyperactivity, choreiform movements, tics) during an exacerbation.

Murphy and Pichichero [44] have published on a cohort of 12 school-aged children with PANDAS. Each patient had an abrupt onset of primarily OCD (two had recurrent tics). Ten of 12 patients had an association with acute GABHS tonsillopharyngitis within 1 month prior to presentation. In those children effectively treated with antibiotics at the sentinel episode, OCD symptoms promptly disappeared. Six of 12 patients had at least 1 distinct recurrence of OCD. In every instance, the recurrence of PANDAS behavior was associated with a GABHS infection.

Critical elements of the PANDAS hypothesis

GABHS infection + host factors

→ antineuronal antibodies → tics/OCD

The above formula provides the components essential for understanding/confirming the PANDAS proposal. As hypothesized, in the presence of a host-derived factor conveying susceptibility, a streptococcal infection triggers the appearance or exacerbation of tics. Other neurobehavioral problems, such as OCD [44,45], myoclonus [8], and anorexia nervosa [46], may also occur but will not be emphasized in this review. Thus, for clinical confirmation, epidemiologic studies must identify a clear association between streptococcal infection and tics. This may be difficult, since both streptococcal infections and tic disorders are common in pediatric populations. For example, in the winter months, the majority of school children in some parts of the country have evidence of streptococcal infection [47] and the estimated prevalence of childhood tics in a classroom setting may be as high as 19% [28]. Secondly, the pathophysiologic hypothesis should be confirmed, i.e., caused by antibodies produced against GABHS cross-reacting with neuronal tissue in specific brain regions.

Evidence supporting PANDAS

A major strength of the PANDAS proposal is its similarity to the widely accepted model of SC. In the latter, 3–5 months after a GABHS infection, children develop movement disorders (chorea, and in a few cases even tics) and psychological problems (personality changes, OCD, emotional lability). In most cases of SC, movement abnormalities resolve in 1–6 months, but some may recur in association with either a repeat GABHS infection or other

environmental precipitants. MRI and functional imaging studies in SC have localized acute changes to the basal ganglia. In an MRI study evaluating the size of the basal ganglia in 24 patients with SC and 48 matched controls, children with SC had a 10% increase in size of the caudate and a 7% increase in size of both putamen and globus pallidus [48]. Similar volumetric analyses in 34 children with PANDAS showed that the average size of the caudate, putamen, and globus pallidus, but not thalamus or total cerebrum, was significantly greater in the affected group than in 82 healthy children [49].

Since many children get GABHS infections without developing PANDAS, a genetic vulnerability or susceptibility has been proposed. Again drawing on the SC model, the search for the trait marker for susceptibility has included assessment of the monoclonal antibody D8/17. This antibody, which is directed against B lymphocytes, has been found to have an expanded expression in individuals with SC (89%) compared with expression in healthy children (17%). Preliminary studies of the D8/17 antibody in individuals with PANDAS have also shown a similar high positivity rate: 85% of children with PANDAS compared with 17% of healthy children [50]. The exact significance of these finding and how this marker is related to the disease process is unknown, especially since it has been reported in patients with other neuropsychiatric disorders of childhood onset, including autism, who have not been diagnosed with RF or SC [51,52].

Challenges for PANDAS

The existence of PANDAS is not free of controversy [3]. A variety of diagnostic shortcomings have been identified, as has the lack of other classical features often associated with RF. Despite these limitations, a major deficiency is the absence of a prospective epidemiologic study confirming that an antecedent GABHS infection is associated with either the onset or exacerbation of tic disorders (or OCD). Two NIH-funded multicenter studies, designed to address these critical issues, are currently in progress.

Diagnostic concerns

The first criterion for PANDAS is the presence of a tic disorder and/or OCD as defined by the Diagnostic and Statistical Manual IV (DSM IV). Thus, for most cases with PANDAS, the actual onset of tics or OC symptoms is not temporally related to a definite GABHS infection. Hence, other etiologies for these individuals' primary initial symptoms must be defined, e.g., genetic or missed preceding infection. Concern has also been raised about lumping two distinctly different disorders together as the first criterion, i.e., the presence of a tic disorder and/or OCD [53]. For example, only a subgroup of pediatric OCD is etiologically linked to tic disorders [54]. Although not widely accepted, the author's of this manuscript further favor the concept that a preexisting diagnosis of a tic disorder, be it transient tics or classical TS, before an "explosive exacerbation" should exclude the diagnosis of PANDAS.

