Sydenham chorea: a practical review of current literature

Corea de sydenham: revisión práctica de la literatura actual

Abstract

The immune-mediated movement disorders have accompanied us throughout history. Sydenham’s chorea is the most common cause of chorea acquired during infancy. Despite its clear association with rheumatic fever, the pathogenesis of Sydenham’s chorea has not been fully elucidated. Autoimmune mechanisms are thought to play a key role in the production of antineuronal antibodies. Cross-reaction between Streptococcus pyogenes proteins and proteins expressed in the striated body would be explained by molecular mimicry. The clinical manifestations of Sydenham’s chorea are diverse. The diagnosis and treatment of Sydenham’s chorea require a multimodal approach.

The present work is a practical and detailed review of the literature of Sydenham’s chorea, including the clinical, pathophysiological and therapeutic aspects of the disease.
Resumen

Los trastornos del movimiento inmuno-mediados nos han acompañado a lo largo de la historia. La corea de Sydenham, el más frecuente de estos trastornos, fue descrito en el siglo XVII y aún es reconocida como la causa más común de corea adquirida durante la infancia. A pesar de su clara relación con la fiebre reumática, la patogénesis de la corea de Sydenham no ha sido completamente dilucidada. La similitud entre determinantes antigénicos de proteínas del estreptococo beta hemolítico del grupo A y proteínas neuronales ubicadas en los núcleos basales del huésped podrían llevar a una reacción inmune cruzada y explicar las anormalidades funcionales y parte de las manifestaciones clínicas, motoras y cognitivas, descritas en este trastorno. Las manifestaciones clínicas de la corea de Sydenham son diversas por lo cual el diagnóstico y el tratamiento a menudo requieren enfoques multimodales.

En la presente revisión se realiza una descripción práctica y detallada de la literatura actual sobre la corea de Sydenham enfatizando en aspectos clínicos, fisiopatológicos y terapéuticos.

Palabras clave

Corea, corea de Sydenham, fiebre reumática.
Introduction

Sydenham Chorea (SC) is the most common cause of chorea acquired in childhood and is the first diagnosis that should be considered in a child with acute onset generalized chorea.\textsuperscript{1,2} The first description of SC was made by Gowers, but Thomas Sydenham in 1686 was the first person to make a complete and detailed description of the disease.\textsuperscript{3,4} In the eighteenth century, it was finally possible to establish a clear association between SC and Rheumatic Fever (RF).\textsuperscript{5} In 1944, Jones designed and published the well-known diagnostic criteria for RF, including chorea as one of the main clinical manifestations or major criteria.\textsuperscript{6,7} Since then, SC is considered one of the clinical forms of RF. Today, SC is part of the so-called immune-mediated movement disorders alongside with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, anti-NMDA encephalitis, some forms of systemic lupus erythematosus, antiphospholipid syndrome, and a variety of other lesser-known diseases.\textsuperscript{8-11}

Objective

To make a practical and detailed description of the current literature on Sydenham chorea, emphasizing clinical, pathophysiological, and therapeutic aspects.

Methodology

We searched the literature in the PubMed database using combinations of the following keywords in English: “Chorea,” “Sydenham,” “Sydenham’s chorea,” “Poststreptococcal chorea,” “Immune-mediated chorea,” “Autoimmune chorea,” and “Immune-mediated extrapyramidal movement disorders.” Additional articles were found through the references in the articles from the PubMed search. Publications were selected in English and Spanish. We reviewed 119 articles, of which 67 were selected that described clinical characteristics and diagnostic approaches and are summarized below.

Epidemiology

It is estimated that 10% to 30% of patients affected by RF develop SC, usually with a latency period of 8 to 12 months. This is reflected in an annual incidence that ranges between 300,000 and 350,000 cases/year.\textsuperscript{12} The most frequent age of SC presentation is between 5 and 14 years old, and a ratio of two girls for each affected boy has been described in some studies.\textsuperscript{8,11,13}

The incidence of RF and SC has decreased dramatically in recent decades in developed countries, but in developing countries, however, these two diseases continue to represent public health problems.\textsuperscript{14,15}

Pathophysiology

Sydenham chorea has been associated with the development of antineuronal antibodies secondary to group A beta-hemolytic streptococcal (GABHS) infection.\textsuperscript{16-19} GABHS is a Gram-positive coccus that is grouped in chains, has a capsule, and its wall is constituted by carbohydrates, proteins, and lipoteichoic acid. This microorganism is microaerophilic and catalase negative and does not belong to the normal flora of the nasopharynx. Initially, GABHS colonizes the upper respiratory tract and initiates its infectious process in the pharynx, where it triggers an immune response mediated by circulating cells which, in certain cases due to molecular mimicry, induce a crossed autoimmune response against structural proteins of their own.\textsuperscript{18,19} The molecular mimicry implies structural similarity between some component of the infectious agent and endogenous proteins of the human being, in such a way that the antibodies and the activated T cells not only react against the infectious agent but also react against the endogenous structural proteins.\textsuperscript{18-20}

