Rheumatic chorea in northern Australia: a clinical and epidemiological study

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Abstract
To describe the epidemiology and clinical features of Sydenham’s chorea in the Aboriginal population of northern Australia a review was conducted of 158 episodes in 108 people: 106 were Aboriginals, 79 were female, and the mean age was 10.9 years at first episode. Chorea occurred in 28% of cases of acute rheumatic fever, carditis occurred in 25% of episodes of chorea, and arthritis in 8%. Patients with carditis or arthritis tended to have raised acute phase reactants and streptococcal serology. Two episodes lasted at least 30 months. Mean time to first recurrence of chorea was 2.1 years compared with 1.2 years to second recurrence. Established rheumatic heart disease developed in 58% of cases and was more likely in those presenting with acute carditis, although most people who developed rheumatic heart disease did not have evidence of acute carditis with chorea. Differences in the patterns of chorea and other manifestations of acute rheumatic fever in different populations may hold clues to its pathogenesis. Long term adherence to secondary prophylaxis is crucial following all episodes of acute rheumatic fever, including chorea, to prevent recurrence.

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With the exception of outbreaks in the USA during the 1980s and early 1990s, most recent cases of acute rheumatic fever have occurred in developing countries or in indigenous populations in industrialised countries. Although the recent studies in the USA offered important insights into the epidemiology of rheumatic (Sydenham’s) chorea, these cases occurred during epidemics of acute rheumatic fever that were mostly attributed to highly virulent, mucoïd strains of group A streptococci. The cases of chorea were severe, and had higher rates of associated cardiac damage and polyarthritis than had been described for many years.1,2 It is not clear whether the pattern of chorea described in the USA is typical of the pattern present in most of the countries where acute rheumatic fever and other group A streptococcal diseases are endemic and remain important public health problems. We conducted the following review of over 150 cases of Sydenham’s chorea in the Aboriginal population of tropical northern Australia to describe some of the clinical features and address particular controversies about the epidemiology of this disease.

Methods
Our study was undertaken as part of a larger project in which a database has been compiled of all patients with known or suspected acute rheumatic fever or rheumatic heart disease in the Top End of the Northern Territory of Australia.5 The methods have been described elsewhere,5 but briefly patients were ascertained through discharge records obtained from hospitals from 1976 through 1996, and from lists obtained from clinicians and community health clinics. Hospital and community medical charts were reviewed to obtain data, and where further information was needed the patient was clinically reviewed and/or echocardiography was performed. All data were stored on a confidential computerised database. Data collection took place between February 1994 and March 1997.

The diagnosis of acute rheumatic fever was made according to the 1992 update of the Jones criteria.7 Cases were considered to be “pure” chorea if there was no evidence of acute carditis (cardiac murmur, pericarditis, or evidence of cardiac failure) or arthritis at the time of presentation with chorea.

Statistical analyses were performed using the Stata Release 5 package (Stata Corporation, East College Station, Texas, USA). Continuous data are expressed as means (SD), and were log transformed where necessary and compared using the Student’s t test or by one way analysis of variance. Categorical data were compared using the χ² or Fisher’s exact test, as appropriate. Relative risks for the association between carditis and later rheumatic heart disease are expressed as risk ratios with 95% confidence intervals (CI). A critical p value of < 0.05 was used.

Results
CLINICAL FEATURES
A total of 555 documented cases of acute rheumatic fever meeting the revised Jones criteria were documented, dating back to 1935, although only five cases were documented before 1965. A total of 158 of these cases (28%) had Sydenham’s chorea. These 158 cases of Sydenham’s chorea occurred in 108 people, 106 of whom (98%) were Aboriginals. Seventy nine patients (73%) were female; the female to male ratio was 2.7:1. The earliest documented case occurred in 1955. Over the 10 years from 1 January 1987 through 31
December 1996, 84 cases occurred. Figure 1 shows the year of diagnosis of first episodes of chorea and the age at diagnosis of first episodes.

First episodes were diagnosed at a mean (SD) age of 10.9 (4.0) years (range, 3.9–28.6). Ninety nine patients (92%) were aged 16.0 years or less. Of the nine patients aged over 16.0 years at the time of their first episode of chorea, one was male (aged 16.8 years) and eight were female (six were aged less than 19 years).