PANDAS is defined as a prepubertal disorder (criterion 2), but age does little to separate "typical tic disorders" from the PANDAS subgroup; in both groups, tics typically have their onset prior to the teenage years. Further confounding the issue of time of onset is the report of a 25-year-old with the sudden onset of OCD after a severe antibiotic-resistant pharyngitis [55]. If confirmed, this case raises concerns about the rigidity of an age criterion.

Criterion 3 for PANDAS requires the "sudden, explosive onset/worsening" of tics. The obvious concern with this criterion is the insufficiently operationalized definition and the phenotypic variability commonly associated with tic disorders. Tics have a waxing and waning course, may improve over time, and can be exacerbated by external factors (stress, anxiety, and fatigue), the presence of infection, temperature elevation, or the use of other medications [26,56,57]. Although patients with tic disorders generally have a slow, more gradually evolving pattern of tics, abrupt changes are not uncommon. In a study of 80 consecutive unselected children with tic disorders, a structured clinical interview found that 42 of 80 (53%) had the sudden explosive onset or worsening of their tic symptoms [56]. This same study also raised the issue of parent bias being a confounding factor; 78% of informants who described an offspring with abrupt onset of tics induced by a streptococcal infection were knowledgeable about PANDAS, compared with only 21% in the group that denied any association.

Confirmation of a temporal association between tic onset and a GABHS infection is essential for the definition of PANDAS (criterion 4). This may be more difficult to confirm than originally proposed given that both conditions are common and the latent period before initial onset is ill-defined. In RF, a strong association with GABHS is supported by epidemiologic studies [58–60] and by successful prevention with penicillin [61,62]. Nevertheless, a preceding pharyngitis was only remembered in about one-half of the cases and no initial illness was noted in up to one-third of cases [63]. In SC, the frequently cited model for PANDAS, chorea typically appears 3–5 months after the streptococcal infection, at a time when microbiologic and serologic evidence of a streptococcal infection are often absent. Thus by analogy, it may be possible to have the abrupt onset of tics in PANDAS without clear confirmation of infection. Furthermore, in the original criteria, Swedo and colleagues implied that an infection up to 9 months before symptom onset might be acceptable. Nevertheless, the NIMH Diagnostic Schedule suggests that an infection should occur within 4 weeks of onset.

In contrast to the potential difficulty associating a GABHS infection and the initial onset of symptoms, all reported individuals with PANDAS had at least one exacerbation temporally associated (4–6 weeks) with GABHS [1]. Perhaps, less emphasis should be placed on the first event and investigators should seek a general

consensus to establish a defined number of exacerbations required for diagnosis. It should also be established whether it is acceptable to diagnose a GABHS infection after the exacerbation of tic symptoms. Additional difficulties in confirming a temporal association with a GABHS infection include a positive throat culture in an asymptomatic carrier and the misinterpretation of a single ASO or antiDNAse-B determination. Too often, clinicians fail to recall the warning of Swedo et al. [1] that "positive antistreptococcal titers obtained at the time of a single exacerbation are not sufficient to prove that a child has PANDAS." Longitudinal laboratory data, rather than just an isolated throat culture or antistreptococcal antibody titer, are necessary to demonstrate that a GABHS infection is associated with PANDAS, i.e., rising titers with symptom exacerbation and falling titers with symptom remission.

The fifth criterion requires the presence of neurologic abnormalities, including tics, hyperactivity, or choreiform movements, during exacerbations. The lack of a clear definition separating chorea-like movements from true chorea is potentially confusing. No individual in the original PANDAS cohort had "overt chorea," but many had varying degrees of "choreiform" movements. This confusion in terminology has led several authors to suggest that some of the original cases of PANDAS may actually have had SC [3].

Differences from RF

As described, PANDAS is claimed to be similar to RF. If true, by strict definition, one might expect to find an increased rate of RF in the relatives of probands with PANDAS, as well as clinical symptoms in affected individuals that include manifestations of carditis, migratory polyarthritis, erythema marginatum, and subcutaneous nodules. Although children were excluded from the diagnosis of PANDAS if they had a history of SC, RF, or other autoimmune disease [1], we are unaware of any case that has subsequently developed rheumatic symptoms. One proposed explanation is that PANDAS may represent a condition similar to poststreptococcal reactive arthritis, i.e., a disorder with only a single manifestation of RF [64,65].

Confirmation of host susceptibility

As previously mentioned, high levels of D8/17 expression, assessed by a somewhat subjective method, have been reported in patients with PANDAS [50]. In studies of D8/17, measured by a more objective flow cytometry method, in patients with tic disorders, overexpression was reported, but about 40% had levels of expression within the range of healthy controls [66]. In any event, D8/17 is not diagnostic for PANDAS and remains a research tool. The search for genetic vulnerability has been further investigated by the historical assessment of families with PANDAS. In a study of first degree relatives of children with PANDAS, the rates of tic disorders and OCD were higher than those in the general population, but similar to those published for tic disorders and OCD [67]. Although Lougee and colleagues suggest that this supports the hypothesis of an environmental trigger in a genetically vulnerable population, they also note the possibility that the proband was destined to develop tics even without any preceding infection.

