Sydenhamo chorėja ir PANDAS

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Santrauka. A grupės beta-hemolizinės streptokokinės (GABHS) infekcijos gali sukelti neurologinius sutrikimus vaikams. Sydenhamo chorėja yra vienas iš reumato diagnostinių kriterijų. Pastaruoju metu aprašoma vaikų neurologinių ir elgesio sutrikimų kombinacija, kurią blogina GABHS infekcija. Ši simptomų plejada pavadinta Pediatrinėmis autoimuninėmis neuropsichiatrinėmis ligomis, susijusiomis su streptokokine infekcija (PANDAS). Straipsnyje apžvelgiama šios būklės klinika ir diagnostiniai kriterijai.

Raktažodžiai: PANDAS, Sydenhamo chorėja, streptokokinė infekcija

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Sydenham's Chorea and PANDAS

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INTRODUCTION

Group A beta-hemolytic streptococcal (GABHS) infections are associated with the development of rheumatic fever in children. The diagnosis of rheumatic fever is based on the modified Jones criteria of 1992 [27] in which either two major criteria, or a combination of one major and two minor criteria are present, along with evidence of recent GABHS infection. The major criteria are carditis, chorea, erythema marginatum, migratory polyarthritis and subcutaneous nodules. The minor criteria are fever, arthralgia, prolonged PR interval on an EKG, and elevated acute-phase reactants (erythrocyte sedimentation rate and C-reactive protein). The central nervous system (CNS) manifestation of rheumatic fever is Sydenham's chorea.

More recently, a combination of neurologic and behavioral abnormalities in children have been described that worsen with GABHS infections. This constellation of symptoms and laboratory findings has been named Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection (PANDAS) [30, 31]. Many of the PANDAS symptoms are similar to symptoms seen in Sydenham's Chorea and thus suggest not only a possible common etiologic pathogenesis, but also more specifically, a common neurologic autoimmune disease process. However, until future research delineates more exactly common pathogenic processes, these must be kept distinct and separate, yet related, entities. This review article will address these two clinical entities, their similarities and dissimilarities.

SYDENHAM'S CHOREA

This neurologic condition was first described by Sydenham in 1684 as St. Vitus's dance [34]. It is worthwhile to review Sydenham's first description of this condition:

> "Chorea Santi Viti is a sort of convulsion, which chiefly invades boys and girls, from ten years of age to puberty. First it shews itself by a certain lameness, or rather instability of one of the legs, which the patient drags after him like a fool. Afterward, it appears in the hand of the same side which he that is affected with this disease, can by no means keep in the same posture for one moment, if it be brought to the breast, or any other part, but it will be distorted to another position or place by a certain convulsion, let the patient do what he can. If a cup of drink be put into his hand he represents a thousand gestures, like juglers, before he brings it to his mouth in a right line, his hand being drawn hither and thither by the convulsions, he turns it often about for some time, till at length happily reaching his lips, he flings it suddenly into his mouth, and drinks it greedily, as if the poor wretch designed only to make sport."

Sydenham aptly described the choreic movements and the clinical difficulties that these patients had from them. It is of interest that in his experience, the majority of cases started with a hemiparetic presentation, which is currently an unusual presentation.

The first suggestion that Sydenham's chorea was associated with rheumatic fever was by Stoll in 1780 [28]. The first published clinical observation of the relationship between rheumatic fever and streptococcal infections was by Fowler in 1880 [6] in which he described 20 cases of streptococcal infection preceding the onset of rheumatic fever. The usual onset of rheumatic fever symptoms was 2 to 3 weeks after tonsillitis or scarlet fever. Because of the relatively prolonged latency in the onset of Sydenham's chorea, typically between 3 and 5 months, but it can extend to 9 months [2, 35], the association between Sydenham's chorea and GABHS was recognized much later. It was only in 1965 that chorea was included in the Jones criteria for diagnosing rheumatic fever [29]. Approximately 25 to 30% of all cases of rheumatic fever develop chorea. Of those that develop chorea, in one-third other major manifestation of rheumatic fever, such as carditis, develop after the onset of chorea [35].

Immunologic investigations have suggested a possible autoimmune basis for the CNS manifestations of Sydenham's chorea. Husby demonstrated the presence of circulating IgG antineuronal antibodies in 46% of children with Sydenham's chorea [15]. The antigens recognized were neuronal cytoplasmic components preferentially located in the caudate and subthalamic nuclei. It was felt that the neuronal antigens were immunologically identified due to cross-reactive antigens found in the surface components of GABHS. These antibodies were present in lower frequency and in lower titers in children with rheumatic fever without chorea, and in normal controls. Since no structural changes have been identified pathologically in Sydenham's chorea, these antibodies may exert their effect by interfering with neurotransmitter production and release. Another immunologic investigation showed that 80% of patients with Sydenham's chorea have circulating antiphospholipid antibodies. It is possible that this finding may be due to GABHS M protein stimulation of T-cells and may thus simply be an epiphenomenon of GABHS infection [5].

