

## **A clinical study of Sydenham's chorea at University Malaya Medical Centre**

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### **Abstract**

This is a retrospective clinical study of Sydenham's chorea admitted to the University Malaya Medical Centre from 1967 to 1997. Three hundred and thirteen patients with acute rheumatic fever were identified. Sydenham's chorea was seen in 12% (37/313) of the patients. The mean age of onset of chorea was 11.5 years (range 2-21 years). The overall male to female ratio was 1.01:1, with a female preponderance among patients greater than 12 years of age. There was a disproportionate predominance of ethnic Indians among patients with acute rheumatic fever as well as Sydenham's chorea. Of the patients with Sydenham's chorea, 65% (24/37) were isolated chorea where there was no other major criteria of acute rheumatic fever. The overall trend was a decline in incidence of acute rheumatic fever over the study period. On the other hand, there were peaks in the incidence of isolated chorea. Isolated chorea was also associated with less frequently raised antistreptolysin O titer, higher recurrence rate, equal sexual predilection, and no development of rheumatic valvular disease after seven years of follow-up, as compared with other patients with mixed chorea, where there was major criteria of acute rheumatic fever.

*Conclusions:* The lack of correlation between the incidence trend of isolated chorea and acute rheumatic fever, with differences in the features of isolated chorea as compared to mixed chorea suggested that some cases of isolated chorea were of non-rheumatic etiology.

### **INTRODUCTION**

Sydenham's chorea is a late manifestation of acute rheumatic fever that occurs 1 to 6 months after pharyngeal infection with group A beta-hemolytic streptococci. The pathogenesis of Sydenham's chorea is ill-defined but is thought to be an antibody-mediated immune reaction against neuronal antigens in the caudate nucleus and putamen.<sup>1</sup> It is characterized by distinctive symptom complex of involuntary, purposeless, rapid movements that are often associated with incoordination, muscle weakness and behavioral abnormalities.<sup>2</sup> Sydenham's chorea may appear in association with other clinical features of acute rheumatic fever or as the sole manifestation (isolated chorea).<sup>3</sup>

The relationship of isolated chorea to acute rheumatic fever has been a subject of debate. A prospective study of patients with rheumatic disorder had shown that isolated chorea always followed immunologically significant streptococcal infection.<sup>4</sup> Another study demonstrated the development of rheumatic valvular disease in 23% of patients with isolated

chorea within 20 years period.<sup>5</sup> Another study using echocardiography revealed significant mitral regurgitation in 57% of patients with isolated chorea and no clinically audible cardiac murmur.<sup>6</sup> Serial streptococcal antibodies studies had been reported to be positive in 63% of patients with isolated chorea.<sup>7</sup> Despite these, some observers doubted the rheumatic etiology of isolated chorea because the clinical or laboratory evidence of streptococcal infection were seldom found in these patients.<sup>8,9</sup> Although it could be argued that isolated chorea may be a late manifestation of acute rheumatic fever when all clinical and laboratory findings had abated.<sup>4</sup>

This is a retrospective study on patients admitted to University Malaya Medical Centre from 1967 to 1997 with the diagnoses of Sydenham's chorea and acute rheumatic fever. The objective of the present study was to describe the clinical and epidemiological features of Sydenham's chorea, with emphasis on the relationship between isolated chorea and acute rheumatic fever.

## METHODS

University Malaya Medical Centre is a teaching hospital in Kuala Lumpur that serves as a community hospital for the 5.6 million population in Kuala Lumpur and Selangor (year 2000 census). It is also a national tertiary medical referral center. The medical records of patients admitted to the Centre from 1967 to 1997 with the diagnoses of acute rheumatic fever and Sydenham's chorea were retrieved. The following details in the medical records were studied: demographic features, clinical features of chorea, other non-choreic manifestations of acute rheumatic fever, investigations including CT brain scan, electroencephalography and echocardiography, drug treatment and clinical outcome.