Other challenges

Several clinical studies are occasionally cited as supporting evidence for PANDAS, but the data actually have little relevance. For example, based on the postulated role of GABHS in the pathogenesis of PANDAS, researchers have sought to identify whether individuals with a tic disorder have increased levels of streptococcal antibodies. In two separate studies, TS subjects were shown to have higher ASO and antiDNAse-B titers than age-matched controls [68,69]. In each study, however, there was no correlation between levels of antistreptococcal titers and clinical symptoms. In two opposing studies [70,71], no association was detected between streptococcal markers and tics; rather, one study suggested that ASO and antiDNAse-B titers correlated with the presence of ADHD [70]. Again, since all of these studies were performed on only a single-point-in-time serum sample and in subjects with tics unrelated to an infection, their direct relevance to PANDAS is unclear. An additional demand for the confirmation of PANDAS is showing that the prevention of GABHS infection reduces the appearance or recurrence of tics. In a double-blind, placebo-controlled cross-over trial with oral penicillin (250 mg penicillin V) undertaken to prevent recurrences of PANDAS, no significant change in either obsessive compulsive or tic symptom severity occurred between the active and placebo arms [72]. Unfortunately, since an acceptable level of streptococcal prophylaxis was not achieved, no firm conclusions were possible.

Evidence for an immune-mediated mechanism in PANDAS

Pathophysiologically, based on a SC model, an immune-mediated mechanism involving molecular mimicry has been proposed for PANDAS. It is suggested that antibodies produced against GABHS cross-react with neuronal tissue in specific brain regions. Three different approaches have been used in attempts to confirm an autoimmune mechanism: immunomodulatory therapy, quantification of serum antineuronal antibodies, and determination of the functional effect of serum infusions into rodent striatum.

Immunomodulatory therapy

Indirect support for an immune hypothesis is derived from a single study examining the response of a small number of patients with PANDAS to two forms of immunotherapy: intravenous immunoglobulin (IVIG) and plasmapheresis (PEX) [73]. Twenty-nine children with PANDAS recruited from a nationwide search were randomized in a partially

double-blind fashion (no sham apheresis) to an IVIG, IVIG placebo (saline), and PEX group. One month after treatment, the severity of obsessive-compulsive symptoms were improved by 58% and 45% in the PEX and IVIG groups, respectively, compared with only 3% in the IVIG control. In contrast, tic scores were significantly improved only after PEX treatment, reductions of 49% (PEX), 19% (IVIG), and 12% (IVIG placebo). Improvements in both tics and obsessive-compulsive behaviors were sustained for 1 year. In a commentary that accompanied the manuscript [74], several methodologic concerns were raised, including the highly selective recruitment process, the small number of subjects, the lack of tic severity matching within treatment groups, limited comparisons with controls, continued use of psychotropic medications, reduced beneficial response to PEX in individuals initially treated with sham IVIG, and side effects that occurred in about two thirds of individuals receiving active therapy. Additionally, several biological questions remained unanswered including: an inconsistency between therapeutic response and rate of antibody removal, the effect of peripheral changes on events across the blood–brain barrier, and the mechanism by which immune therapy produces its beneficial response. Consequently, the NIH has recommended that immunotherapy be reserved for patients participating in controlled double-blind protocols.

Measurement of antineuronal antibodies

Studies of antineuronal antibodies have been reported on patients with SC (see discussion of SC) and on children with tics and TS. In the TS population antineuronal antibodies have been quantified by ELISA (against human basal ganglia and human neuroblastoma cells) and immunofluorescent (against human basal ganglia and rat striatum) methods [20,23,75,76]. One recent ELISA study has shown that, compared with control subjects ($n = 39$), children with TS ($n = 41$) had a significant increase in the mean and median optical density (OD) levels of serum antibodies against the putamen, but not the caudate or globus pallidus [23]. The authors, however, found no simple association between putamen ELISA OD levels and indicators of streptococcal infection and a risk ratio calculation for abnormal antistreptococcal titers in children with TS was similar to that in controls. Total antineural antibodies, measured by immunofluorescence on frozen sections of rat striatum, were higher in 81 subjects with TS (age 8–51 years) compared to controls [20]. The difference in antibody titers, however, was not significant when children and adolescents with TS ($n = 54$) were compared to normal controls. Only limited studies have been performed in individuals with PANDAS. In preliminary studies, mean ELISA assay OD values, using homogenate, supernatant, and subcellular fractions (synaptosomes, synaptic membrane, and mitochondria) from fresh postmortem human caudate and putamen as the epitope, did not differ between sera from PANDAS ($n = 24$) and age-matched controls ($n = 12$) [4].

