Recurrence of Sydenham Chorea

Implications for Pathogenesis

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Background: Sydenham chorea (SC), a major sign of rheumatic fever (RF), is related to systemic streptococcal infection and is treated with antibiotics. Recurrence usually occurs within a short interval following the initial event and is considered part of RF.

Objective: To evaluate the rate, nature, and course of recurrent SC during an extended follow-up period.

Design: Prospective assessment of a cohort of patients with SC who were admitted between 1985 and 2002.

Setting: General community hospital.

Methods: Diagnosis of RF was based on the revised Jones criteria. Other causes of chorea were excluded. Recurrence was defined as the development of new signs, lasting more than 24 hours and separated by a minimum of 2 months from the previous episode. Patients were observed from 1 to 14 years following the initial SC episode and for at least 1 year after recurrence. At recurrence, patients were assessed for RF clinical and laboratory activity, including change in cardiac involvement.

Results: Twenty-four patients had SC. In 19 patients (79%), the chorea was associated with other RF signs, and 5 suffered from pure chorea. Ten patients (42%, 7 women) developed 11 recurrent episodes of chorea 3 months to 10 years after the initial episode. Association of recurrent chorea with RF could be suspected in only 6 episodes: cessation of prophylactic antibiotic treatment or poor compliance in 4 patients and rise in anti-streptolysin O titers in 2. In an 18-year-old woman, chorea recurred during her first pregnancy. At recurrence, chorea was the sole rheumatic sign in all 9 patients who had 1 recurrent episode. In the patient with 2 recurrent episodes, mitral regurgitation developed into mitral stenosis. No statistical differences in previous RF activity and rheumatic cardiac involvement between patients with recurrent SC and patients with a single episode could be found.

Conclusions: In a significant subgroup of patients, SC recurrence might not be a true relapse of rheumatic fever. It might represent either a primary underlying abnormality that renders patients susceptible to developing such a movement disorder or the outcome of permanent subclinical damage to the basal ganglia following the initial SC episode.

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Sydenham chorea (SC) is the central nervous system manifestation and one of the major criteria of rheumatic fever (RF). Although the decline in RF incidence in developed countries has been associated with a decrease of SC, there are still outbreaks of both RF and SC. The prevailing hypothesis is that the chorea in RF is mediated by group A Streptococcus infections triggering an autoimmune response directed at the basal ganglia. However, with no definite laboratory confirmation, diagnosis of SC is based on the clinical context and requires exclusion of other conditions. It is recommended to treat patients with SC with penicillin prophylaxis to prevent recurrent attacks, even if they do not appear to have rheumatic heart disease.

Sydenham chorea is usually a monophasic event. However, in 20% of patients, recurrences, usually within several months of the initial episode, take place and are considered RF relapses. We have observed several patients with delayed recurrences of chorea that were not accompanied by active RF. This prompted us to conduct a prospective study of patients with SC to evaluate the rate, nature, and course of recurrences and to examine their relation to RF activity, signs, and antibiotic treatment.

Methods

All patients diagnosed with RF between 1985 and 2002 at the Bikur Cholim Hospital, Jerusalem, Israel, were screened for SC. Diagnosis of...
RF was based on the revised Jones criteria. Cardiac involvement was assessed clinically and by echocardiography in all patients. The diagnosis of SC was made after exclusion of other causes. All patients underwent routine blood, throat culture, C-reactive protein, erythrocyte sedimentation rate, thyroid function, rheumatoid factor, antinuclear antibodies, anti-cardiolipin antibodies, antistreptolysin O titers, serum ceruloplasmin, electrocardiogram, 2-dimensional echo-Doppler cardiology, electroencephalogram, and brain computed tomography tests. Patients were considered to have pure chorea if there was no evidence of other signs of RF. Chorea severity was graded as minimal, moderate, or severe. At time of diagnosis, all patients with SC received prophylaxis with 250 mg of oral penicillin twice daily until the age of 18 years.

