Review Article

Sydenham’s Chorea: A Practical Overview of the Current Literature

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Sydenham’s chorea is characterized by uncoordinated movements, emotional instability, and hypotonia. It can occur up to several months after group A β-hemolytic Streptococcus infection. A diagnosis of Sydenham’s chorea in a patient with acute chorea involves an application of the Jones criteria and the exclusion of other causes of chorea. In patients with an atypical history or hemichorea, cranial magnetic resonance imaging is indicated to exclude other cerebral pathologies. A pathogenesis has not been elucidated, and therapy has not been investigated in placebo-controlled trials. Antibiotic treatment and a 2-week or 3-week schedule of antibiotic prophylaxis are recommended. If the chorea is severe, valproate or carbamazepine can be effective. In more severely affected patients, dopamine receptor blocking agents or corticosteroids can be used. © 2010 by Elsevier Inc. All rights reserved.


Introduction

Sydenham’s chorea is the most common form of acquired childhood chorea, and represents one of the major diagnostic criteria of rheumatic fever, caused by a group A β-hemolytic Streptococcus infection [1]. Sydenham’s chorea is named after the British physician Thomas Sydenham, who first described the syndrome in 1686 under the name “Saint Vitus dance” [2].

Because of improved socioeconomic and sanitary conditions, along with the widespread use of penicillin, the incidence of both Sydenham’s chorea and rheumatic fever has declined dramatically in developed countries. However, in less affluent countries, Sydenham’s chorea and rheumatic fever remain serious health concerns [3]. Moreover, in developed countries, epidemics and isolated cases still occur [4-6]. Familiarity with Sydenham’s chorea is therefore required of physicians, especially because Sydenham’s chorea can be a marker of life-threatening carditis. We present a practical overview of Sydenham’s chorea, from its diagnostic process and pathogenesis to treatment, based on all English-language articles from the last 20 years according to a literature search in PubMed, using the search term “Sydenham chorea.”

Clinical Characteristics and Diagnosis

The majority of patients with Sydenham’s chorea present at age 5-15 years, with a female preponderance [5,7-10]. Sydenham’s chorea is characterized by unwanted nonstereotyped choreatic movements, which disappear during sleep. Although all muscles may be involved, with the exception of the eye muscles, an involvement of the face and extremities is most typical [11]. The chorea is usually generalized, although hemichorea occurs in 20-35% of patients [12,13]. Neuropsychiatric signs such as emotional lability, obsessive-compulsive signs, anxiety, and attention deficit often precede the chorea [2,6,14]. These neuropsychiatric signs occur frequently, and can lead to major dysfunction [2,6,14,15]. One common sign is motor impersistence, which can be demonstrated by an inability to sustain eye closure or tongue protrusion [16]. Other associated signs include grimacing, clumsiness, dysarthria, difficulty in dressing, writing, and feeding, muscle weakness, and hypotonia [13,14,16-19]. Rarely (in <2% of cases), these patients become bedridden because of generalized hypotonia, the so-called “chorea paralytica” [2,20]. The severity of Sydenham’s chorea can be...
assessed using the Universidade Federal de Minas Gerais Sydenham’s Chorea Rating Scale (Online Table 1) [21].

Sydenham’s chorea is present in 10-30% of patients with rheumatic fever [5,8,22-25]. The clinical criteria for rheumatic fever, i.e., the Jones criteria, were formulated in 1944 by the American Heart Association (Table 1) [1]. In contrast to other manifestations of rheumatic fever, such as arthritis and carditis, which emerge 1-3 weeks after group A β-hemolytic Streptococcus infection, Sydenham’s chorea can present up to several months after infection [2]. A wide variance in the frequency of accompanying major signs was reported in the literature. Sydenham’s chorea is accompanied by carditis in 40-80% of patients, and by arthritis in 10-30% of patients. In 20-70% of patients, chorea is the only manifestation [7,10,12,13,16,18,23,26-29].

A throat culture can confirm a preceding group A β-hemolytic Streptococcus infection. However, this culture is positive in only a minority of cases (<15%) [24,28]. More often, serum analysis can demonstrate an elevation of the erythrocyte sedimentation rate, of the C-reactive protein concentration, or of the anti-DNase B titer. The antistreptolysin-O titer peaks at 8-12 weeks, and remains elevated for weeks or months. The percentage of patients with an elevation of these markers, according to the literature, varies from 15-80% [6,22,28,29]. The presence of anti-basal ganglia antibodies can be determined using Western immunoblotting, with a sensitivity of 92.5% and a specificity of 94.7%, although these reported percentages also vary [30-33].

