International Journal of Neuropsychopharmacology (2001), **4**, 191–198.

SPECIAL SECTION

Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)

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Abstract

The evidence to date, both published and unpublished, which addresses the validity of the proposed unique subgroup of children with early and abrupt onset of obsessive–compulsive disorder (OCD) and/or tic disorders subsequent to streptococcal infections was reviewed. The aetiology of OCD and tic disorders is unknown, although it appears that both disorders may arise from a variety of genetic and environmental factors. Post-streptococcal autoimmunity has been postulated as one possible mechanism for some. The acronym PANDAS (for paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) has been given to a subgroup of paediatric patients who meet five inclusionary criteria: presence of OCD and/or tic disorder, pre-pubertal symptom onset, sudden onset or episodic course of symptoms, temporal association between streptococcal infections and neuropsychiatric symptom exacerbations, and associated neurological abnormalities. The proposed model of pathophysiology provides for several unique treatment strategies, including the use of antibiotic prophylaxis to prevent streptococcal-triggered exacerbations, and the use of immunomodulatory interventions (such as intravenous immunoglobulin or therapeutic plasma exchange) in the treatment severe neuropsychiatric symptoms. For the latter study group, long-term (2–5 yr) follow-up revealed continued symptom improvement for the majority of patients, particularly when antibiotic prophylaxis had been effective in preventing recurrent streptococcal infections. In addition, the episodic nature of the subgroup's illness provides for opportunities to study brain structure and function during health and disease, as well as allowing for investigations of the aetiologic role of anti-neuronal antibodies and neuroimmune dysfunction in both OCD and tic disorders. Although much research remains to be done, an increasing body of evidence provides support for the postulate that OCD and tic disorders may arise from post-streptococcal autoimmunity. The unique clinical characteristics of the PANDAS subgroup, the presence of volumetric changes in the basal ganglia, and the dramatic response to immunomodulatory treatments, suggest that symptoms arise from a combination of local, regional and systemic dysfunction. Ongoing research is directed at understanding the nature of the abnormal immune response, as well as identifying at-risk children, in order to provide for novel strategies of prevention and treatment.

Received 11 September 2000; Reviewed 13 December 2000; Revised 25 February 2001; Accepted 26 February 2001

Key words: Obsessive–compulsive disorder, tic disorders, Tourette syndrome, streptococcal infection, basal ganglia disease.

Introduction

Although much research has focused on childhood onset obsessive–compulsive disorder (OCD) and tic disorders, their aetiology remains unknown. The identificatcon of specific phenotypes, and the extent to which non-genetic factors may influence illness expression, are important issues that deserve continued research attention. It appears that OCD is a heterogeneous illness with a number of different aetiologies and a variety of risk factors. Specific symptom content, age of onset, course, gender, and patterns of comorbidity have all been studied in an attempt to identify potential phenotypes and aetiologic subgroups. For example, Leckman et al. (1995) and Holzer et al. (1994) have suggested that tic-related OCD and non-tic-related OCD may represent two different patient populations.

OCD associated with tics may be more familial, more common in boys and early onset cases, and may require unique pharmacological treatment approaches (McDougle et al., 1994; Pauls et al., 1995). Early age of onset of OCD may be associated with higher male:female

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ratio, have more severe symptoms, and be more likely to have comorbid tics and disruptive behaviour disorders (Geller et al., 1996, 1998). Nestadt et al. (2000) recently reported that age at onset is valuable in characterizing a familial subtype. In their large, epidemiologic-based genetic study, age of onset of OCD in the proband was strongly related to familiality (having a first-degree relative with OCD), and no cases of OCD were found among the relatives of probands whose age at onset of illness was 18 yr or older (Nestadt et al., 2000).