The basal nuclei have been implicated as the primary target of post-infectious immunity.\textsuperscript{8,12} In fact, several studies suggest that the
development of basal antinuclear antibodies and anti-streptococcal IgM antibodies have a direct pathogenic role by inducing functional changes in the caudate nuclei, accumbens, and in the motor cortex—brain structures involved in motor control and behavior. On the other hand, there is evidence suggesting that specific antibodies directed against neuronal tubulin would be an important target in the pathogenesis of SC. Other antibodies described are: glycolytic enzyme antibodies, anti-gangliosides, and anti-dopamine receptors D1 and D2. The cell signaling mediated by anti-D2 antibodies could lead to an excess in the release of dopamine that would be clinically reflected with the development of abnormal movements.

In general, all anti-neuronal antibodies are related to the activity of the disease and the number or duration of choreic attacks, but not to the severity of the illness. The chronicity of the disease seems to be caused by the activation of monocytes and by the susceptibility that persists in some neurons that encounter circulating anti-neuronal antibodies after infection. The previous physiopathological mechanisms have not only been linked to the appearance of SC, they have also been observed in other disorders of the central nervous system such as Tourette syndrome, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, anorexia nervosa, autism spectrum, encephalitis of diverse origins, acute disseminated encephalomyelitis, and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).

**Clinical manifestations**

The clinical manifestations of SC are diverse and include neurological, neuropsychiatric, and rheumatic manifestations.

**a. Neurological manifestations:** chorea is the main characteristic of this disease. The term chorea comes from the Greek “κορεία” (chorea) which means dance and reflects the phenomenology of this disorder. Chorea is characterized by involuntary, non-stereotyped, abrupt, rapid movements, usually of low amplitude, without any rhythm or purpose, that occur both at rest and in action and that flow from one part of the body to another, affecting it in an asymmetric, asynchronous way. Although chorea is typically generalized, up to 20% of cases can present unilaterally. The movements are usually exacerbated by stress, improve with relaxation, and disappear during sleep. The most affected regions of the body are the extremities, but it can also compromise the neck, face, and trunk. Eye movements may be affected in some cases, especially when there are abnormalities in the connections between the basal nuclei and the superior colliculus. The onset of chorea is usually insidious, but it can occur abruptly. Unlike carditis and arthritis which appear in the first three weeks after GABHS infection, chorea has a variable and often longer latency period of between eight weeks and eight months, so it can even be presented as an isolated finding. Other neurological signs and symptoms include athetosis, ballism, ataxia, gait disturbance, dressing apraxia, swallowing disorders, decreased verbal fluency, impaired language comprehension, and dysarthria. Less than 2% of patients present with generalized hypotonia called "paralytic chorea" or “chorea mollis.” Tics have also been described, but their characteristics are different from those in Tourette syndrome. When choreic symptoms occur in pregnancy, it is called “chorea gravidarum.” The neurological manifestations do not typically persist for more than eight months, although a variable number of cases have been reported with manifestations lasting more than two years.

**b. Neuropsychiatric manifestations:** often precede the development of chorea although they may present simultaneously or rapidly, sequentially. These manifestations include: emotional lability, obsessive-compulsive traits and disorder, anxiety, sleep and behavior disorders, and even psychotic disorder, as well as attention-deficit/hyperactivity disorder. Some cases have been described in the pediatric population.
c. Rheumatic manifestations: symptoms such as polyarthritis, carditis, marginal erythema, and subcutaneous nodules appear around three weeks after the onset of pharyngitis on average. These neuropsychiatric manifestations greatly impact the quality of life of these patients and are an important cause of long-term disability, which is why they require a multidisciplinary approach including psychiatry, psychology, and neurology.