Almost three quarters of initial episodes and recurrences consisted of “pure” chorea (Table 1). Although about one quarter of all episodes (initial and recurrent) had clinical evidence of carditis at presentation, severe carditis was uncommon; there were no cases of cardiac failure, four cases had cardiomegaly (all at the initial episode), and one case had pericarditis. Of the 37 cases with acute carditis, 31 had mitral and aortic regurgitation and stenosis, two had mitral and aortic regurgitation, and one had mitral and aortic regurgitation and stenosis. Arthritis was uncommon: of 142 total cases where the presence or absence of joint involvement was known, there was no joint arthritis in 118 (83%), polyarthritis in eight (6%), monoarthritis in four (3%), and arthralgia without arthritis in 12 (8%). Carditis and arthritis occurred together in seven of 144 presentations (5%) where this information was known.

Many cases presented with little evidence of acute inflammation; the mean (SD) peak temperature at the initial episode was 37.5°C (0.71°C), the mean (SD) peak erythrocyte sedimentation rate (ESR) was 45.8 (30.8) mm in the first hour, the mean (SD) peak C reactive protein (CRP) was 45.3 (48.9) IU, and the mean (SD) peak peripheral white blood cell count was 12.8 (6.0) × 10^9/l. However, a subset of cases had fever and raised acute phase reactants: the 75th to 100th centile ranges were 37.9–39.5°C for peak temperature, 65–150 mm in the first hour for ESR, 87–132 IU for CRP, and 13.6–46.0 × 10^9/l for peripheral white blood cell count. Raised acute phase reactants were related to the presence of other non-chorea manifestations of acute rheumatic fever: 42 episodes were classified as having other rheumatic manifestations because there was evidence of acute carditis, polyarthritis, or monoarthritis. Mean peak values for ESR, CRP, and peripheral white blood cell count were, respectively, 38.8 mm in the first hour, 8.0 IU, and 11.0 × 10^9/l in patients with “pure” chorea, compared with 60.4 mm in the first hour, 60.9 IU, and 13.6–46.0 × 10^9/l in those with other rheumatic manifestations. Mean anti-DNAse B titres were not significantly different between those with “pure” chorea (1376 IU) and those with other rheumatic manifestations (1711 IU; p = 0.26), but mean antistreptolysin O titres were substantially higher in the group with other rheumatic manifestations (593 IU v 410 IU in those with “pure” chorea; p = 0.08), although the difference was not significant.

Although 12 of 117 cases (10%) gave a history of sore throat, group A streptococci were isolated in only two of 141 presentations (1.4%) where throat swabs were done. The antistreptolysin O titre was raised (≥ 256 IU/l) in 58 of 76 cases where a result was available.

Figure 1 Year of diagnosis of 107 cases of chorea (first diagnosis of chorea only) (excludes one case that presented in early 1997), and age at diagnosis of 108 cases of chorea (initial episode only).

### Table 1  Clinical features of 158 cases of chorea in 108 people

<table>
<thead>
<tr>
<th>Feature</th>
<th>First presentations</th>
<th>Recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n*  Number with feature (%)</td>
<td>n* Number with feature (%)</td>
</tr>
<tr>
<td>“Pure” chorea</td>
<td>99  71 (72)</td>
<td>45  31 (69)</td>
</tr>
<tr>
<td>Carditis</td>
<td>100  24 (24)</td>
<td>48  13 (27)</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>99  5 (5)</td>
<td>45  3 (7)</td>
</tr>
<tr>
<td>Monoarthritis</td>
<td>99  3 (3)</td>
<td>45  1 (2)</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>99  0</td>
<td>46  0</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>99  0</td>
<td>46  0</td>
</tr>
<tr>
<td>Arthralgia†</td>
<td>97  11 (11)</td>
<td>45  5 (11)</td>
</tr>
<tr>
<td>Prolonged PR on ECG</td>
<td>46  5 (11)</td>
<td>46  0</td>
</tr>
</tbody>
</table>

*Number of people for whom results available (total number of people with first presentation, 108; total number of recurrences, 50).
†Includes three people with monoarthritis.

ECG, electrocardiogram.
and the mean (SD) titre at first presentation was 507 (438) IU/l. The anti-DNAse B titre was raised (>300 IU/l) in 34 of 55 cases where a result was available and the mean (SD) titre at first presentation was 1631 (973) IU/l. Of 55 cases where both serology results were available, in only one case were both titres normal; in 42 cases both titres were raised, in 12 cases the anti-DNAse B titre was raised but the antistreptolysin O titre was normal, and in no case was the antistreptolysin O titre raised but the anti-DNAse B titre normal.