The finding that healthy individuals also have antibodies directed against neuronal tissue further complicates the identification of pathogenic antigens and interpretation of ELISA data [77–80]. Although the function of these "natural" autoantibodies remains unclear, they are generally considered to be largely nonspecific, with little physiologic importance. It should also be recognized that alterations in autoantibodies do not necessarily provide evidence of a primary immune process, because variations may represent changes over the course of a disease [81]. Lastly, additional potential difficulties with several investigations include the use of poorly reproducible techniques and nonhuman brain tissue as the antigenic substrate.

Impasses in interpreting measurements of total antineuronal antibody levels and the desire to identify disease-specific changes in regional brain epitopes has prompted investigators to perform Western blot analyses. Using a direct visual analysis, investigators [23] have shown that antibodies to caudate/putamen occur more frequently in TS subjects at 83, 67, and 60 kDa. Using a similar approach, others [82] have confirmed the presence of a specific brain protein at an apparent molecular weight of 83 kDa that was recognized by antibodies in the serum of 80–90% of patients with TS or OCD. Recent methodologic advances (e.g., assessment of scanned blots using multivariate analysis of discriminance) have enhanced the ability to detect and quantify minor changes in the antigenic composition of autoantibody repertoires [83]. For example, discriminant techniques showed that numerous, rather than only three molecular weight values, contributed to the overall difference between TS and control antibody repertoires against striatal epitopes [84]. Results from this latter study suggest that the 60-kDa region is representative of TS antibody repertoires, whereas antibodies against 83- and 67-kDa antigens do not differentiate as strongly between groups. A discriminant analysis of serum antibodies detected by Western blot from patients with PANDAS is currently in progress.

Rodent striatal infusions

The mere presence of autoantibodies in the serum of patients with SC, TS, or PANDAS does not imply causation. Hence, animal models have been developed to study whether serum (IgG) can induce stereotypies in rodents that may be analogous to tics in humans. Cannulas are placed in regions of the neostriatum known to induce stereotypies, either serum or IgG is microinfused, and animals are observed for development of movements or utterances. Results from three studies have been intriguing, but inconsistent. Hallett et al. [85] infused dilute serum from five TS patients, with high antibody titers against human neuroblastoma, bilaterally into the ventral striatal region of the rat. Results showed a significant increase in stereotypic behaviors (e.g., licks and forepaw shakes) and episodic utterances in the TS group. Taylor and colleagues [86] infused serum from 12 TS patients, with high antibody titers against rat striatum, bilaterally into the ventrolateral striatal region of rats. Results

showed a significant increase of high titer-induced oral stereotypies over a five day period of observation. Loiselle et al. [87] microinfused serum from five TS children, with high antibody titers against human postmortem putamen, bilaterally into the ventral and ventrolateral striatum. In this study, despite infusion of patient sera at the same coordinates used in the Hallett and Taylor protocols, no rat developed any audible abnormality and there was no significant increase in stereotypic behaviors. Further studies using TS sera are in progress. In preliminary studies using sera from children with PANDAS, no dysfunction has occurred after injections into either ventral or ventrolateral rodent striatal sites [87].

Conclusion

The originators of the PANDAS diagnosis had the laudable goal of defining a clinical syndrome in which a subset of individuals with diagnoses of tic disorders and/or OCD could be subcategorized based on the induction of symptoms after a GABHS infection. This concept has generated broad interest from divergent groups and caused many physicians to become polarized on opposing sides of the issue. If true, identification of factors that convey susceptibility or render the host less susceptible would be a major advance. Our goal in this manuscript was not to confirm or refute the diagnosis, but rather to discuss the numerous challenges that persist. As noted, despite claims of a distinct clinical syndrome, multiple areas of concern remain, involving the current diagnostic criteria and the presumed mechanism of pathogenesis. We suggest that confirmation will require careful longitudinal studies of sufficient size to establish significance. Additionally, until further clarification is available, treatment should continue to focus on the use of standard approaches to control symptoms. Although there is the risk of delaying potential advances, there is a longstanding rationale to support the concept of ''putting the horse before the cart.'' Along with the scientific community, we anxiously await the result of longitudinal case-controlled studies now in progress.

Acknowledgments

The authors thank Pamela Talalay PhD for her editorial assistance. This work was supported in part by a grant from the National Institutes for Health, NS 37706.

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