Cerebrospinal fluid analyses usually produce normal results. An electroencephalogram often produces nonspecifically abnormal results, with general slowing and some posterior prominence [2,18,29,34]. Imaging studies demonstrated that the results of computed tomography are virtually always normal [8,12,17,18,29]. Magnetic resonance imaging can sometimes reveal abnormalities consisting of basal ganglia enlargement and increased signal intensity on T2-weighted images during the acute phase of Sydenham’s chorea. Some studies reported recovery of these abnormalities 6-14 months after the onset of Sydenham’s chorea. Persistence of lesions in the basal ganglia seems correlated with a more prolonged course of the disease [12,14,17,19,35-41]. Reversible striatal hypermetabolism and striatal hyperperfusion or hypoperfusion were detected in some patients, using positron emission tomography and single-photon emission computed tomography, respectively [36,39,40,42-44]. Imaging often appears normal in patients with Sydenham’s chorea. However, imaging is a good tool for excluding other causes of chorea (Fig 1).

A diagnosis of Sydenham’s chorea is largely presumptive in some cases, based merely on the clinical manifestations of chorea in young patients, and by the exclusion of systemic lupus erythematosus, drug intoxication, Wilson’s disease, familial chorea (including Huntington’s disease), and hormonal causes such as hyperthyroidism. An association with chorea gravidarum and oral contraceptive-induced chorea was also described [45-47].

Pathogenesis

Sydenham’s chorea is caused by antibodies against group A β-hemolytic Streptococcus bacteria, which cross-react with the basal ganglia, and which are therefore called anti-basal ganglia antibodies [31,48,49]. Two group A β-hemolytic Streptococcus antigens were identified. The M protein is located on the outer surface of streptococcal fimbria, and immunoglobulins directed against this M protein cross-reacted with brain proteins. The second cross-reactive antigen is N-acetyl-β-D-glucosamine, the immunodominant epitope of the group A carbohydrate. Sydenham’s chorea antibodies specific for N-acetyl-β-D-glucosamine were observed to cross-react with mammalian gangliosides. Gangliosides are glycolipids with specific developmental and differential expressions within the brain, and they contribute to multiple functions mediated at the cell surface, including signal transduction [50-52].

Anti-basal ganglia antibodies are hypothesized to alter the corticostriatal circuits, leading to basal ganglia dysfunction. This phenomenon causes motor signs via putamen involvement, and behavioral disturbances via caudate involvement and cortical dysfunction. An animal model demonstrated the pathogenicity of these antibodies through the passive transfer of immunoglobulin G, which resulted in repetitive behavior and movements [53]. In patients with Sydenham’s chorea, 83% manifest anti-basal ganglia antibodies in cerebrospinal fluid [30]. Pathologic studies demonstrated neuronal loss, arteritis, endothelial swelling, perivascular round-cell infiltration, and petechial hemorrhages in the basal ganglia [2].
Sydenham’s chorea cannot occur without group A β-hemolytic Streptococcus pharyngitis. There may be an inherited predisposition to respond to the infection with the production of autoantibodies directed at the brain. This predisposition was suggested by the clustering of Sydenham’s chorea in families, and by a more frequent presence of the D8/17 alloantigen in the B lymphocytes of patients [2,22,54-57].

In the 1990s, a localized increase in the number of children presenting with tics after a localized epidemic of group A β-hemolytic Streptococcus pharyngitis led to the concept of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. The criteria for this group of disorders are outlined in Table 2 [58]. However, a link between pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and both group A β-hemolytic Streptococcus and Sydenham’s chorea remains to be proven. A detailed description of this concept is beyond the scope of this review. The reader is referred to several previous reviews and commentaries [59-65].

**Treatment**

No large, placebo-controlled, randomized trials have been performed in patients with Sydenham’s chorea. Most descriptions of treatment were contained in case reports, and only a few of these entailed more than 15 patients. However, the majority of studies described a treatment regime in three parts: (1) treatment of the underlying infection, (2) prophylaxis, and (3) symptomatic treatment.

**Treatment of Group A β-Hemolytic Streptococcus Infection**

Treatment of group A β-hemolytic Streptococcus infection is recommended, although substantial evidence is lacking that antibiotic treatment is effective, and most patients no longer harbor a symptomatic pharyngitis by the time the chorea becomes evident. A full 10-day course of oral penicillin V therapy or an injection of benzathine penicillin G provides effective treatment for patients with
symptomatic or nonsymptomatic group A β-hemolytic Streptococcus infection. This course of treatment also reduces the pathogenic potential of rheumatogenic group A β-hemolytic Streptococcus strains carried in the pharynx, and prevents the spread of virulent strains [2].

