Genetics of Childhood Disorders: XXXI. Autoimmune Disorders, Part 4: Is Sydenham Chorea an Autoimmune Disorder?

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For many years Sydenham chorea (SC) has been considered the prototype of an autoimmune disorder triggered by an infectious agent. Nevertheless, despite its description more than 300 years ago by Thomas Sydenham, its defined association with rheumatic fever in 1838, and linkage to a preceding group A β-hemolytic streptococcal (GABHS) infection, there are numerous unanswered questions about the underlying pathology and pathophysiology of SC. Recently, clarification of the underlying mechanism in SC has assumed renewed importance as the disorder has been proposed as a model for a spectrum of childhood neurobehavioral disorders, including tics and obsessive-compulsive disorder, termed PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection).

The distinguishing clinical manifestation of SC is the presence of spontaneous, involuntary choreiform movements affecting the face and extremities that typically persist for several months before subsiding. Diagnosis is made strictly on clinical observation. No confirmatory laboratory test for SC is available, although an elevated titer against antistreptolysin O, anti-deoxyribonuclease B, or anti-nicotinamide adenine dinucleotidase is demonstrated in 80% of SC patients.

Onset is usually between ages 5 and 15 years, and a female predominance is observed in most studies. Associated neurological symptoms may include dysarthria, hypometric saccades, hypotonia, weakness, hemiballismus, and gait disturbances that correlate with severity of chorea. Affected individuals may present with behavioral or emotional difficulties that predate the motoric abnormalities by weeks to months. For example, most patients have concomitant psychological dysfunction presenting as personality changes, emotional irritability, distractibility, and age-regressed behaviors. Studies have also shown a higher frequency of obsessive-compulsive symptoms in children with SC or nonchoreic rheumatic fever. Motor or vocal tics and oculogyric crises have also been reported in patients with SC. Despite a relatively common occurrence of EEG abnormalities, seizures are uncommon. Rheumatic valvular cardiac disease is seen in about one third of patients, although echocardiogram screenings suggest a higher prevalence. Arthritis is uncommon.

The outcome in SC is quite favorable. Most cases resolve in 1 to 6 months. Some investigators have identified residual abnormal EEGs, minor lingering motor abnormalities, persistent neuropsychiatric problems, and future development of valvular heart disease. About 20% to 60% of cases have recurrent episodes of chorea, usually within 1 to 2 years after the original event. An individual may have multiple attacks with reactivation precipitated by a GABHS infection or by another environmental stimulus. Pregnancy and oral contraceptives may stimulate the reappearance of chorea after many years of quiescence.

Magnetic resonance imaging (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. A limited number of postmortem brain studies have demonstrated

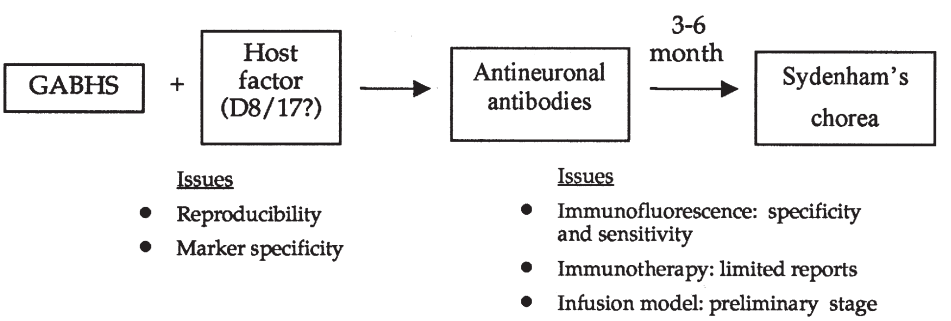

Fig. 1 Overview of the putative pathophysiological mechanism in Sydenham chorea and highlights of the concerns. GABHS = group A β-hemolytic streptococcus.

a variety of cerebral abnormalities, including acute and chronic neuronal degenerative changes as well as vascular and inflammatory lesions. Pathological changes within the cerebral cortex, basal ganglia, and thalamus have included a reduction in neurons, cytoplasmic and nuclear cell changes, gliosis, hyperemia, endothelial swelling, perivascular round cell infiltration, and petechial hemorrhages. Primarily on the basis of measurements of the dopamine metabolite homovanillic acid (HVA) in cerebrospinal fluid, SC has been postulated to be associated with dopaminergic dysfunction. Nevertheless, the results of studies have varied from showing an elevated baseline HVA to reduced accumulation after administration of probenecid.