Brain imaging studies also suggest that the locus of illness is the basal ganglia. MRI scans have shown that the T2-weighted images reveal increased signal in the caudate and putamen [14]. Quantitative MRI studies have shown an increase in the size of the caudate, putamen and globus pallidus, as finding that one would expect to see if there was ongoing autoimmune inflamation in these areas [10, 16]. With clinical improvement, the quantitative MRI findings also improved. SPECT scans revealed a similar picture of increased perfusion in the

thalamus and the basal ganglia during the acute phase of this illness, a finding that then gradually resolved with clinical improvement [3, 20].

As in many immunologic and autoimmune disorders, genetic factors are also important in Sydenham's chorea. In Sydenham's patients 26% have a family history of rheumatic fever, 3.5% have a parent with Sydenham's, and 2.1% have a sibling with Sydenham's chorea [1]. Also, there is an increased incidence of expression of the D8/17 B-cell alloantigen in patients with Sydenham's chorea, but not in systemic lupus erythematosus [4].

Clinically, Sydenham's chorea usually begins between 3 and 13 years of age with a slightly higher frequency in girls. The choreic movements affect mainly the face, hands and arms and usually start insidiously and inconspicuously. Gradually the movements become frequent and extensive, severely impairing the child's functional capacity, disappearing only during sleep. In addition, muscular weakness is prominent in the involved extremities, and actually, may be the most prominent aspect of the disorder. The muscular hypotonia can be demonstrated by having the patient extend the hands in front of the body. The wrist is flexed and the metacarpophlangeal joints are overextended producing the "choreic hand". The grip cannot be maintained and with forced contraction the strength of the finger varies producing the "milkmaid's grip". The deep tendon reflexes are normal, but the knee jerk tends to be "hung up"—meaning that the knee tends to momentarily remain extended after the patella is hit.

Approximately 18% of Sydenham's patients have hemichorea where there is a prominent asymmetry in the symptoms [1]. In paralytic chorea the weakness and hypotonia can be so prominent that even the chorea movements may disappear.

The chorea lasts from 1 month to 2 years. One third of patients have only one attack, whereas the others can have up to five attacks, despite adequate penicillin prophylaxis. There are extremely rarely reported complications of Sydenham's chorea, such as occlusion of the central retinal artery and pseudotumor cerebri. Complete gross neurologic recovery is the rule in this condition, but minor symptoms such as tics, chorea-like movements, tremors and incoordination may persist [7]. Behavioral disturbances, particularly OCD symptoms, occur quite commonly. In many instances, OCD symptoms had been noted before the onset of chorea.

In those children with severe chorea, medical treatment may be necessary. Phenobarbital, chlorpromazine and haloperidol had been used in the past. It appears that sodium valproate may be as effective, without the side effects of these other medicines. It should be used in anticonvulsant blood level dosages, and after tapered offer after 2 to 6 months of effectiveness. Sodium valproate is usually effective in 5 to 10 days of treatment.

PANDAS

Tic disorders, Tourette syndrome and obsessive-compulsive disorder (OCD) are neurologic disorders whose pathogenesis has been linked to abnormalities in the basal ganglia or the basal ganglia-thalamo-cortical circuits [8]. Also, tics and OCD symptoms are frequently seen in the same individual, or in other members of the family, such that these are considered by many investigators to be alternate manifestations of the same disease process [23, 36]. The pathogenesis of tic disorder and OCD seems to follow a similar pattern of genetic predisposition along with a triggering environmental factor. In these conditions, there is a genetic defect that renders the individual susceptible and then an inciting factor triggers the illness. One inciting factor appears to be GABHS.

The first description of bacterial infection associated with tics was by Selling in 1929 [25] when he described three children whose tic disorder started and exacerbated in association with sinusitis symptoms. Subsequently isolated case reports of acute onset of tics were associated with GABHS infection [19, 21]. Kiessling et al, in 1989, reported a sudden increase in the number of children with tic disorder in association with a community outbreak of GABHS

infection [17]. Using sera from these children, they found the presence of circulating antineuronal antibodies that were similar to ones found in Sydenham's chorea [18].