Recurrence was defined as the development of new signs, lasting more than 24 hours and separated by a minimum of 2 months from the previous episode. At time of recurrence, patients were assessed for RF activity. Workup consisted of clinical examination, echo-Doppler cardiology, electrocardiogram, erythrocyte sedimentation rate, C-reactive protein, antistreptolysin O titers, antinuclear antibodies, anti-cardiolipin antibodies, and throat culture tests. Patients were observed from 1 to 14 years after the initial SC episode, and at least for 1 year after recurrence. For statistical analysis, categorical variables were compared by the Fisher exact test, and continuous variables were compared by t test.

### RESULTS

#### CHARACTERISTICS OF ALL PATIENTS WITH SC

Twenty-four patients had SC (Table 1). These included 16 women and 8 men. Age at onset ranged from 4 to 13 years. Most patients (18/24) came from large families of 4 or more siblings. Familial chorea/RF was present only in 2 cases. Chorea severity was minimal in 8 patients, moderate in 12, and severe in 4. Chorea was mostly bilateral at initial examination (19/24); hemichorea was detected in 5 patients. Other than the chorea findings, the neurological examination results were normal in 12 patients, hypotonia was found in 10, and unilateral weakness ipsilateral to the hemichorea was found in 2. In most patients (14/24), valproic acid treatment was effective.

In all patients, laboratory results for causes other than RF were negative, and brain computed tomographic results were normal. Electroencephalogram was unremarkable in all but 2 patients who had abnormal tracings with intermittent slow wave activity.

Diagnosis of SC was easily established in 19 patients (79%), based on the clinical setting and the presence of other major RF signs, which coincided with the appearance of chorea in 11 patients, preceded the appearance of chorea for 6 to 12 months in 6 patients, or appeared 3 months to 1 year after the appearance of chorea in 2 patients. Major signs included valvular pathologic features in 18 patients and arthritis in 1. Mitral regurgitation was the typical finding present in all patients with cardiac involvement: isolated in 16 or associated with mitral stenosis or tricuspid insufficiency (1 patient each).

In 5 patients with pure chorea, there were no other major RF signs or any laboratory evidence of an acute RF attack, except for increased antistreptolysin O titers in 1 patient. In these patients, diagnosis was based on exclusion of other causes. There were no cases of persistent chorea.

#### CHARACTERISTICS OF PATIENTS WITH RECURRENT SC

Eleven recurrences were recorded in 10 (7 women) of the 24 patients with SC (Table 1 and Table 2). The interval between the initial episode and the recurrence ranged from 3 months to 10 years. Eight recurrences occurred within the first 18 months following the primary episode. One patient had a second relapse 2.5 years later, and in 2 others the second relapse appeared 5 and 10 years after the initial event. Antistreptolysin O titer at recurrence was elevated only in 2 patients and borderline in 1. At time of diagnosis, all patients with SC had abnormal tracings with 250 mg of oral penicillin twice daily until the age of 18 years.

Chorea severity was graded as minimal, moderate, or severe. At time of diagnosis, all patients with SC received prophylaxis with 250 mg of oral penicillin twice daily until the age of 18 years.

Recurrence was defined as the development of new signs, lasting more than 24 hours and separated by a minimum of 2 months from the previous episode. At time of recurrence, patients were assessed for RF activity. Workup consisted of clinical examination, echo-Doppler cardiology, electrocardiogram, erythrocyte sedimentation rate, C-reactive protein, antistreptolysin O titers, antinuclear antibodies, anti-cardiolipin antibodies, and throat culture tests. Patients were observed from 1 to 14 years after the initial SC episode, and at least for 1 year after recurrence. For statistical analysis, categorical variables were compared by the Fisher exact test, and continuous variables were compared by t test.