The greater prevalence of rheumatic fever among relatives compared with unrelated subjects has led to suggestions of a genetic predisposition. The monoclonal antibody D8/17 directed against a polymorphic protein on the surface of B lymphocytes has been found to have an expanded expression in individuals with rheumatic fever and is hypothesized to be a trait marker for susceptibility. The monoclonal antibody reacts with epitopes present on a significantly higher proportion of B lymphocytes in patients with acute rheumatic fever or rheumatic heart disease (100%) than in controls (12%). A significantly higher frequency of D8/17 positive cells has also been identified in children with SC (89%) compared with healthy children (17%). How this marker relates to the disease process is unknown, especially since it has been reported in patients with other neuropsychiatric disorders of childhood onset who have not had a diagnosis of rheumatic fever or SC. Researchers have also failed to reproduce some of these findings with automated techniques, rather than by manual counting of stained cells with a fluorescent microscope.

Studies of human lymphocyte antigen (HLA) report conflicting results in detecting associations between class I or class II major histocompatibility complex antigens and acute rheumatic fever. Investigators have proposed that immunogenetic susceptibility to rheumatic fever varies according to the major clinical symptom manifested by the patient. Specific HLA alleles were overrepresented in rheumatic carditis and arthritis subgroups, but were not increased in frequency in a subgroup with SC only.

An autoimmune process has been confirmed in rheumatic fever. For example, in carditis, anti-heart antibodies cross-reactive with streptococcal antigens have been well established. Myosin has been identified as the heart autoantigen, and monoclonal anti-heart antibodies recognize streptococcal M protein as well as streptococcal membranes.

In contrast to the situation for the heart in nonchoreic rheumatic fever, the case for autoimmunity in SC is less well defined. In SC, it is generally hypothesized that antibodies against GABHS cross-react against CNS neurons through the process of molecular mimicry. Support for the antineuronal antibody proposal is based on results in three areas: the measurement of serum antineuronal antibodies, proposed success of immunomodulating therapies, and the establishment of an animal model (Fig. 1).

Husby and colleagues were the first to describe antineuronal antibodies that putatively arise in response to a GABHS infection. The investigators used an immunofluorescent antibody staining technique to show specific cross-reactivity of IgG to neuronal cytoplasmic antigens in caudate and subthalamic nuclei in 47% (14/30) of acutely ill SC patients compared with 0% in child controls (0/24) and 3% (1/31) in adult controls. In 1993, Swedo and colleagues, using similar methods, showed that 91% (10/11) of SC patients (9 with obsessive-compulsive behavior) tested positive for antineuronal antibodies, but 50% (9/18) of healthy controls were also positive. More recently, this immunofluorescence technique was used to study 40 individuals with acute, chronic, or remote rheumatic chorea, compared with 40 controls; antineuronal antibodies were found in 100%, 93%, and 44% of the SC patients, respectively. In comparison, no control subjects had antineuronal antibodies. A possible association between the antineuronal antibodies and GABHS is supported by studies showing that antibodies to streptococcal M protein can cross-react with human brain tissue.

Although the results of the immunofluorescent antibody technique in SC are intriguing, they nevertheless raise several concerns. The methodology uses a visually graded estimate of immunofluorescent staining against tissue sections from human caudate, putamen, and subthalamic nuclei. Normal brain itself, however, especially in older adults, contains autofluorescing lipofuscins. The degree of sensitivity and specificity of the assay raises further concerns. Percent positive rates in SC cases have ranged from 47% to 100%, while positive rates in control populations have ranged from 0% to 50%. Moreover, there was a lack of correlation with clinical features. More recently, other investigators have used enzyme-linked immunosorbent assay (ELISA) and Western blot techniques to detect the presence of antineuronal antibodies in the serum of patients with acute SC. ELISA titers against subcellular fractions (synaptosome, mitochondria, and synaptic membrane) from unfrozen postmortem human caudate and putamen showed no difference between an SC cohort and control group (Singer et al., unpublished). The presence of specific serum antibodies against a synaptosomal preparation of putamen and caudate tissue was assessed by Western blotting and discriminant analysis. Preliminary results show a separation in discriminant space between the SC and control groupings in the putamen but not in the caudate. Further analyses are in progress to determine the reproducibility of these findings and to delineate specific epitopes that contribute to the changes.