Recently, post-streptococcal autoimmunity has been postulated as another potential cause of childhood onset OCD (Swedo, 1994). This hypothesis was based on findings from two parallel lines of research: investigations of childhood onset OCD and Tourette syndrome (TS) and from studies of Sydenham's chorea (SC), the neurological manifestation of rheumatic fever. SC is believed to result from cross-reactivity of antibodies directed at group A β-haemolytic streptococcal bacteria (strep.) (GABHS) with neurons in the central nervous system (CNS) (Husby et al., 1976). Historical reports, and more recent systematic investigations, have demonstrated that obsessive–compulsive (OC) symptoms are common in SC, and that the time-course of OCD mirrors that of the chorea (Asbahr et al., 1999; Swedo et al., 1989a, 1993). Further, recurrences of SC carry a greater risk of OCD, with rates increasing from 60 to 100% in one study (Asbahr et al., 1999). The frequency of association, and the presence of OC symptoms prior to the onset of choreatic movements, suggested that OCD might arise as a result of post-streptococcal autoimmunity.

In the late 1980s, a large cohort of children and adolescents with OCD was being evaluated prospectively at the NIMH (Leonard et al., 1992, 1993; Swedo et al., 1989b). Among a subgroup of these children, symptom exacerbations were noted to occur most frequently following strep. infections. The subgroup of children shared a unique clinical course, characterized by an abrupt onset of symptoms and/or dramatic exacerbations 'that came on overnight'. Further study revealed that this subgroup was distinguished by pre-pubertal onset of symptoms, and neurological abnormalities (choreiform movements and a unique pattern of motoric hyperactivity), as well as by their relapsing and remitting symptom course. A preliminary report described infectious triggered symptoms, although 2 of the 4 cases were probably virally triggered episodes at the time of presentation (Allen et al., 1995). These clinical characteristics were used to denote a subgroup of OCD patients now known by the acronym PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) (Swedo et al., 1998). Patients with primary tic disorders are also included in the PANDAS subgroup, based on work by a number of groups demonstrating an association between strep. infections and movement disorders, particularly tics and TS (DiFazio et al., 1998; Kerbeshian et al., 1990; Kiessling et al., 1993, 1994).

The major distinguishing feature of the PANDAS subgroup is the temporal association between neuropsychiatric symptom exacerbations and strep. infections. A methodological difficulty in establishing this association stems from the fact that strep. infections occur so frequently during childhood, that randomly collected anti-streptococcal titres are frequently elevated. Throat cultures may also be artifactually positive, particularly during the grade-school years, when up to 20% of students are 'strep. carriers' (positive throat culture, but no serologic evidence of infection). To avoid these epiphenomena, the PANDAS criteria specify that strep. infections must be 'temporally related' to the OCD/tics exacerbations. This temporal relationship can only be established by demonstrating a clear association between symptom exacerbations and preceding GABHS infections. As noted in the report of the original PANDAS cohort: 'it is necessary to demonstrate that not only is seropositivity associated with symptom exacerbations, but also that seronegativity (or falling titres) is associated with symptom remission' (Swedo et al., 1998, p. 269).

Prospective longitudinal evaluations are often the only means available to make the determination of whether or not the child belongs in the PANDAS subgroup. The relationship between OCD/tics symptom exacerbations and strep. infections is frequently difficult to demonstrate retrospectively, because the medical records fail to provide documentation of the presence of strep. infections. In the original cohort, over 40% of the OCD/tics symptom exacerbations occurred after an episode of pharyngitis for which no throat culture had been obtained (Swedo et al., 1998). If physicians diagnose a pharyngitis as 'viral' without obtaining a throat culture (the only means of identifying strep. infections), it not only obscures the strep.–OCD/tics relationship, but also raises concerns about the consequence of untreated or improperly treated strep. infections in vulnerable individuals.

