Sydenham's Chorea – An Entity In Progress

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Sydenham's chorea is the principal neurologic manifestation of rheumatic fever, and together with carditis, polyarthritis, subcutaneous nodules and erythema marginatum comprise the major criteria for the diagnosis of rheumatic fever. As first described by Husby et al. in 1976 [1], Sydenham's chorea is thought to occur when antineuronal immunoglobulin G antibodies that arise in response to a group A beta hemolytic streptococcus infection cross-react with specific antigens on neurons of the caudate and subthalamic basal ganglia nuclei, causing specific motor and behavioral disturbances.

After a continuing decline in previous decades [2], the prevalence of rheumatic fever, and subsequently of SC, has been on the rise since the 1980s with no concomitantly apparent rise in GABHS infection [3], perhaps due to changes in streptococcal production rates of pyrogenic exotoxins.

Korn-Lubetzki and Brand, in their retrospective study of SC in Jerusalem published in this issue of *IMAJ* [4], report the occurrence of SC in 13% of children (24/180) diagnosed as having rheumatic fever during the years 1985–2002. This significant number of cases may represent a fraction of actual cases as the occurrence of SC usually reported is higher, occurring in approximately 26% to one-third of rheumatic fever patients [5]. Indeed, recent surveys from Brazil and Australia in the same years showed the incidence of SC in rheumatic fever patients to be 28–30% [6,7]. Since the appearance of SC may lag for months after GABHS infection, does not always occur with carditis or arthritis and has a relatively low frequency of elevated streptococcal antibodies and acute-phase reactants [8], the diagnosis of SC may be complicated. As this report is a retrospective study of rheumatic fever patients only, it may be possible that some chorea cases were not diagnosed as having a prior GABHS infection and are therefore not included in the report.

The clinical manifestations of pronounced SC create a fairly recognizable entity [5]. These include spontaneous involuntary movements affecting mainly the face and upper limbs, incoordination of skilled voluntary movements (e.g., fine motor activities and speech), and an occasionally severe general muscular weakness. Motor symptoms observed in patients with SC may include facial grimacing, swift protrusion of the tongue ("chameleon tongue"), speech abnormalities (e.g., dysarthria and explosive speech), loss of fine and gross motor control (e.g., deteriorated handwriting, ballismus and gait disturbance), and inability to maintain muscular contraction (e.g., "milkmaid's grasp"). Any portion of the body may be affected. While the classic symptoms are bilateral, SC may be unilateral (hemichorea) in a significant number of patients. Here, Korn-Lubetzki and Brand reported hemichorea in 21% of patients, concurring with previous figures in the literature [5].

Although SC is widely accepted as a major cause of chorea in children and young adults, it is by far not purely a movement disorder. The behavioral changes affecting the child with SC are well recognized. Patients with SC were historically described as having obsessive-compulsive traits, irritability and emotional instability. Psychiatric symptoms may present before, during, and after the neurologic presentation. In a systematic investigation of the psychological aspects of 11 children with SC (10 of whom had positive titers of antineuronal antibodies), all children exhibited concomitant psychological or psychiatric symptoms in addition to movement disorders. These included obsessive-compulsive symptoms (with four children meeting the diagnostic criteria for obsessive-compulsive disorder), increased emotional lability, hyperactivity, irritability, distractibility, and age-regressed behavior. These symptoms began well before the appearance of chorea and diagnosis of SC [9]. The present report from Jerusalem does not address this issue, but it is possible this was not feasible in a retrospective study.

The behavioral aspects of SC are of special interest, since the recognition of a relatively new entity regarding the neuropsychiatric aspects of GABHS infection, namely PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection). Debate exists regarding the association of PANDAS with SC and other disorders (e.g., Tourette's syndrome) and their role in the putative broad-spectrum neurologic phenomena after GABHS infection [10].

The criteria for the diagnosis of PANDAS include abrupt onset of episodic obsessive-compulsive disorder and/or tic disorder symptoms in the pediatric age range, temporally associated with GABHS infection. An association with neurologic abnormalities exists during symptom exacerbations, including "choreiform" movements, tics and hyperactivity, while the presence of frank chorea would suggest a diagnosis of SC, rather than that of PANDAS [11]. Indeed, in a comprehensive study of 50 patients diagnosed with PANDAS,

GABHS = group A beta hemolytic streptococcus
SC = sydenham's chorea

choreiform movements were observed in all 26 children undergoing formal testing for choreiform movements, with movements reported as "marked" in 50% of the children [11]. The main clinical feature distinguishing SC from PANDAS seems to be the chronic "sawtooth" exacerbation pattern of the latter [10], although recurrent SC is known to occur, as reported in 42% of the Jerusalem study [4].

Despite the progress that has been made in delineating the pathophysiologic basis for PANDAS as a separate entity, the clinical overlap between SC and PANDAS produces a challenge for the clinician who must make a decision regarding treatment options for a patient presenting with behavioral changes and choreiform movements. Due to the fact that the diagnosis of SC implies penicillin prophylaxis, and PANDAS does not, this is not a trivial issue.

Another possible factor linking rheumatic fever, SC and PANDAS involves a peripheral marker of susceptibility to rheumatic fever. The monoclonal antibody D8/17 reacts with a B cell alloantigen in 90–100% of patients with rheumatic fever, and thus may be considered to be a disease-specific marker for rheumatic fever [12]. D8/17 reactivity has been shown in SC, obsessive-compulsive disorder and Tourette's syndrome patients. In addition, D8/17 has been demonstrated to bind with increased rates to B cells in patients with PANDAS [13], however a recent study failed to demonstrate a value of D8/17 positivity in predicting later susceptibility to tics or obsessive-compulsive disorder [14].

As the title of the Jerusalem report implies, SC is here to stay. Moreover, SC is a clinical entity in progress, and as we understand more about the relationship of SC with closely related clinical entities we are bound to see changes in definitions, case inclusion criteria, and possibly in diagnostic criteria and treatment recommendations in the future.

PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection

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Capsule

Making and breaking prions

Chaperones and protein amyloids are involved in prion diseases, protein-based elements of inheritance, and mechanisms of learning and memory. Shorter and Lindquist describe in detail the multiple mechanisms by which the chaperone protein Hsp104 governs the inheritance of the yeast prion phenotype [PSI+]. Hsp104 has multiple reaction mechanisms, not just one. The nature of its interactions with the prion depends upon three things: the relative concentrations of the Hsp104 and the prion protein, the physical state of the prion protein when it interacts with Hsp104, and whether adenosine triphosphate (ATP) hydrolysis takes place. Prion oligomers are not only on the amyloidogenesis pathway, but are an obligate form for amyloid nucleation, being regulated stringently by Hsp104.

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