The responsiveness of SC symptoms to immunomodulatory treatment has been cited as supporting evidence of an

immune process. Swedo described a child with SC who had improvement of choreic and obsessive-compulsive symptoms after plasma exchange. Others have suggested that immunosuppressive measures such as corticosteroids, intravenous immunoglobulin (IVIG), and plasmapheresis are effective treatments of chorea in SC. The number of reported cases, however, is small, and studies have been performed without appropriate controls. Of interest, Voss and colleagues reported that IVIG treatment failed to alter the natural history of acute rheumatic fever, with no detectable difference in the clinical, laboratory, or echocardiographic parameters of the disease process during the subsequent 12 months. Finally, in an attempt to develop an animal model, Hallett and colleagues have unilaterally infused SC serum into rodent subthalamic nucleus. After infusion, apomorphine-stimulated ipsilateral circling was greater in rats infused with SC sera than in animals receiving control sera. This model suggests that sera from SC patients can cause immune-mediated, physiologically meaningful damage to the rodent subthalamic nucleus. As this information has yet to be published, further analysis of the model will be forthcoming.

The mechanism by which autoimmunity, if present, may proceed in SC remains unclear. Conventional wisdom holds that circulating antibodies do not enter the CNS without a breach of the blood–brain barrier. Gadolinium-enhanced MRI scans of two patients with SC suggest, however, that such a breach of the blood–brain barrier may actually occur. Alternative mechanisms in which the blood–brain barrier remains intact have been proposed. For example, antigen-specific B cells can migrate into the CNS, possibly as lymphoblasts, and after receiving antigen-dependent cytokine stimulation, differentiate into antibody-producing plasma cells within the CNS. One facet of rheumatic chorea unexplained by proposed mechanisms is its latent onset, i.e., why is the onset of chorea delayed for 3 to 5 months after GABHS infection, unlike the other features of rheumatic fever?

In summary, an autoimmune hypothesis for SC has been built around the measurement of serum antineuronal antibodies, results of immunomodulating therapy, and limited studies in an animal model. Nevertheless, there are significant concerns relating to each of these areas and further investigation into the pathology of SC is required. The current wide acceptance of SC as an "established" model for CNS autoimmunity highlights the need for further studies of this hypothesis.

WEB SITES OF INTEREST

http://www.neurologychannel.com/movementdisorders/
http://merckmedco.adam.com/ency/article/003940.htm

ADDITIONAL READINGS

Cunningham MW (2000), Pathogenesis of group A streptococcal infections. *Clin Microbiol Rev* 13:470–511

Donadi EA, Smith AG, Louzada-Júnior P, Voltarelli JC, Nepom GT (2000), HLA class I and class II profiles of patients presenting with Sydenham's chorea. *J Neurol* 247:122–128

Garvey MA, Swedo SE (1997), Sydenham's chorea: clinical and therapeutic update. *Adv Exp Med Biol* 418:115–120

Husby G, van de Rijn I, Zabriskie JB, Abdin ZH, Williams RCJ (1976), Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons in chorea and acute rheumatic fever. *J Exp Med* 144:1094–1110

Kotby AA, El Badawy N, El Sokkary S, Moawad H, El Shawarby M (1998), Antineuronal antibodies in rheumatic chorea. *Clin Diagn Lab Immunol* 5:836–839

Marques-Dias MJ, Mercadante MT, Tucker D, Lombroso P (1997), Sydenham's chorea. *Psychiatr Clin North Am* 20:809–820

Murphy TK, Goodman WK, Ayoub EM, Voeller KK (2000), On defining Sydenham's chorea: where do we draw the line? *Biol Psychiatry* 47:851–857

Swedo SE (1994), Sydenham's chorea: a model for childhood autoimmune neuropsychiatric disorders (clinical conference). *JAMA* 272:1788–1791

Voss LM, Wilson NJ, Neutze JM et al. (2001), Intravenous immunoglobulin in acute rheumatic fever: a randomized controlled trial. *Circulation* 103:401–406

Zabriskie JB, Lavenchy D, Williams RC et al. (1985), Rheumatic fever associated B cell alloantigens as identified by monoclonal antibodies. *Arthritis Rheum* 28:1047–1051

Accepted April 20, 2001.

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