Phenomenology

The PANDAS subgroup is defined by five clinical characteristics: (1) presence of OCD and/or a tic disorder; (2) pre-pubertal symptom onset; (3) episodic course of symptom severity; (4) temporal association between symptom exacerbations and strep. infections; and (5) associated neurological abnormalities (Swedo et al., 1998). A group of 50 children meeting these criteria was

evaluated at the NIMH and revealed that symptom onset was usually acute and dramatic, and occurred at a very early age [mean age at onset of tics = 6.3 (±2.7) yr and OCD = 7.4 (±2.7) yr]. The symptom course was characterized by a relapsing–remitting pattern, with significant psychiatric comorbidity accompanying the exacerbations. The comorbid symptoms during the relapses included, not only emotional lability which is a hallmark of SC, but also separation anxiety, attentional difficulties, oppositional behaviours, and motoric hyperactivity. Even during periods of symptom quiescence, psychiatric comorbidity was common with 40% of patients meeting DSM-IV criteria for attention deficit hyperactivity disorder (ADHD), 42% for an affective disorder, and 32% for an anxiety disorder. Structured neurological assessments revealed that 25 of 26 children evaluated at presentation to the NIMH had choreiform movements (and the 1 without at baseline, developed it subsequently). Both the choreiform movements and the tics waxed and waned in severity over time, with exacerbations temporally linked to streptococcal infections in a manner similar to the OC symptoms.

Phenomenologically, the children in the PANDAS subgroup are similar to others previously described with OCD and/or tic disorders. The content of the obsessive thoughts and the patterns of motor and vocal tics show little variation from other samples of childhood-onset cases (Leonard et al., 1992; Swedo et al., 1989b). And, as with other populations, boys outnumber girls approx. 3:1.

The clinical characteristic which best delineates the PANDAS subgroup is the sudden, dramatic symptom onset. The PANDAS subgroup is also distinguished by the very early age at onset of symptoms (nearly 3 yr younger than that of previous groups of childhood onset OCD and tic disorders), and the relapsing–remitting symptom course. Additionally, the motoric hyperactivity, impulsivity, and distractibility, which arise anew at the onset of the OCD/tic disorder and remit between episodes, may also characterize this subgroup. The comorbid symptoms occur so frequently in conjunction with the strep.-triggered OCD/tic exacerbations, that it has led some to speculate that some, or all, of these symptoms may be alternative manifestations of the post-streptococcal autoimmunity.

Peterson et al. (2000) recently reported an association between ADHD and elevated anti-streptococcal antibody titres. Antistreptolysin-O (ASO) and antideoxyribonuclease B titres were compared among 105 patients diagnosed with chronic tic disorder (CTD), OCD, or ADHD, and 37 community controls (of note, both groups were selected without regard for their history of streptococcal exposure). A diagnosis of ADHD was associated with significant increases in both ASO and anti-DNAse B titres, and this remained significant after controlling for the effects of CTD and OCD comorbidity. Although the study was limited by significant between-group age differences (the younger age of the ADHD group could have contributed to the finding of elevated anti-streptococcal titres as a result of school exposures), the results suggested that post-streptococcal neuropsychiatric disorders might include ADHD. Given the similarities of brain regions involved in ADHD, OCD and tic disorders, this would not be surprising. If the cross-reactive antibodies induce basal ganglia dysfunction, the resulting symptoms could vary from OCD, tics or ADHD alone, to a combination of all three (as was seen in 40% of patients in the PANDAS subgroup) (Swedo et al., 1998).

Novel treatment strategies for the PANDAS subgroup

The pathophysiological model proposed for SC and the PANDAS subgroup offers several opportunities for intervention. If strep. infections are the inciting agent for OCD/tics exacerbations, then antibiotic prophylaxis could be used to eliminate future recrudescences, as is done for children with rheumatic fever. The cross-reactive antibodies could be cleared with therapeutic plasma exchange (TPE) or administration of intravenous immunoglobulin (IVIG), which have additional immunomodulatory effects that might be of benefit (Garvey et al., 1996). Finally, if the precise nature of the abnormal immune response were known, then targeted immunomodulatory therapies could be used to correct the deficit and reduce the neuropsychiatric symptom severity. Unfortunately, despite decades of research, the specific immune abnormalities in SC are not yet known, so that the latter alternative is still not possible.