"Perseverativeness" of behavior was noted in early reports of Sydenham's chorea [7, 13]—a symptom that suggests the presence of OCD. In a report from the National Institutes of Mental Health, 70% of children with Sydenham's chorea have OCD symptoms [32]. Subsequently identification of 50 children was done, who had exacerbations of tic or OCD symptoms in association with GABHS infection and this led to the identification of the criteria for the diagnosis of PANDAS [31]:

1. Pediatric onset. In the majority of patients onset of symptoms is between 3 and 10 years.
2. Presence of tics and/or OCD. Each case must meet the lifetime diagnostic criteria for tic disorder and/or OCD according to DSM III-R or DSM IV criteria.
3. Episodic clinical course. The onset of a specific symptom exacerbation can often be assigned to a particular day or week, at which time symptoms acutely worsen in severity. Symptoms may resolve completely between episodes or continue at a lesser severity.
4. Symptom exacerbation must be associated with GABHS infection. Since streptococcal infections and tics are common in children, confirming an association between the two can be made only over time. At least two exacerbations must be observed and documented to occur shortly after a GABHS infection.
5. Adventitious movements. During symptom exacerbations, patients may have adventitious movements: motor hyperactivity and/or choreiform movements.

PANDAS does have clinical similarities to Sydenham's chorea [33]. Children with PANDAS have emotional lability with hyperactivity and inattentiveness, symptoms that are common in Sydenham's chorea. Also, children with PANDAS have abnormal motor movements of their hands that are similar to mild chorea. Eventhough there are clinical similarities, these two conditions should be clearly differentiated. There have been no cases of PANDAS that have had rheumatic carditis, whereas up to 60% of Sydenham's chorea patients have carditis [8]. With Sydenham's chorea the primary pathogenic mechanism appears to be a GABHS triggered autoimmune process, in PANDAS, the autoimmune mechanism is less direct.

As mentioned previously in a MRI study of 24 patients with Sydenham's chorea, there was an increase in the size of the caudate, putamen and globus pallidus [10]. In a case report of one PANDAS patient treated with plasmapheresis treatment, with treatment there was clinical improvement and a decrease in the size of the caudate, putamen and globus pallidus volumes on MRI scanning [11]. In a subsequent larger study of 34 PANDAS patients, similar MRI findings were made: there is a significantly increase in the size of the basal ganglia nuclei, but not of other brain regions [12].

Investigations of immunogenetic factors also revealed similarities between these two conditions. As mentioned previously, there is a high incidence in the B cell expression of the DR surface antigen D8/17 in Sydenham's chorea, but not in other rheumatologic conditions [4]. Similar findings have been reported in PANDAS where 85% of patients were positive [31], and in another study of childhood-onset OCD, where 100% were positive [22].

As mentioned above, there has been a report identifying the presence of circulating IgG anti-neuronal antibodies in Sydenham's chorea that specifically recognize cytoplasmic antigens in the basal ganglia [15]. Using similar immnocytochemical techniques, these results were confirmed in 19 of 20 Sydenham's chorea patients in whom the titers of these antibodies fell when clinical symptoms improved [33]. Similar antibodies were identified in children with PANDAS, but not in the siblings of the patients [30]. Anti-neuronal antibodies have also been identified by two different group of researchers in children with tic disorders [18, 26]. However,

these antibodies are present in up to 50% of normal individuals, indicating that they are not particularly specific for these conditions. Further, there was no relationship to the presence of anti-neuronal antibodies and various clinical parameters including tic severity, duration of illness, family history, presence of inattentiveness, hyperactivity or of OCD symptoms [26]. Thus, although circulating anti-neuronal antibodies may play a role in the pathogenesis of Sydenham's chorea and PANDAS, the exact mechanism is far from clear.

Possibly the strongest evidence for an autoimmune basis for PANDAS is clinical reponsiveness to immunologic treatments. There is an early report of two children with post-streptococcal tic disorder responded to adrenocortricosteroid and prednisone treatment, with relapses when the steroids were discontinued [21]. In a controlled study comparing intravenous immunoglobulin (IVIG) and plasmapheresis, PANDAS children treated with intravenous immunoglobulin (IVIG) tended to respond within 3 weeks, and the effectiveness lasted up to a year or more [24]. A similar response was seen with the use of plasma exchange. It appeared that tic symptoms responded better to IVIG, whereas OCD symptoms responded equally with both modes of treatment. A program of prophylactic penicillin to prevent GABHS infections and secondary worsening of PANDAS symptoms was not effective in 37 studied children [9].

CONCLUSION

Although there are clinical similarities between Sydenham's chorea and PANDAS, and both are associated with GABHS infection, their clinical coarse and pathogenic mechanism are different. Therefore, until such time as future research delineates otherwise, it is important to maintain a clear distinction between these two clinical entities.

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