### Table 1. Clinical Characteristics of 24 Patients With Sydenham Chorea

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range at onset, y</td>
<td>4-13 y</td>
</tr>
<tr>
<td>Women</td>
<td>16 (66)</td>
</tr>
<tr>
<td>Large families (&gt;4 children)</td>
<td>18 (75)</td>
</tr>
<tr>
<td>Familial chorea/rheumatic fever</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Chorea severity</td>
<td></td>
</tr>
<tr>
<td>Mild-minimal</td>
<td>8 (33)</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (50)</td>
</tr>
<tr>
<td>Severe</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Chorea characteristics</td>
<td></td>
</tr>
<tr>
<td>Bilateral symmetric</td>
<td>13 (54)</td>
</tr>
<tr>
<td>Bilateral asymmetric</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Hemichorea</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Neurological findings</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>12 (50)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>10 (42)</td>
</tr>
<tr>
<td>Ipsilateral weakness</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Neuroleptic agents</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Presence of other major rheumatic fever signs</td>
<td>19 (79)</td>
</tr>
<tr>
<td>Pure chorea</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Recurrences</td>
<td>11 (10 patients) (42)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1-14 y</td>
</tr>
</tbody>
</table>
CASE REPORT

A 9-year-old girl of Jewish Ashkenazi origin, the youngest of 16 children, was hospitalized with mild left hemichorea and arthralgia. Cardiologic examination revealed mitral regurgitation confirmed by echo-Doppler cardiology. Acute RF with SC was diagnosed. Chorea disappeared spontaneously within a few weeks. Prophylactic treatment with oral penicillin (250 mg twice a day) continued until the age of 18 years and was stopped after her marriage. At the age of 19, during the third month of her first pregnancy, she developed a new episode of left hemichorea with left hypotonia and hyperreflexia. The following examinations had normal or negative results: routine blood, erythrocyte sedimentation rate, antinuclear antibodies, and antcardiolipin antibodies tests. Antistreptolysin O titers were borderline (239 IU/mL, normal up to 200). Throat culture results were negative. There was no change in the cardiac findings. Penicillin prophylaxis was reintiated, but because the patient was pregnant, no symptomatic therapy for the chorea was added. A month later, and because the disabling movements were still present, haloperidol treatment was begun. The chorea disappeared after a few weeks, and treatment was discontinued. She delivered a normal baby. A year later, without penicillin prophylaxis, a second pregnancy and delivery were uneventful.

The age and sex distribution and the clinical profile of our patients with SC are similar to those reported in other series. In most of our patients, the presence of other RF signs established the rheumatic origin of the chorea and indicated antibiotic prophylactic therapy. In 1 of the 5 patients with pure chorea, recurrence occurred after antibiotic discontinuation, confirming retrospectively the probable infectious cause of the chorea.

In the present study, a relatively high rate of recurrence was observed (42% of our patients), as compared with previous reports: 25% in Australia and 20% in Brazil, Israel, and the United States. This could be attributed, in part, to the long follow-up period and to the fact that in 3 cases the recurrence of chorea took place more than 2 years and up to 10 years after the initial episode. Thus, SC recurrences might be underestimated. However, in contrast with a recent publication, none of our patients had persistent chorea.

We were unable to delineate any clinical parameter that might distinguish between patients with and without recurrence and thus identify at the first episode patients with a higher risk of recurrence.

Surprisingly, RF recurrence was clinically restricted to central nervous system involvement in nearly all cases (10 of 11), and only 1 patient had a change in cardiac involvement during recurrence. Moreover, at the time of SC recurrence and up to 1 year of follow-up, none of the 9 other patients showed other major RF signs.

Recurrence of chorea was associated in 2 patients with a rise of antistreptolysin O titer; in 4 other episodes, it occurred after discontinuation of the antibiotic prophylactic therapy or poor compliance. In the remaining 5 recurrences, no clinical or laboratory evidence could support linking the relapse of the chorea with RF activity. One of these patients was the woman who suffered a recurrence during pregnancy, a recognized setting for chorea (chorea gravidarum).

These findings might suggest that recurrent chorea in patients with a history of previous SC is not always due to RF activity and that recurrent chorea and RF do not share the same underlying pathogenesis. In some of the
patients, a recurrent choreiform episode might either represent another primary underlying abnormality that renders patients susceptible to developing such a movement disorder, SC inclusive, or be the outcome of permanent subclinical damage to the basal ganglia following the initial SC episode. Further studies comparing immunological aspects of recurrent vs nonrecurrent cases would be important in further elucidating the pathogenesis of recurrent chorea in this patient population.20

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REFERENCES