Initial case reports of open immunomodulatory treatments in several patients were published (Allen et al., 1995; Tucker et al., 1996). To systematically investigate whether or not immunomodulatory therapies would be of benefit to children in the PANDAS subgroup, a randomized, placebo-controlled trial of therapeutic plasma exchange TPE and IVIG was conducted (Perlmutter et al., 1999). Thirty children participated in the trial, which was approved by the institutional review board of the NIMH. Children were randomized to receive TPE (five single-volume exchanges over a 2-wk period), IVIG (1 g/kg daily on 2 consecutive days), or saline solution (placebo) administered in a manner identical to IVIG. Investigators and subjects were unaware of whether the child received IVIG or placebo, but were not blinded to the TPE arm. The outcome was assessed at 1 month. After symptom ratings were completed, the IVIG/placebo blind was

broken; if the child received placebo and had experienced no improvement in symptoms, open treatment with IVIG or plasmapheresis was offered.

Of the 29 subjects that completed the trial; 10 received TPE, 9 IVIG, and 10 placebo. At 1 month, both TPE and IVIG had produced significant improvements from baseline in OC symptoms (58 and 45% decrease, respectively), anxiety (47 and 31%), depression (44 and 26%) and global impairment (35 and 33%) ($p < 0.01$ for all). Significant improvements in tic severity were seen in the TPE group (49% decrease vs. 12% in placebo and 19% in IVIG groups.) Of interest, OC symptoms, anxiety and depression showed little or no response to placebo administration (3, 3, and 2%, respectively.) Treatment gains were maintained at 1 yr, with 82% (14/17) children 'much' or 'very much' improved over baseline. The results of this systematic, controlled trial suggest that immunomodulatory therapies may provide benefits to some children in the PANDAS subgroup. However, because of the invasive nature of the currently available therapies, we recommend that they be reserved for severely ill children with clear evidence of immune dysfunction. Children with mild-moderately severe symptoms should not undergo TPE or IVIG administration, as the risk:benefit ratio is not clearly tipped towards the immunomodulatory therapy. Similarly, children without evidence of immune-mediated symptoms should not be treated with these therapies, as they are unlikely to be helpful, and carry a risk of adverse effects (vasovagal reactions during TPE, and nausea, vomiting, headache with IVIG administration.)

The lack of benefit of TPE for 'non-PANDAS OCD' was confirmed by a recent study conducted by Nicolson and colleagues at the NIMH. Five patients with severe, treatment-refractory OCD who did not meet criteria for inclusion in the PANDAS subgroup were treated with a course of TPE similar to that used in the randomized trial. No patient showed meaningful improvements in response to the therapy (Nicolson et al., 2000). The negative results were not surprising, given the lack of psychotropic effects of TPE, and suggested that the benefits seen in the PANDAS group were a direct result of the immunomodulatory effects of the therapy, and not a placebo response to the high-tech nature of the procedures.

Antibiotic prophylaxis

Penicillin is routinely used to prevent recurrences in rheumatic fever and SC, and its efficacy is well established (Stollerman, 1975). A double-blind, placebo-controlled trial of penicillin prophylaxis was undertaken to test the hypothesis that neuropsychiatric symptom exacerbations could be prevented by penicillin prophylaxis against strep. infections (Garvey et al., 1999). Thirty-seven children were enrolled in the 8-month long cross-over study and were randomly assigned to receive either penicillin-V 250 mg b.i.d or placebo for 4 months, and then the alternate compound for the next 4 months. Patients were seen monthly for symptom ratings, throat culture, and anti-streptococcal titres (ASO and anti-DNaseB). Nineteen children were randomized to receive penicillin followed by placebo and 18 to receive placebo followed by penicillin. A total of 35 streptococcal infections occurred during the study – 14 of these occurred during the penicillin phase. Thirty-six children had a total of 73 symptom exacerbations during the study, and there were no differences in the distribution across the placebo or penicillin phase. Repeated-measure ANOVA showed significant improvement in the NIMH depression and NIMH anxiety scales during the penicillin phases compared to the placebo phase. There were no between phase differences in the ratings of tic or OCD severity. Similarly, the GAS and the CGI ratings were not significantly improved during the penicillin phase.