**Prophylaxis**

Antibiotic prophylaxis is the most important therapeutic measure to prevent a recurrence of acute rheumatic fever. Gebremariam [66] and al-Elissa [67] indicated that penicillin G prophylaxis reduces recurrence, compared with no prophylaxis. This finding implies that recurrent carditis and progression to heart failure are prevented, as are recurrent bouts of Sydenham’s chorea and the risk of psychiatric signs. Intramuscular penicillin prophylaxis seems more effective than oral penicillin [68,69]. An injection of benzathine penicillin G every two or three weeks seems preferable to an injection every four weeks, because of consistent findings that rheumatic fever recurs less frequently in those who received the injection every two or three weeks compared to every four weeks [68-72]. The World Health Organization formulated indications for the duration of prophylaxis, depending on the patient’s cardiac condition (Table 3) [73].

**Treatment of Chorea and Neuropsychiatric Signs**

The chorea often requires no specific treatment, because in most cases it is a benign, self-limiting condition with a mean duration of 2-4 months [74]. However, for patients in whom the chorea is debilitating and protracted, treatment is necessary.

**Table 3. Duration of prophylaxis**

<table>
<thead>
<tr>
<th>Category of Patients</th>
<th>Duration of Prophylaxis</th>
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<tbody>
<tr>
<td>Patients without proven carditis</td>
<td>For 5 years after most recent attack, or until age 18 years (whichever is longer)</td>
</tr>
<tr>
<td>Patients with carditis</td>
<td>For 10 years after most recent attack, or at least until age 25 years (whichever is longer)</td>
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<tr>
<td>(mild mitral regurgitation or healed carditis)</td>
<td></td>
</tr>
<tr>
<td>More severe valvular disease</td>
<td>Lifelong</td>
</tr>
<tr>
<td>After valve surgery</td>
<td>Lifelong</td>
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Treatment of choreatic movements is based on two principles: (1) a pharmacologic correction of the neurochemical imbalance within the basal ganglia, and/or (2) a reduction of inflammation within the brain structures:

(1) The abnormal movements may be the result of excessive dopaminergic neurotransmission and a deficit of cholinergic and γ-aminobutyric acid neurotransmission in the basal ganglia. Valproate stimulates γ-aminobutyric acid activity, effectively suppressing the motor signs [26,54,75-79]. Several studies demonstrated that haloperidol, pimozide, and tiapride can effectively reduce choreatic signs by blocking dopamine receptors [13,17,76,77,80]. Good results were also reported using tetrabenazine and carbamazepine [54,76,81-83]. Based on these studies, we conclude that there is no specific first-choice drug. However, because of the more numerous side effects, dopamine receptor blockers should only be used in patients who do not respond to valproate, or in those rare patients with chorea paralytica [46,77].

(2) Because of the autoimmune pathogenesis of Sydenham’s chorea, anti-inflammatory medications such as salicylates and corticosteroids can effectively reduce movement abnormalities [7,84-88]. In general, corticosteroids should only be used in chorea paralytica, when conventional medication produces no response or when unacceptable side effects occur. This precaution is recommended because of the side effects of corticosteroids, and because most patients respond well to conventional medications with a more favorable side-effect profile [89].

The presence of autoantibodies suggests that intravenous immunoglobulin therapy or plasma exchange may be beneficial, because both therapies aid the clearance of abnormal antibodies. A small-scale study indicated that these therapies shorten the course of Sydenham’s chorea [88]. However, because of the efficiency of available medications, and the potential complications and high costs of these alternative treatments, intravenous immunoglobulin and plasma exchange are not recommended.

All these treatments also alleviate psychiatric signs. Even without therapy, the psychiatric signs are usually short-lived and bearable. If these signs are severe and resistant to antichoreatic mediation, benzodiazepines or phenobarbital can be beneficial. In some patients, antidepressive drugs are helpful. Selective serotonin reuptake inhibitors are particularly effective in alleviating obsessive-compulsive signs [2].

**In Practice**

Sydenham’s chorea is characterized by uncoordinated movements, emotional instability, and hypotonia. To diagnose Sydenham’s chorea in a patient with acute chorea (Fig 1), the Jones criteria should be applied. Especially when evidence of an antecedent group A Streptococcus infection is lacking, laboratory tests should include thyroid, renal, and hepatic function, ceruloplasmin levels, rheumatoid factor and antinuclear antibodies, and an erythrocyte count, to exclude other causes of chorea.
Although imaging reveals no abnormalities in most patients with Sydenham’s chorea, imaging is useful for excluding other causes of chorea, e.g., infarction of the basal ganglia. Cranial magnetic resonance imaging is therefore recommended, especially when a patient’s history is atypical. Antibiotic treatment and a 2-week or 3-week schedule of antibiotic prophylaxis are recommended. If the chorea is severe, the most effective treatment involves agents affecting or blocking dopamine (pimozide, haloperidol, or tiapride). An alternative is tetrabenazine. As a third option, valproic acid (first choice because of side effect profile) or carbamazepine or corticosteroids can be used.

References


