Genetics of Childhood Disorders: XXXIII. Autoimmunity, Part 6: Poststreptococcal Autoimmunity

SUSAN E. SWEDO, M.D.

In the late 1980s, studies of children with Sydenham chorea (SC), the neurological manifestation of rheumatic fever, suggested that the disorder might serve as a useful model of pathophysiology for some forms of childhood-onset obsessive-compulsive disorder (OCD) and tic disorders. The disorders share anatomic similarities. Both OCD and SC have evidence of basal ganglia dysfunction, particularly in the caudate nucleus, which is thought to disrupt signals traveling along the orbitofrontal-striatal pathways. Furthermore, over 70% of children with SC reported that they had experienced an abrupt onset of repetitive, unwanted thoughts and behaviors 2 to 4 weeks before the onset of their chorea. These obsessions and compulsions peaked in intensity concomitantly with the chorea and waned away slowly over the ensuing months. Because the obsessive-compulsive symptoms began earlier than the chorea, it seemed possible that poststreptococcal OCD might occur in the absence of chorea, a hypothesis confirmed by prospective observations of a large cohort of children with primary OCD.

Among those children, a subgroup was noted to have dramatic symptom exacerbations following infections with group A β-hemolytic streptococcal bacteria (GABHS) such as occurs with strep throat and scarlet fever. The symptom exacerbations were accompanied by a cluster of comorbid symptoms, including emotional lability, separation anxiety, and attentional difficulties. The children were young (6–7 years old at symptom onset), predominantly male, and had frequent comorbid tics. To indicate the subgroup's common clinical characteristics and presumed pathophysiology, it was identified by the acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections).

The etiology proposed for the PANDAS subgroup is similar to that postulated for SC. In SC, host susceptibility is thought to play a crucial role in symptom expression, as fewer than 5% of children are vulnerable to poststreptococcal sequelae. Familial clustering suggests that genetic factors are involved in the susceptibility, but is not the sole explanation as developmental and immunological factors may also play a part.

The constitution of the streptococcal bacteria appears to play an etiological role in rheumatic fever and other poststreptococcal sequelae. Although most strains of GABHS produce only acute symptoms, certain "rheumatogenic" strains incite the production of antibodies that cross-react with host tissues, producing an "autoimmune"; reaction. Unlike typical autoimmune disorders, the autoantibodies in rheumatic fever are not

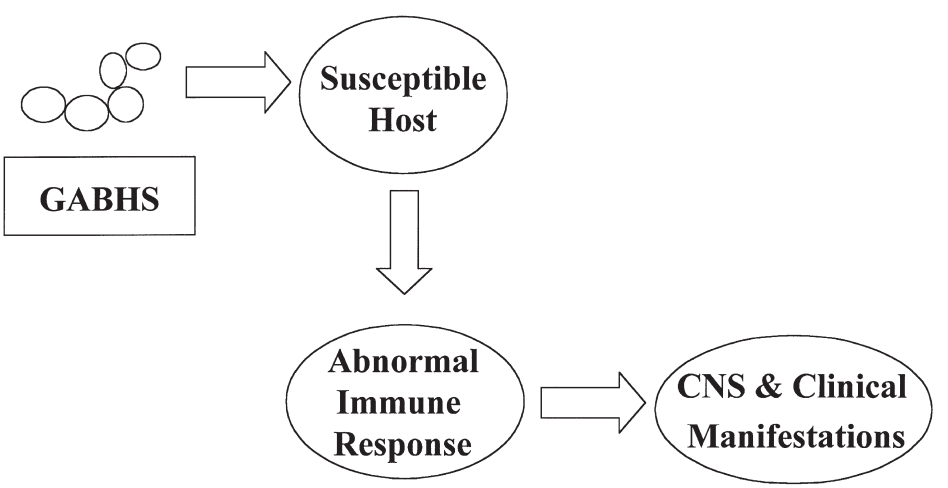

Fig. 1 Model of pathogenesis for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Individuals are infected by group A β-hemolytic streptococcal bacteria (GABHS). Susceptible individuals respond to the infection by producing antibodies in a normal fashion. However, these antibodies presumably cross-react with neuronal tissue and compromise their function, leading to the observed clinical symptoms.

directed primarily against the host tissue, but rather against streptococcal epitopes that resemble antigens on host cells. In SC, the cross-reactive antibodies are thought to recognize epitopes on basal ganglia neurons (particularly in the caudate, putamen, and globus pallidus). The resulting inflammation disrupts basal ganglia function, causing chorea, emotional lability, and other neuropsychiatric symptoms. After the streptococcal infection is eliminated from the nasopharynx, antibody production ceases and circulating antibodies are cleared over the ensuing weeks to months. The neurological symptoms also remit—often with no lasting sequelae. However, recrudescences can occur, particularly when the child is infected again with microbes resembling the inciting organism.