The 14 documented strep. infections which occurred during the penicillin phase indicated that the antibiotic failed to achieve adequate levels of prophylaxis. Thus, it was not surprising that it also failed to improve OCD/tics severity. Overall, the study failed to provide support for the use of penicillin prophylaxis in children with neuropsychiatric disorders. The study did provide important information about the shortcomings of current prophylactic strategies, and future trials may show that antibiotics with a longer half-life or easier administration may be effective. Until that time, the management of children in the PANDAS subgroup should include careful surveillance and appropriate treatment for strep. infections, but not prophylactic antibiotics administration.

Neuroimaging studies in PANDAS

The cerebral magnetic resonance images (MRI) of 34 children with PANDAS were compared to those from 82 healthy controls (Giedd et al., 2000). The average size of the caudate, putamen, and globus pallidus (but not the thalamus) were larger in the PANDAS group than the control. There were no significant correlations between basal ganglia size and symptom severity for the group as a whole, although at least one subject showed a decrease in caudate (24%), putamen (12%), and globus pallidus (28%) volumes concomitant with response to therapeutic plasma exchange (Giedd et al., 1996). The basal ganglia enlargements found were similar to those reported for SC (Giedd et al., 1995) and in keeping with the finding by

Peterson et al. (2000) that patients with ADHD or OCD have structural changes in putamen and globus pallidus nuclei volumes.

The neuroimaging studies are consistent with the hypothesis of selective cross-reactive antibody-mediated inflammation of the basal ganglia underlying the development of post-streptococcal OCD or tics. They may also be consistent with previous findings from a study using computerized tomography to evaluate caudate size in adult males with childhood-onset OCD (Luxenberg et al., 1988). That study found significant decreases in caudate size among the OCD patients, compared with age-/sex-matched healthy volunteers. It is tempting to speculate that the volumetric decreases were the result of scarring or caudate atrophy resulting from repeated strep.-mediated autoimmunity or prolonged inflammation of the basal ganglia tissues. However, it is not possible to reconstruct the clinical histories necessary to support such conjecture, so proof of the hypothesis must await future, prospective studies of basal ganglia structural changes occurring after documented episodes of post-streptococcal autoimmunity. Such studies might include not only volumetric assessments, but also functional studies and investigations of the integrity of the blood–brain barrier during acute illness.

Anti-neuronal antibodies and the immune system

Husby et al. (1976) demonstrated that children with SC had elevated titres of 'anti-neuronal antibodies' recognizing human caudate and subthalamic tissue. The anti-neuronal antibodies were adsorbed out by strep. cellular components, consistent with the hypothesis that they had been produced initially in reaction to foreign antigens on the strep. bacteria, and then had mistakenly cross-reacted with CNS tissue. Replication of these findings led to the hypothesis that SC was an 'anti-neuronal-antibody mediated disorder' (Kotby et al., 1998).

In children with TS, Kiessling et al. (1993, 1994) and Singer et al. (1998, 1999) have attempted to identify similar anti-neuronal antibodies. Early results were promising, with children and adolescents with TS having significantly higher serum levels of anti-neuronal antibodies against putamen than did controls (Singer et al., 1998) and having a higher median, but not mean, levels of anti-neuronal antibodies (as measured by the HTB-10 neuroblastoma cell membrane assay) (Singer et al., 1999). However, it should be noted that 20–40% of the healthy controls also demonstrated anti-neuronal antibodies in their serum. Further, Black et al. (1998) tested serum from 13 adult patients (4 of those with pre-pubertal onset of illness) with OCD for panels of autoantibodies and did not find any evidence of humoral autoimmunity. In one small study, 20 adults with OCD had increased CD8+ and decreased CD4+ lymphocytes when compared to healthy controls, which suggests that a continued study of immunological profiles in OCD patients is required (Marazziti et al., 1999).