Because ascertainment was likely to have been incomplete in early years of the study, we analysed the clinical data separately for cases presenting during the 15 years from 1 January 1982 until 31 December 1996. Over that time, 110 cases occurred in 77 people, and there were 73 people presenting with a first episode of chorea. During these years, there were 427 total cases of confirmed acute rheumatic fever; chorea constituted 26% of these. The clinical data for these years were almost identical to the overall data. Of first cases where the information was known, 51 of 71 had “pure” chorea, 16 of 72 had carditis, five of 71 had arthritis; the mean peak ESR was 44.1 mm in the first hour, the mean peak antistreptolysin O titre was 460 IU, and the mean peak anti-DNAse B titre was 1646 IU. Comparing the clinical data for first episodes in the periods before and after 1981, there were no significant differences in the proportion of patients with carditis, arthritis, or chorea, or in the mean values of peak ESR, peak antistreptolysin O titre, or peak anti-DNAse B titre (data not shown; p > 0.2 for all comparisons). The same was true when clinical data for all episodes were compared for the two time periods (data not shown).

DURATION OF CHOREA

Because of the retrospective nature of our study, reliable information could not be collected about the duration of most episodes of chorea, although full recovery eventually occurred in all cases. However, there were two documented episodes of prolonged duration. One girl from a remote Aboriginal community had her first episode of chorea in 1989 at the age of 13 years, and had persistent chorea at six successive consultations by specialist physicians and a general medical practitioner over the ensuing 32 months; by the next visit at 39 months her chorea had resolved. Her family reported that at no time over the initial 32 months did the chorea resolve. During this time, she received over 80% of her monthly injections of benzathine penicillin G for secondary prophylaxis. Systemic lupus erythematosis, hyperthyroidism, and Wilson’s disease were excluded as causes of her chorea. Another girl from a different remote Aboriginal community presented with her first episode of (non-chorea) acute rheumatic fever in 1988 at the age of 8 years, and adhered only intermittently to her regimen of secondary prophylaxis. She presented in 1992 at the age of 12 years with chorea and acute carditis. Her chorea continued without resolution for at least the next 30 months; she was first documented to be free from chorea after 39 months. Both of these children were closely reviewed by specialist physicians, and neither had any episodes consistent with recurrent acute rheumatic fever to explain the prolonged duration of their chorea. Another girl, also from a remote Aboriginal community, had chorea noted repeatedly over an eight year period between 1971 and 1979 (from age 8 to 16 years), without evidence of resolution. It is not known how well she adhered to oral penicillin secondary prophylaxis. She had at least four episodes of exacerbations of her symptoms over the eight years, none of which was fully investigated to determine whether it was a result of recurrent acute rheumatic fever, so it is possible that her prolonged chorea was caused by multiple recurrences.

RECURRENCES OF CHOREA

Fifty recurrent episodes of chorea occurred in 30 people. The 30 first recurrences occurred a mean (SD) of 2.1 (2.2) years after the initial episode. Ten people had second recurrences and these occurred a mean (SD) of 1.2 (1.0) years after the first recurrence; a third recurrence in six people occurred a mean (SD) of 1.8 (0.8) years after the second. Two people had fourth recurrences at a mean (SD) of 2.7 (2.8) years after a third, and one person had six recurrences. Although the time to second recurrence was substantially less than the time to the first recurrence, there was no significant decrease in the interval between recurrences as the number of recurrences increased (one way analysis of variance on log transformed data for first through fourth recurrences: F = 0.65; p = 0.59. Student’s t test comparing time to first recurrence with all subsequent intervals (mean, 1.6; SD, 1.2 years): t = 0.98; p = 0.33). It is possible that the lack of significance of these data relates to the small numbers of subsequent recurrences. Most recurrences of chorea were attributed to poor adherence to secondary prophylaxis regimens.

