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IMMUNOLOGY OF NEURODEVELOPMENTAL DISORDERS

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

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Parallels between Sydenham chorea (SC), the neurologic manifestation of rheumatic fever, and childhood-onset OCD suggest that the two disorders may have a shared etiopathogeneis.[1] The disorders have similar regional localization—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. Further, over 70% of children with SC report that they have experienced an abrupt onset of repetitive, unwanted thoughts and behaviors 2–4 weeks prior to the onset of their chorea.[2] The obsessions and compulsions peak in intensity concomitantly with the chorea and wane away slowly over the ensuing months. A subgroup of patients with childhood-onset OCD was noted to have a similar symptom course. The OCD exacerbations occurred following GAS infections, 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 often had comorbid tics.[3] To indicate their shared clinical features (and presumed etiopathogenesis), the subgroup was identified by the acronym PANDAS—Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections.[3]

The postulated pathophysiology of Sydenham chorea and PANDAS involves a series of factors, including the 'rheumatogenic' GAS bacteria, genetic susceptibility, and abnormal immune responsivity. As shown in Figure 1, the proposed model not only provides a framework for understanding the etiology of OCD and tic disorders, but also for the development of novel intervention and prevention strategies.

The major distinguishing feature of the PANDAS subgroup is the temporal association between neuropsychiatric symptom exacerbations and GAS infections—that is, positive (or rising) antistreptococcal antibody titers or a positive throat culture during neuropsychiatric symptom relapses and evidence of GAS negativity during periods of remission.[3] This one-to-one correlation is necessary to distinguish GAS-triggered exacerbations of the PANDAS subgroup from the more typical waxing and waning course seen in Tourette disorder and some cases of childhood-onset OCD.[4]

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.[5] 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 GAS 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.

Host susceptibility for the PANDAS subgroup is likely to be the result of a combination of genetic, developmental and immunologic factors. Developmental vulnerabilities are suggested by the increased rates of disease among grade-school age children. For the PANDAS subgroup, the peak age at onset of symptoms is 6–7 years, with prepubertal symptom onset serving as a defining characteristic of the subgroup.[3]

To examine the potential for genetic vulnerabilities, a family history study was conducted with 21 children with Sydenham chorea and 15 children in the PANDAS subgroup, and 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 post-streptococcal sequelae similar to that reported for children with SC.

Children in the PANDAS subgroup also appear to

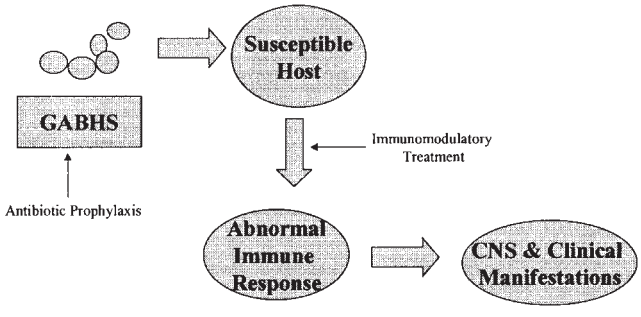

Figure 1 Model of pathogenesis for PANDAS.

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have increased rates of OCD and tics among their family members. In a recently completed study of 54 probands in the PANDAS subgroup, rates of both OCD and tics were substantially higher among the first degree relatives surveyed, than those reported for the general population, and were similar to rates previously reported for childhood-onset OCD and tic disorders.[6] The combination of increased familial rates of OCD/tic disorders and 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 post-streptococcal sequelae. Proof of this hypothesis must come from genetic determinations, rather than family history studies, and awaits future testing.

The role of the immune system in the etiology of OCD and tic disorders is unclear, but clinical observations suggest that symptoms result from a combination of local, regional and systemic abnormalities.[7] 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.[8] MRI scans reveal enlargements of the basal ganglia, which points to regional inflammatory changes, while local autoimmune reactions are suggested by the presence of serum antibodies which cross-react with neurons of the caudate, putamen and globus pallidus.[7]

A randomized, placebo-controlled trial of IVIG and plasma exchange revealed that both therapies produced significant improvements in neuropsychiatric symptom severity—obsessive-compulsive symptoms were reduced by 45–58% one month post-treatment with IVIG or plasma exchange (respectively), while one-year follow-up revealed that 14 of 17 children (82%) were 'much' or 'very much' improved from baseline.[8] The effectiveness of both IVIG and plasma exchange suggests that circulating immune factors play a role in the pathophysiology of the symptoms. Both treatments have a broad spectrum of action; if the specific therapeutic effect could be determined for those in the PANDAS subgroup, then it might be possible to elucidate the nature of the post-streptococcal autoimmune response and 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 post-streptococcal 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.[9] These abnormalities resolved as the chorea remitted, suggesting that they were etiologically related to the neuropsychiatric symptomatology. 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 among patients in the PANDAS subgroup.[10,11]

Husby and colleagues[12] were the first to describe cross-reactive antibodies in Sydenham chorea. Although the antibodies were labeled 'antineuronal', they noted that the antibodies must have been raised against epitopes on GAS, and then cross-reacted with cells of the caudate nucleus and subthalamus. It was the cross-reactivity which distinguished the antibodies found in the SC patients from antineuronal antibodies found in patients with lupus erythematosus and other neurologic disorders.[12] Several groups have subsequently reported the presence of 'antineuronal' antibodies in patients with childhood-onset OCD and/or tic disorders. If these antibodies can be used to identify the specific receptor or neuronal cell-type involved in the neuropsychiatric symptoms, it might lead to the development of novel neuroimmunologic therapies for childhood-onset OCD and tic disorders. Until that time, investigations of the PANDAS subgroup should continue to provide new insights into the cause and nature of these troublesome disorders.

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