The monoclonal antibody D8/17 that identifies a B lymphocyte antigen with expanded expression in nearly all patients with rheumatic fever is thought to be a trait marker for susceptibility (Zabriskie et al., 1985). Pilot data from NIMH reported that the frequency of D8/17-positive individuals was significantly higher in children with PANDAS ($n = 27$) and in SC ($n = 9$) in comparison to normal controls ($n = 24$) (Swedo et al., 1997). This had led to discussions as to whether children who present with OCD and or TS, and who may have post-streptococcal autoimmunity, may also have expanded expression of the D8/17 marker. Murphy et al. (1997) reported that patients with a childhood onset of OCD or TS had significantly greater B-cell D8/17 expression than comparison subjects, suggesting that it might serve as a marker for susceptibility among some forms of childhood onset OCD and TS, but it may not be specific to PANDAS. At this point, this investigational assay is not used clinically, and systematic longitudinal prospective investigations are needed to clarify the issues.

Other infectious triggers of OCD and tic disorders

It is not known whether other infectious triggers may be implicated in the onset of some OCD or tic disorders. For rheumatic fever, the inciting organism is always a strep. bacteria, but recrudescences can be caused by a variety of organisms, including non-strep. bacteria and viruses. Berrios et al. (1985) noted that recurrences of rheumatic fever were caused more commonly by viruses than by strep. infections, and suggested that the inciting strep. infection had 'primed' the immune system for hyper-reactivity. If cross-reactive antibodies are the aetiologic agent of the post-infectious autoimmunity, then any infection (or antigenic stimulus) could trigger a recurrence of symptoms, because of the non-specific nature of the initial immune response. Essentially, once the pathologic mechanism is in place, any immunogenic stimulus may be associated with exacerbations.

It is also possible that viral-triggered illnesses occur via a different mechanism entirely. In fact, Von Economo's description of post-influenza OCD was the earliest report of infection-triggered symptomatology (Von Economo, 1931). Further, Fallon et al. (1993, 1994, 1998) have suggested that *Lyme borreliosis* (Lyme disease) can produce OCD and/or tics. Lyme disease, a tick-born spirochetal illness, is a multisystemic illness in which up to 40% of patients have neurological involvement. Recently, Riedel

et al. (1998) reported the case of a 9-yr-old boy who developed Tourette-like symptoms of severe motor and vocal tics subsequent to CNS Lyme disease. Treatment with intravenous antibiotics resulted in rapid resolution of the tics. [Of note, 5 yr earlier, the boy had a simple motor (blinking) tic that had resolved within a year.] The authors concluded that the rapid efficacy of antibiotic treatment followed by a decrease in *Borrelia*-specific antibody titres were evidence that the multiple motor and vocal tics were caused, at least in part, by the tertiary stage of borreliosis.

Mycoplasma pneumoniae encephalitis has also been reported to cause a Tourette-like syndrome. Two children with mild tics were reported to have a dramatic exacerbation in symptoms concomitant with their *M. pneumoniae* infection. In both cases, the tics resolved rapidly in response to successful antibiotic treatment of the infection (Muller et al., 2000). *Mycoplasma pneumoniae* encephalitis has been reported to cause basal ganglia lesions and movement disorders, but this was the first report of severe motor and vocal tics. The authors suggested that tics might be a final common pathway of various disorders that have different aetiologies. A variety of infectious and non-infectious illnesses that impact on the basal ganglia could cause similar symptoms, if regional localization was similar.

Does PANDAS represent a rheumatic fever spectrum disorder?