RHEUMATIC HEART DISEASE

Sixty three of the 108 people with chorea (58%) were diagnosed with rheumatic heart disease at some time. For 15 of these people, the diagnosis of rheumatic heart disease was made within six months of the first diagnosis of chorea. For the remaining 43 people the diagnosis of rheumatic heart disease was made at a mean (SD) of 7.0 (6.2) years after the first diagnosis of chorea. The presence of acute carditis with chorea significantly increased the risk of later development of rheumatic heart disease: 21 of the 24 people with carditis at their first episode of chorea later developed rheumatic heart disease, compared with 26 of 76 people without carditis (risk ratio, 1.85; 95% CI, 1.39 to 2.45). This risk remained significant when considering people who were known to have had carditis with any episode of chorea: 28 of 32 people with carditis at any time later developed rheumatic heart disease, compared with 35 of 68 people who did not
have carditis with any episode of chorea (risk ratio, 1.70; 95% CI, 1.30 to 2.22).

Eight people underwent 13 cardiac surgery procedures for rheumatic heart disease, including eight mitral valve replacements, four aortic valve replacements, and one mitral valvotomy. Two prosthesis valve recipients had embolic strokes following surgery, and one other person with mitral stenosis had an embolic stroke and, later, a transient ischaemic attack. There was one episode of clinically important bleeding: a retroperitoneal haematoma complicating anticoagulation treatment in one of the prosthetic valve recipients. There were three episodes of definite endocarditis: two episodes in one prothetic valve recipient, and one episode in a patient with severe mitral stenosis and aortic regurgitation. Two of the prosthetic valve recipients had paravalvar leakage diagnosed after surgery. Four people died as a result of rheumatic heart disease: two people died with severe cardiac failure, one person died of overwhelming acute carditis, and one person died of presumed sepsis after refusing to complete a full course of treatment for bacterial endocarditis. There was only one other death in the cohort; the cause of death was unknown, but the patient had severe rheumatic heart disease and may have died as a result of this.

Discussion

Our study shows the following: (1) almost 30% of all Aboriginal people with acute rheumatic fever in the Top End of Australia have chorea; (2) almost three quarters of all episodes of chorea present only with chorea; (3) over one quarter of all people with chorea will have recurrences, and many will have multiple recurrences; (4) almost 60% of people who present with chorea will later develop chronic rheumatic valvar heart disease.

There is a great disparity in the proportion of cases of acute rheumatic fever with chorea between different populations from many industrialised and developing countries in various regions of the world (table 2).\(^1, 3, 7-37\) With some exceptions, studies from Africa, South and East Asia, the Pacific, the Caribbean, and the Arabian peninsula have shown relatively few cases of chorea (< 15% of all cases of acute rheumatic fever), whereas studies from the USA, Pakistan, and Turkey and studies in Aboriginal Australians have shown higher proportions (up to 52%). Studies from India have shown considerable variability, with as low as 5% and as high as 21% of cases of acute rheumatic fever having chorea. Diagnostic bias may account for higher rates of chorea in some studies; because it is often a dramatic clinical presentation, chorea may be less likely to be underdiagnosed than non-chorea acute rheumatic fever, but the consistency of the pattern in different regions (with the exception of India) is striking.

The apparent predilection of certain populations to Sydenham’s chorea may offer clues to its pathogenesis. Sibling studies suggested an inherited susceptibility to patterns of acute rheumatic fever.\(^38\) Studies in subjects from the USA and the Caribbean have identified a B cell alloantigen (D8/17) present in a high percentage of this population at diagnosis of acute rheumatic fever/rheumatic heart disease; in different populations, this marker was found that identified acute rheumatic fever and rheumatic heart disease; in different populations this marker was found that identified acute rheumatic fever/rheumatic heart disease patients and their families with similar accuracy as D8/17 in the USA.\(^40\) Further studies of this kind in other populations may not only result in a genetic marker for acute rheumatic fever susceptibility, but may also help to clarify how populations may differ in their immune response to group A streptococcal infections and develop different rates of certain clinical manifestations of acute rheumatic fever.

The varying incidences of chorea in different populations may also, or instead, relate to characteristics of the group A streptococci that cause acute rheumatic fever. Studies of the
pathogenesis of Sydenham’s chorea have concentrated on the ability of certain group A streptococci to elicit antibody responses that might damage brain tissue. However, little work has been done on the characteristics of the particular group A streptococcal strains that induce chorea rather than other manifestations of acute rheumatic fever. Until now the main impediment to this work in regions where the disease remains common has been the difficulty in identifying organisms that can be said to have induced chorea because of the long latent interval from group A streptococcal infection until the development of many cases of chorea, and because of the multiple strains circulating in these endemic regions, most of which cannot be M typed. The first problem can only be surmounted with large scale prospective studies, but the second problem could be alleviated through the development of new, PCR based molecular typing techniques, which allow rapid and accurate differentiation of group A streptococcal strains regardless of their ability to be M typed.