Diagnosis

The diagnosis of chorea is clinical and is based exclusively on semiological evaluation. To consider a diagnosis of SC, the evaluation should initially focus on confirming the diagnosis of RF, which includes measurement of anti-GABHS antibodies and a cardiac evaluation. Inflammatory markers should be measured, although their value is limited due to the prolonged latency between the infection and the appearance of chorea. The anti-GABHS antibodies decrease significantly in the following two months after infection. It is also necessary to exclude other causes of chorea, especially lupus erythematosus, since about 2% of these patients can develop chorea and present a relapsing-recurrent course, although they usually also present other neurological and extra-neurological manifestations. Table 1 Other complementary tests include throat culture, erythrocyte sedimentation rate, C-reactive protein, and biomarkers such as anti-streptolysin O or anti-DNase B. The throat culture can confirm the presence of GABHS, but it’s positive in less than 15% of patients with chorea. Despite this, it is recommended that the culture be performed in all cases. The anti-streptolysin O reaches its maximum peak from three to five weeks after the onset of pharyngitis and gradually decreases during the following weeks. The anti-DNase B titer reaches a peak between eight and twelve weeks, and remains high for weeks or months and even up to a year. The percentage of elevation of the biomarkers varies from 15% to 80%. Basal antinuclear antibodies have also been described and a sensitivity close to 92% is estimated but with low specificity. The cerebrospinal fluid is usually not altered so it is not necessary to perform this test in patients with clear suspicion of SC; however, in cases with atypical features, such as altered consciousness, a lumbar puncture should be performed to rule out alternative diagnoses. Neuroimaging is also reserved for atypical cases including hemichorea. Brain magnetic resonance is usually normal, although there have been descriptions of findings such as regions of abnormal intensity in the white matter and selective enlargement of the caudate, putamen, and globus pallidus nuclei which could be related to an underlying inflammatory process during the acute phase. In studies performed with positron emission computed tomography and single photon emission tomography, striatal hypermetabolism and hyperperfusion have been demonstrated in the basal nuclei during and even after the acute episode of SC.

Treatment

The treatment of SC requires a multimodal approach, which includes medication and therapy for chorea and other neuropsychiatric manifestations, as well as treatment to reduce the rheumatogenic potential of GABHS infection and, finally, antibiotic prophylaxis. Although at the time of diagnosis of chorea there might be no evidence of active pharyngitis, it is recommended to administer a 10-day oral penicillin V regimen or a dose of intramuscular penicillin G benzathine to prevent recurrence, reduce the risk of rheumatic heart disease, and spread of virulent strains.
The treatment is based on two physiopathological principles. The first is the correction of a neurochemical imbalance in the basal nuclei, and the second is the reduction of inflammation. The recommendations regarding the treatment to be used are based on the interference that chorea has in the activities of the patient’s daily life. If the interference in the activities of daily life is mild, the use of medication may not be necessary because the natural course is usually toward remission; however, some authors believe that these patients could benefit from the use of valproic acid, carbamazepine, clonidine, or guanfacine. These drugs’ side effects profiles are more tolerable than those of drugs reserved for more symptomatic cases. It has been demonstrated that patients affected by chorea show an increase in dopaminergic activity, as well as deficiency in cholinergic and GABAergic activity. It seems that valproic acid influences through GABA stimulation in the suppression of motor symptoms. It is recommended to start valproic acid at low doses such as 250 mg twice a day and titrate according to efficacy and tolerability up to 1500 to 2000 mg daily. The same principle applies for carbamazepine. Carbamazepine at a dose of 15 mg/kg/day has been shown to be as effective as valproic acid at 20-25 mg/kg/day.

### Table 1. Differential diagnosis for sydenham chorea.

| | 2. Huntington's chorea.  
| | 2. Stroke.  
| | 3. Antiphospholipid syndrome.  
| | 5. Moyamoya disease.  
| | 2. Hypocalcemia.  
| | 3. Hypo/hypernatremia.  
| | 5. Hyperosmolality.  
| | 6. Hepatopathies.  
| Post-infectious: | 1. Viral encephalitis.  
| | 2. Epstein-Barr virus infection.  
| | 3. Human immunodeficiency virus infection.  
| | 2. Gangliosidosis.  
| | 3. Lesch–Nyhan syndrome.  
| | 4. Niemann-Pick disease type C.  
| Other: | 1. Chorea, drug-induced.  
| | 2. Toxins (carbon monoxide, methanol, manganese).  
| | 3. Paraneoplastic tumors.  
| | 4. Chorea after cardiac surgery.  

day to achieve remission of chorea.\textsuperscript{56} In more symptomatic cases, when chorea generates greater interference in the activities of the patients’ daily life—in particular if there are gait abnormalities—as well as in those patients who do not respond to initial management, a short course of dopamine receptor blockers D2, high potency but at low doses, such as haloperidol and risperidone, is recommended.\textsuperscript{14} Risperidone is preferred over the other D2 blockers due to its better tolerability profile. This medicine can be started at a dose of 1 mg twice a day and increased to 2 mg twice a day if there is no adequate control of chorea.\textsuperscript{14} It is important to be alert to the possibility of the appearance of other abnormal movements such as akathisia and dystonia, which are potentially inducible by drugs that block dopamine receptors.\textsuperscript{57} If these complications appear, the use of anticholinergic drugs such as benztropine and diphenhydramine is recommended.\textsuperscript{57} Once the remission of chorea is achieved, a gradual decrease in the doses of these drugs can be initiated until they are suspended.\textsuperscript{14,56} Although there are no guidelines on the proper way to perform this drug clearance, some authors recommend reducing 25% of the dose every two weeks after at least one month of chorea remission.\textsuperscript{14}

Immune modulation therapy has been used in moderate to severe cases. Suppression with corticosteroids is a reasonable therapeutic option, although controversial.\textsuperscript{58,59} In comparative studies, the use of corticosteroids has been shown to reduce the duration of symptoms.\textsuperscript{58,59} The most frequently used scheme has been oral prednisone at a dose of 1-2 mg/kg/day for two weeks, continuing with a progressive reduction during the following two to three weeks.\textsuperscript{58} The use of methylprednisolone has also been described for patients with SC associated with severe carditis or in cases of SC refractory to the therapies described above. The doses are 25 mg/kg/day in children, and 1 gram daily in adults, for five days, followed by prednisone at a dose of 1 mg/kg/day.