Although the SC model has proven to be a useful research model of pathophysiology for post-streptococcal OCD/tic disorders (PANDAS), the OCD/tic disorders are not candidates for inclusion in the rheumatic fever spectrum. In fact, evidence of rheumatic fever (carditis, chorea, and/or arthritis) excludes children from the PANDAS subgroup, because it carries therapeutic requirements (i.e. mandatory antibiotic prophylaxis until age 25 yr) that are not appropriate for the PANDAS research subgroup. Therefore, studies of children in the PANDAS subgroup cannot answer the question of whether or not OCD/tic disorders represent alternative manifestations of rheumatic fever.

That question can only be answered by examining adult cohorts of early-onset OCD/tic disorders. If adult OCD patients meet criteria (by history) for the PANDAS subgroup, and have evidence of increased rates of post-rheumatic fever heart disease, then it would suggest that post-streptococcal OCD/tic disorders are part of the rheumatic fever spectrum. On the other hand, if rates of rheumatic fever are not elevated in the population, it would not argue against the PANDAS model, as nearly three-quarters of SC patients also lack evidence of rheumatic heart disease. Further, the spectrum of post-streptococcal autoimmune disorders is broader than rheumatic fever, and includes such diverse disorders as glomerulonephritis and post-streptococcal arthritis. Therefore, OCD/tic disorders may fall outside the rheumatic fever spectrum, and still be the result of post-streptococcal autoimmune mechanisms.

Although there is an increased rate of OCD in SC, this does not mean that PANDAS is in the spectrum of rheumatic fever. Although one might speculate that PANDAS represents a dual genetic vulnerability (OCD/tics and rheumatic fever) this will require systematic family studies to determine whether it is valid. Preliminary family studies of first-degree relatives of PANDAS probands reported that the rates of tic disorders and OCD were higher than those reported in the general population and similar to those reported previously for tic disorders and OCD (Lougee et al., 2000). Identification of risk of genetic vulnerability for rheumatic fever, will have to come from future genetic studies (e.g. identification of HLA profiles).

Current theories of post-streptococcal autoimmunity include theories of humoral (presence of anti-neuronal antibodies), cell-mediated (cytokine shifts and/or V-beta abnormalities), and super-antigen aetiologies. All of these mechanism are possible explanations for post-streptococcal OCD/tic disorders, but none have been proven and further research is needed before any conclusions can be drawn (Mittleman et al., 1997; Trifiletti and Packard, 1999). In addition, the prevalence and magnitude of autoimmune factors in unselected cases of TS or OCD, the specificity and sensitivity of anti-streptococcal and anti-neuronal antibodies, and the presence of genetic risk factors merit further study (Kurlan, 1998). Thus, as the field debates the boundaries of PANDAS, it is clear that longitudinal documentation of the relationship between strep. infections and neuropsychiatric symptomatology is desperately needed (Murphy et al., 2000; Shulman, 1999).

Summary

The identification of a subgroup of children with OCD and/or tic disorders has diagnostic, aetiologic, and treatment implications. First, children who develop OCD, tics, and motor hyperactivity as sequelae of streptococcal infection (e.g. PANDAS) may share a common symptom profile that is distinct from other (non-PANDAS) cases of the disorders, and thus require unique diagnostic assessments. Secondly, the OCD/tics of the PANDAS subgroup may respond to different short-term (antibiotic or immunomodulatory therapy) and long-term monitoring (surveillance for strep. infections), which raises the possibility that novel therapies might be developed to treat the underlying pathological process, rather merely

providing symptom palliation. Finally, such a subgroup might provide opportunities for identifying at-risk individuals, and developing strategies for prevention of disease onset.

In summary, the working diagnostic criteria appear to define a meaningful subgroup of patients with childhood-onset OCD and tic disorders, and with further study, other neuropsychiatric symptoms may also be found to be appropriately included in the PANDAS spectrum.

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