Although the antineuronal antibody model of SC appears quite convincing, it has not yet been proven, despite decades of research. Furthermore, recent studies by a number of research groups have demonstrated several crucial limitations of the antineuronal antibody model, including its failure to account for the presence of similar antibodies in the serum of 20% to 40% of healthy children. Thus, for the PANDAS subgroup, the model has been modified to indicate that the immune response is not limited to the antineuronal antibodies. As shown in Figure 1, our working model of pathophysiology involves a series of factors, including the streptococcus bacteria, host susceptibility, and abnormal immune responsivity.

The major distinguishing feature of the PANDAS subgroup is the temporal association between the neuropsychiatric symptom exacerbations and the infections. Because strep infections are common during childhood, antistreptococcal titers and throat cultures might be positive during a symptom exacerbation by chance alone. Thus the PANDAS criteria specify that GABHS infections must be temporally related to the OCD/tics exacerbations, that is, positive (or rising) antistreptococcal antibody titers or a positive throat culture must be present during neuropsychiatric symptom relapses and there must be evidence of strep negativity during periods of remission.

In some cases, the dramatic onset of severe OCD and/or tics following a single, prolonged strep infection is sufficient to warrant inclusion in the PANDAS subgroup. Usually, however, the temporal relationship can be established only through prospective documentation of both seropositivity during symptom exacerbations and seronegativity during periods of remission. This 1 to 1 correlation is necessary to distinguish strep-triggered exacerbations of the PANDAS subgroup from the more typical waxing and waning course seen in Tourette's syndrome and some cases of childhood-onset OCD. For rheumatic fever, the etiological role of strep infections was demonstrated indirectly, through three lines of research: (1) epidemiological investigations which demonstrated a close temporal relationship between scarlet fever epidemics and subsequent outbreaks of rheumatic fever; (2) the prevention of rheumatic fever recrudescences by penicillin prophylaxis; and (3) demonstration of declining rates of rheumatic fever following the widespread application of antibiotic treatment for GABHS pharyngitis. For the PANDAS subgroup, there are no epidemiological data that yet demonstrate increased rates of OCD and/or tics following strep epidemics, although a school-based study of the relationship between strep infections and neuropsychiatric symptoms is currently under way.

The use of penicillin prophylaxis for the prevention of neuropsychiatric symptom exacerbations was evaluated in a double-blind, placebo-controlled, 8-month-long crossover study by Garvey and colleagues in 1999. Although individual cases demonstrated between-phase differences, the trial failed to show overall superiority of penicillin over placebo. This may have been due to the failure of oral penicillin to prevent strep infections (14 of the 35 infections documented during the study occurred during the penicillin phase). Ongoing trials are investigating the utility of other antibiotics as prophylactic agents for the PANDAS subgroup, but at present, there are no systematic data to support the use of antibiotic prophylaxis for children with OCD and/or tic disorders. Similarly, the specific strains of strep bacteria responsible for symptom onset in the PANDAS subgroup remain to be identified. Knowing which types of bacteria are capable of inducing the poststreptococcal sequelae may help elucidate the nature of the abnormal immune response.

As discussed above, host susceptibility is likely to be the result of a combination of genetic, developmental, and immunological factors. Developmental vulnerabilities are suggested by the increased rates of disease among elementary school–age children. Rheumatic fever is rare among children younger than 3 years of age, peaks in incidence during the elementary school years, and declines in frequency at adolescence to become rare again during young adulthood. This pattern might reflect developmental differences in immune responsivity, or it may be merely the result of changing risks of exposure to strep infections. These are most common during the elementary school years, and nearly all children develop protective immunity by age 12 to 13 years. For the PANDAS subgroup, the peak age at onset of symptoms is 6 to 7 years, with prepubertal symptom onset serving as a defining characteristic of the subgroup.

Family history studies have been used to evaluate the role of genetics in host susceptibility. For rheumatic fever, familial clusters suggested an autosomal (dominant or recessive, depending on the sample studied) pattern of inheritance. Preliminary data from 21 patients with SC and 15 children in the PANDAS subgroup revealed significantly increased rates of rheumatic fever among the children's parents and grandparents, in comparison with the parents and grandparents of 35 healthy controls (5/126 [4.0%], 6/90 [6.7%], and 3/210 [1.4%], respectively; Swedo et al., unpublished data, 2001). The between-groups differences were small in this pilot data set, but suggested that children in the PANDAS subgroup may inherit a susceptibility to poststreptococcal sequelae similar to that reported for children with SC.