The diagnosis of *acute rheumatic fever* was based on the revised Jones criteria<sup>10</sup>, which normally required the presence of laboratory evidence of group A streptococcal infection. The antistreptolysin O titer (ASOT) was considered elevated if found to be more than 200 Todd units. *Sydenham's chorea* referred to patients with mixed chorea and isolated chorea. *Mixed chorea* was defined as presence of chorea plus any one or more of the major criteria of acute rheumatic fever. *Isolated chorea* was defined as presence of chorea without any other major criteria of acute rheumatic fever, when other known causes of chorea had been excluded. The inclusion of isolated chorea as acute rheumatic fever is according to the revised Jones criteria.<sup>10</sup> *Non-choreic acute rheumatic fever* were acute rheumatic fever patients without Sydenham's chorea. *Persistent chorea* was defined as chorea lasting two years or more despite optimal drug treatment. *Recurrence of chorea* was defined as presence of chorea after at least six months without symptoms and medications. Statistical analyses were carried out using Student's t test and Chi square test when necessary.

## RESULTS

### *Demographic features*

Three hundred and thirteen patients with acute rheumatic fever were identified. Thirty-seven patients (12%) with Sydenham's chorea were seen in the same period. The mean age of onset of Sydenham's chorea was 11.5 years (range 2-21 years). Majority (68%) of patients were 12 years and below. The overall male to female ratio was 1.01:1. At age 12 years and below, the male to female ratio was 1:1, whereas above 12 years the

male to female ratio was 1:5. There was female predominance among patients with mixed chorea when compared with isolated chorea, however the difference was not statistically significant (Table 1).

The ethnic composition consisted of 22 Indians (60%), 8 Chinese (22%) and 7 Malays (19%). There were a disproportionately higher proportion of Indians among patients with Sydenham's chorea (60%) and non-choreic acute rheumatic fever (42%) when compared with other ethnic groups (Figure 1). Though the proportion of Indians among patients with Sydenham's chorea was higher when compared to non-choreic acute rheumatic fever, the difference was not statistically significant ( $p=0.068$ ).

### *Incidence trend of isolated chorea and acute rheumatic fever*

The overall trend was a decline in the incidence of acute rheumatic fever and acute rheumatic fever excluding isolated chorea by the end of 1990's (Figure 2). However, the incidence trend of isolated chorea fluctuated with peaks in the years 68-69, 78-79, 84-87 and 90-91.

### *Clinical characteristics*

Isolated chorea was seen in 65% (24/37) of the Sydenham's chorea. The onset of chorea was usually gradual over several days. The chorea was generally moderate to severe and affected the patients' daily activities. It was bilateral in two-third of patients and unilateral in another one-third. The mean duration of chorea was 3.5 weeks (range: 1-9 weeks). The exception was a 12 years old boy who had isolated chorea that persisted up to two years of follow-up. The characteristics of chorea in patients with mixed chorea and isolated chorea are compared on Table 1.

The associated neurological manifestations were: facial grimacing (38%), gait disturbance (21%), dysarthria (25%), muscle weakness (17%), tongue dyskinesia (17%), and extensor plantar response (8%). None had seizure or cerebellar signs.

The other manifestations of acute rheumatic fever were: carditis (35%), arthralgia (24%), fever (22%), subcutaneous nodule (11%), arthritis (5%), and erythema marginatum (3%). Clinically overt cardiac failure was not seen in any of the patients. Preceding history of pharyngitis was seen in 49% (18/37) of patients. Only one patient had preceding history of acute rheumatic fever (arthritis and