Just as the incidence of chorea as a proportion of cases of acute rheumatic fever varies between populations, the clinical features associated with chorea also show considerable variation. It has been noted in the past that carditis often coexists with chorea, but that polyarthritis rarely does. Our study confirms that chorea coexists uncommonly with joint symptoms: only 17% of episodes were associated with arthritis or arthralgia. Moreover, when joint involvement occurs, arthralgia is more common than polyarthritis or monoarthritis.

During recent outbreaks of acute rheumatic fever in the USA, up to 71% of patients with chorea had associated carditis. However, in the USA during the 1930s and the 1960s the incidence of carditis in chorea was found to be from 10% to 22%. In studies from developing countries, the incidence of carditis in chorea has often been between 10% and 15%. Carditis occurred in 25% of cases of chorea in our study. The recent outbreaks in the USA appeared to be caused by new, virulent strains of group A streptococci; the features of those strains might explain the high rates of carditis and, possibly, polyarthritis that coexisted with chorea.

Clinically evident carditis has been shown to increase the risk of later development of rheumatic heart disease. The findings of our report suggest that carditis almost doubles the risk of developing later rheumatic heart disease. However, most of the 58% of people with chorea who eventually developed rheumatic heart disease did not have florid carditis at the time of their initial attack of acute rheumatic fever. The importance of Sydenham’s chorea to long term outcomes even in the absence of clinically apparent carditis at the time of the acute episode has been shown in the past. It appears that this is a result of silent cardiac damage in a substantial number of people with chorea who do not have clinical evidence of acute carditis.

We confirmed the finding that acute phase reactants were significantly raised in patients who had other rheumatic manifestations compared with those with “pure” chorea, although the mean ESR in the cases of “pure” chorea was higher than the normal range. Mean antistreptolysin O titres were substantially (although not significantly) higher in patients with other rheumatic manifestations than in those with “pure” chorea. This is consistent with the finding that “pure” chorea follows a prolonged latent period after group A streptococcal infection, when antistreptococcal antibody titres are raised but falling, whereas chorea which occurs together with carditis or arthritis follows a shorter latent period, when antistreptococcal antibody titres are near their peak. The very high anti-DNase B titres in both groups probably reflect the high background values of anti-DNase B titres in the Aboriginal population as a result of endemic group A streptococcal infections, particularly pyoderma.

Our data support the finding that Sydenham’s chorea mainly affects female patients; postpubertal cases occur almost exclusively in women. Although the sex association of acute rheumatic fever in other populations is not always uniform, the female predilection of chorea is an almost constant finding, and must hold some clues to its pathogenesis.

An early study concluded that the median duration of Sydenham’s chorea was 15 weeks with a range of up to 27 months. Others have reported individual cases of chorea lasting 21 months, two years, and three years. In the data presented here, two cases were documented that lasted at least 30 and 32 months, possibly up to 39 months, without obvious evidence of recurrences of acute rheumatic fever. In the absence of prospective monitoring of streptococcal antibody titres, recurrences caused by very mild, transient group A streptococcal infections or even stimuli other than group A streptococcal infections could not be excluded, but it is important for clinicians to realise that, although most cases of Sydenham’s chorea will resolve within six months, some cases may last for over three years.

It has long been known that the incidence of recurrences of acute rheumatic fever is highest in the two years following the last attack of acute rheumatic fever, although the increased susceptibility appears to last well into adulthood. It is postulated that the age distribution of acute rheumatic fever could be explained by the concept of immunological priming by recurrent streptococcal infections. This is supported by our data, which show that the time to the second recurrence of chorea in people who already had one recurrence was less than the time to first recurrence, although this was not significant. This trend should be investigated further in large, prospective studies, which can only take place in countries where the incidence of acute rheumatic fever is high; unfortunately, many of these countries do not have facilities and resources to conduct such research. In the meantime, these data support the need to concentrate on optimising
adherence to secondary prophylaxis regimens in the years immediately following an episode of acute rheumatic fever, but also to ensure long term adherence.

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