In severe cases, intravenous immunoglobulin or plasmapheresis has been used.\textsuperscript{60,61} However, the data regarding efficacy are limited. Different studies have found that both therapies reduce the time of symptoms but do not decrease the risk of relapse.\textsuperscript{60,61} It has also been described that treatment with plasmapheresis or immunoglobulins could be more effective in patients in whom circulating serum antineuronal antibodies presence is demonstrated. One study compared the use of plasmapheresis, immunoglobulins, and corticosteroids, and found that patients who received immunoglobulin and plasmapheresis had a significant improvement in chorea, superior to that described with the use of corticosteroids.\textsuperscript{62}

### Prophylaxis

Prophylaxis is the most important therapeutic measure to prevent recurrences of RF and SC and to decrease the risk of developing neuropsychiatric symptoms. It has been shown that prophylaxis with intramuscular penicillin G is more effective than oral penicillin and should be applied every two to three weeks. The duration of treatment is controversial and dependent on cardiac involvement.\textsuperscript{53} In patients without proven carditis, it is recommended that the antibiotic be administered for five years after the most recent episode of chorea, or if the person is under 13 years of age to prolong the treatment until 18 years of age, preferring the most long-term therapeutic scheme.\textsuperscript{53} Patients with carditis (mild mitral regurgitation or resolved carditis) should continue therapy for 10 years after the most recent episode of chorea or up to 25 years of age—again preferring the longer treatment schedule—while those patients with severe valvular disease or those who underwent valvular surgery should receive antibiotic therapy all their life.\textsuperscript{53} The World Health Organization (WHO) recommends that secondary prophylaxis be extended to 21 years, without clarity as to the duration of treatment after that age.\textsuperscript{63} Other authors consider that due to the risk of serious cardiac complications, prophylaxis should be maintained indefinitely.\textsuperscript{14}
Prognosis and recurrence

The time of resolution of SC manifestations is variable. Initial studies described that most patients with SC recovered completely in the first six weeks and almost all in the following six months. However, though the most recent studies described that in the majority of patients the neurological manifestations would spontaneously self-limit, in others it took years before they were completely resolved. In a study conducted in Brazil that included 69 patients, it was evidenced that the choreic movements remitted in 62.3% of the patients during the first year since the onset of symptoms.

Recurrence of symptoms occurs in approximately 25% of patients and is mainly due to a new exposure to GABHS. An increased risk of recurrence of the disease has also been described if complete remission of SC is not achieved within the first six months or if any neurological symptoms persist for more than a year. Pregnancy and the use of oral contraceptives have also been associated with SC recurrence, which should be reported to patients with a history of this disease.

Discussion

Today, SC is recognized as part of the immune-mediated disorders, in fact, the most representative and known of them. However, its pathogenesis and other aspects have not been fully clarified. After the description of 50 cases by Swedo et al. in 1998, the importance of mentioning the emergence of the diagnosis of PANDAS was born, due to its close similarity with SC and the relationship with GABHS and a probable autoimmune basis. It is important to recognize the clinical manifestations, not only neurological, but also neuropsychiatric. Despite the fact that the first descriptions of the disease surfaced several centuries ago, in many cases the diagnosis of SC is made late even today. In fact, since the earliest descriptions, SC was confused with hysteria. Currently, one of the reasons for its diagnosis delay is that it can be confused with behavioral or psychogenic disorders. Furthermore, the treatment relies on clinical analysis and judgment, since it will be chosen depending on the severity of the manifestations or on their interference in the activities of daily life.
Conclusions

Rheumatic Fever remains a public health problem in developing countries. An important percentage of these cases will have a neurological manifestation of Sydenham Chorea, so it is fundamental to take it into account in the spectrum of syndromes of this infection. Clinical evaluation is the main tool for the diagnosis of this pathology and it is vitally important to recognize the various manifestations and keep in mind the associations and similarities with other disorders. Currently, there is a lack of specific laboratory diagnostic tools for SC. Thanks to the deeper understanding of the physiopathology and the use of molecular studies in recent decades, the possible usefulness of measuring specific antibodies for SC has appeared with a promising future, but its role still remains a controversial issue.

Conflicts of interest
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References