**Table 1. Clinical features of isolated chorea and mixed chorea**

Clinical features	Isolated chorea (n=24)	Mixed chorea (n=13)	p value
Mean age in years (SD)	11.3 (4.4)	11.8 (3.8)	0.743*
Male : female ratio	1.2 : 1	0.6 : 1	0.362**
Ethnic groups (no of patients)	Malays (6), Chinese (4), Indians (14)	Malays (1), Chinese (4), Indians (8)	0.345**
Laterality of chorea (no of patients)	Unilateral (8) Bilateral (16)	Unilateral (4) Bilateral (9)	0.883**
Mean duration of chorea (SD)	3.0 (1.5) weeks	4.2 (2.6) weeks	0.095*
No of patients having recurrence of chorea (%)	6 / 24 (25%)	1 / 13 (7.7%)	0.199**
Fever (no of patients)	6	2	0.498**
Arthralgia (no of patients)	3	5	0.067**
No of patients with raised ASOT	3/9	7/8	< 0.05**
Mean ASOT in Todd units (SD)	235.4 (200.1)	409.4 (211.3)	0.079*
Mean ESR in mm / hr (SD)	24.7 (23.4)	33.3 (22.8)	0.288*
Mean white cell count (SD)	11.0 x 10 <sup>6</sup> /l (4.4 x 10 <sup>6</sup> /l)	9.6 x 10 <sup>6</sup> /l (4.0x 10 <sup>6</sup> /l)	0.340*
Subsequent rheumatic valvular heart disease (no of patients)	4/24	0	0.119**

\*Student's t test

\*\*Chi-square test

carditis) that occurred one year before the onset of chorea. None of the patients had family history of chorea or acute rheumatic fever.

#### Investigations

Group A streptococci was isolated in 8% (2/26) of patients. The ASOT and ESR were elevated in 50% and 74% of patients respectively. Elevated ASOT was less frequently found ( $p < 0.05$ ) in patients with isolated chorea as compared to patients with mixed chorea (Table 1). The mean ASOT and ESR in patients with isolated chorea were also lower than those with mixed chorea. However, the differences were not statistically significant. Electrocardiography showed prolonged PR interval in 3% of patients. Electroencephalography was abnormal in 4 out of 7 (57%) of patients performed, showing non-specific focal abnormalities in three patients and diffuse slowing in another patient. CT brain scan and cerebrospinal fluid studies were carried out in three patients, all of which were normal. Other investigations including red cell count, serum

complement, antinuclear factor, serum copper, ceruloplasmin, acanthocytes, thyroid function test were all normal.

#### Treatment and outcome of chorea

Majority of patients (79%) were given drug treatment for the chorea. The drugs used were: phenobarbitone 30-60 mg three times daily (50%), haloperidol 0.75-1.5 mg twice daily (29%), chlorpromazine 25 mg twice to thrice daily (13%), benzhexol 2 mg twice to thrice daily (8%) and perphenazine 2 mg twice to thrice daily (8%). The percentage of good clinical response to these drugs was: haloperidol (100%), benzhexol (100%), perphenazine (100%), phenobarbitone (83%) and chlorpromazine (67%). Only one patient had to stop drug treatment (phenobarbitone) due to drowsiness. Except the patient with persistent isolated chorea, drug therapy could be successfully withdrawn in all other patients. There was no difference in the clinical response of chorea to drugs in patients with isolated chorea compared with mixed chorea.

**Table 2. Comparison of first presentation and recurrences of chorea**

Clinical features	Number of patients with features (%)		p value*
	First presentation (n=37)	Recurrences (n=7)	
Male : female ratio	1.1 : 1	2.5 : 1	0.269
Ethnic breakdown	Malays (7), Chinese (8), Indians (22)	Malays (1), Chinese (1), Indians (5)	
Isolated chorea	24 (65)	6 (86)**	0.282
Carditis	13 (35)	1 (14)	0.282
Arthritis	2 (5)	0	
Subcutaneous nodule	4 (11)	0	
Erythema marginatum	1 (3)	0	
Arthralgia	9 (24)	2 (29)	0.812
Prolonged PR	1 (3)	0	