Children in the PANDAS subgroup also appear to have increased rates of OCD and tics among their family members. In a recently completed study by Lougee of 54 probands in the PANDAS subgroup (24 with a primary diagnosis of OCD and 30 with a primary diagnosis of a tic disorder), 21 (39%) had at least one first-degree relative with a history of a motor or vocal tic and 14 (26%) had at least one first-degree relative with OCD. Six mothers (11%), 9 fathers (19%), and 8 siblings (16%) had a motor or vocal tic, while 10 mothers (19%), 5 fathers (11%), and 2 siblings (5%) had OCD. These rates are substantially higher than those reported for the general population and are similar to rates previously reported for childhood-onset OCD and tic disorders. The combination of increased familial rates of OCD/tic disorders and of increased rates of rheumatic fever suggests that children in the PANDAS subgroup may have a dual genetic vulnerability—with inherited susceptibilities to both OCD/tic disorders and poststreptococcal autoimmune sequelae. Proof of this hypothesis must come from genetic determinations, rather than family history studies, and awaits future testing.

At present, the role of the immune system in the etiology of OCD and tic disorders is unknown. Clinical observations suggest that symptoms result from a combination of local, regional, and systemic abnormalities. The striking effectiveness of immunomodulatory therapies, such as therapeutic plasma exchange and intravenous immunoglobulin (IVIG), suggests that there is systemic involvement, at least in severely affected individuals. Magnetic resonance imaging (MRI) scans reveal enlargements of the basal ganglia, a finding which points to regional inflammatory changes, while local autoimmune reactions are suggested by the presence of serum antibodies that cross-react with neurons of the caudate, putamen, and globus pallidus.

The effectiveness of both plasma exchange and IVIG in the treatment of severely affected patients in the PANDAS subgroup suggests that circulating immune factors play a role in the pathophysiology of the symptoms. Both treatments have a broad spectrum of potential mechanisms of action, from clearance of circulating antibodies and cytokines to activation of subpopulations of T cells and B cells, but the precise mechanism of effect is unknown. If it could be determined, then it might be possible to elucidate the nature of the poststreptococcal autoimmune response in the PANDAS subgroup, as well as to develop targeted therapeutic interventions suitable for use in less severely ill patients.

Regional inflammation is thought to play a role in the specificity of the poststreptococcal neuropsychiatric symptomatology. In SC, functional imaging studies obtained during the acute symptomatic period have demonstrated increased basal ganglia blood flow, as well as disruptions of the blood-brain barrier in the caudate nuclei. These abnormalities resolved as the chorea remitted, suggesting that they were etiologically related to the neuropsychiatric symptoms. Volumetric MRI scans have revealed bilateral enlargements of the caudate, putamen, and globus pallidus in a group of patients with SC, and similar abnormalities have been demonstrated recently in a group of patients with OCD/tic disorders. In both samples, however, there was substantial overlap between the patients and control subjects; thus the volumetric measurements cannot be used as a diagnostic test.

In a small series of PANDAS patients treated with plasma exchange, baseline caudate enlargements returned to normal after successful treatment. This result suggests that the enlargement might be a reflection of basal ganglia inflammation. To evaluate this possibility, all children currently being treated with plasma exchange at the National Institute of Mental Health are undergoing a series of MRI scans, in which a variety of specialized techniques are used to assess interstitial edema and disruptions of the blood-brain barrier.

The final area of research interest is the cross-reactive antibodies first described in SC by Husby and colleagues. The original report describes the presence of serum antibodies that recognized cells of the caudate nucleus and subthalamus. The antibodies recognized epitopes on the strep bacteria as well. It was the cross-reactivity that distinguished the antineuronal antibodies found in the SC patients from those found in patients with lupus erythematosus and other neurological disorders.

Several groups have subsequently reported the presence of "antineuronal" antibodies in the majority of patients with childhood-onset OCD and/or tic disorders. These antibodies were directed against a variety of tissue targets including human caudate, neuroblastoma cells, and rat striatum, among others. Of note, antibodies were noted to be present frequently in the serum of healthy children (20%–40%), raising the question of whether or not the antibodies are the cause of the poststreptococcal neuropsychiatric symptoms. This question might be answered by cross-reactivity studies, such as those reported by Husby and colleagues, but these have not been done in the majority of recent studies. Future research should include such assessments, as well as techniques that will identify specific epitopes recognized by the antibodies. If the antibodies are interacting with a specific receptor or a single neuronal cell-type, they might be used to open doors to better treatments for childhood-onset OCD and tic disorders and might lead to a greater understanding of the cause and nature of these troublesome disorders.

WEB SITES OF INTEREST

http://www.niaid.nih.gov/factsheets/strep.htm
http://www.nami.org/youth/ocdstrep.html

ADDITIONAL READINGS

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Dr. Swedo is Chief, Pediatrics and Developmental Neuropsychiatry Branch, National Institute of Mental Health, Bethesda, MD.

Correspondence to Dr. Lombroso, Child Study Center, Yale University School of Medicine, 230 South Frontage Road, New Haven, CT 06520; e-mail: Paul.Lombroso@Yale.edu.

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