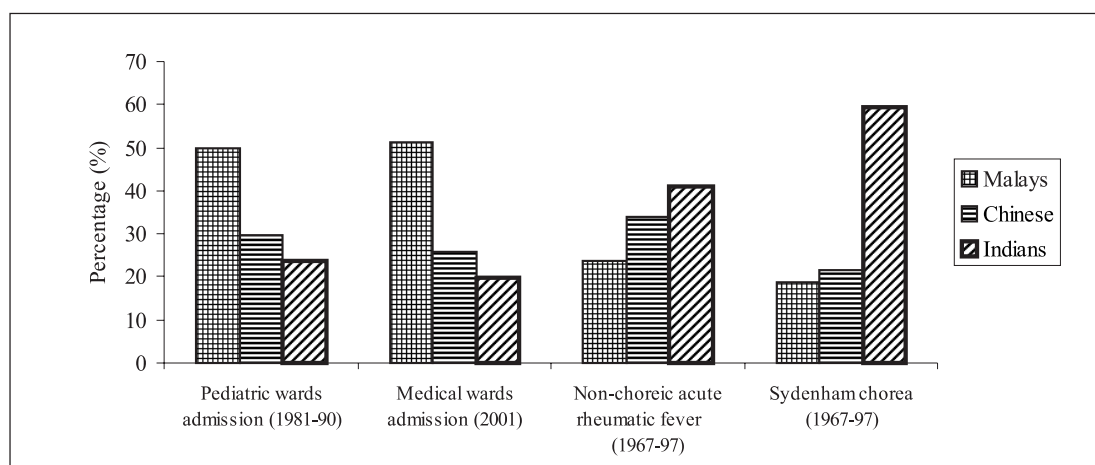


Figure 1: Ethnic breakdown of patients with Sydenham's chorea compared with acute rheumatic fever, total pediatric wards admission (1981-90) and total medical wards admission (2001) at University Malaya Medical Centre.

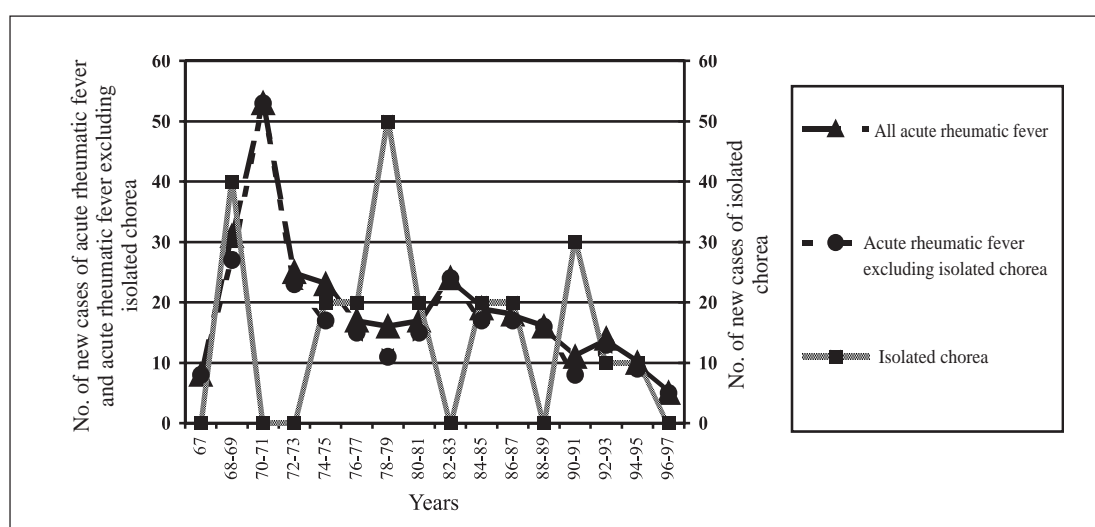


Figure 2: Incidence of acute rheumatic fever, acute rheumatic fever excluding isolated chorea and isolated chorea from 1967 to 1997 at University Malaya Medical Centre.

### *Recurrence of chorea*

Single episodes of recurrence were seen in 19% (7/37) of patients at mean 1.9 years (range: 1.2 to 2.6 years) after the initial illness. The 6 patients who had isolated chorea during recurrences also had isolated chorea during the first attacks. The chorea was bilateral in four patients and unilateral in three patients. Among the three patients with unilateral chorea, the chorea recurred on the same side of the body in two patients and the opposite side of body in one patient. There was no obvious precipitating factor such as drugs, infection and pregnancy.

### *Long-term complications*

During the mean follow-up period of 6.8 years (range: 2 months - 21 years), 16% (6/37) of patients defaulted. None of the patients had infective endocarditis, valvular surgery and mortality during follow-up. Rheumatic valve disease was found in 4 patients confirmed by echocardiography. All the 4 patients had carditis previously. None of the patients had isolated chorea previously (Table 1).

## **DISCUSSION**

Majority (78%) of our Sydenham's chorea patients were in the usually quoted age range of five to 15 years.<sup>2</sup> The mean age of onset of chorea of 11.5 years in our study was comparable to 10.9 years and 11.1 years in other studies.<sup>11-12</sup> The female predominance after puberty was similar to previous reports<sup>11-13</sup> and suggested a role of female hormones in the pathogenesis of Sydenham's chorea.<sup>13</sup>

Among the three major ethnic groups in Malaysia (Malays, Chinese and Indians), Indians had the greatest susceptibility for developing Sydenham's chorea and non-choreic acute rheumatic fever. Various factors have been known to influence the incidence of acute rheumatic fever such as host factors (genetics), environmental factors (climate), socio-economic factors (poverty, crowding) and streptococcal virulence.<sup>14</sup> The most important determinants of ethnic susceptibility among Malaysian Indians were likely to be the socioeconomic and genetic factors. A previous study carried out at University Malaya Medical Centre showed that low socioeconomic status was an important risk factor for acute rheumatic fever.<sup>15</sup> The Indians are the most economically deprived ethnic group in Malaysia. Sibling studies had demonstrated an

inherited susceptibility to certain patterns of acute rheumatic fever.<sup>16</sup> Several studies carried out in India, the country of origin for the ethnic Indians in Malaysia, had identified B lymphocyte surface "rheumatic" antigens among acute rheumatic fever and rheumatic heart disease patients and siblings.<sup>17-18</sup> These findings suggested that there could be genetic susceptibility of Indians to acute rheumatic fever.

The clinical characteristics of chorea of our patients were similar to previous reports.<sup>3,12,13</sup> Its onset was usually gradual, progressing over several days. In majority of patients, the chorea was bilateral and occurred as the sole neurological manifestation. The chorea was usually self-limiting followed by complete clinical recovery. Carditis was present in one-third of patients and coexisted with chorea much more often than joint involvement (arthritis or arthralgia).<sup>3,13</sup> The recurrence rate of chorea was close to 20% as previously reported.<sup>13</sup>

This study showed an overall trend of decline in the incidence of acute rheumatic fever as observed in other countries.<sup>3,13,19</sup> The fall in the incidence of acute rheumatic fever has been attributed to several factors that included the improvement in the standard of living and medical care.<sup>20</sup> Unlike acute rheumatic fever, the incidence trend of isolated chorea fluctuated with peaks every few years. As mentioned earlier, the relationship of isolated chorea to acute rheumatic fever has been a subject of debate. Thus, other than the frequent absence of findings to support a previous streptococcal infection, the lack of correlation between the incidence trend of isolated chorea and acute rheumatic fever would suggest that some cases of isolated chorea could have non-rheumatic etiology. There have been previous reports of disproportionately high incidence of Sydenham's chorea compared with acute rheumatic fever.<sup>21-22</sup> A notable feature of these studies was that a large proportion of patients had isolated chorea; 53% in one study<sup>21</sup> and 70% in the other.<sup>22</sup> There are other differences in the isolated chorea group as compared with patients with mixed chorea in this study. The isolated chorea has a higher recurrence rate, equal sex predilection, and none of the patients developed rheumatic valvular disease compared with 4 patients with mixed chorea during the 7 years follow-up. Previous study has also shown that recurrences of isolated chorea could occur without serologic evidence of preceding streptococcal infection, suggesting a role for non-streptococcal stimuli such as hormonal factor, infection and

others.<sup>23</sup> The possible role for non-streptococcal infective agent in isolated chorea has been proposed in previous reports.<sup>24,25</sup>

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