Survival and prognostic factors of motor neuron disease in a multi-ethnic Asian population

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Abstract
Our objective was to determine the survival and prognostic factors of motor neuron disease (MND) in a multi-ethnic cohort of Malaysian patients. All patients seen at a university medical centre between January 2000 and December 2009 had their case records reviewed for demographic, clinical and follow-up data. Mortality data, if unavailable from records, were obtained by telephone interview of relatives or from the national mortality registry. Of the 73 patients, 64.4% were Chinese, 19.2% Malays and 16.4% Indians. Male: female ratio was 1.43: 1. Mean age at onset was 51.5 ± 11.3 years. Onset was spinal in 75.3% and bulbar in 24.7% of the patients; 94.5% were ALS and 5.5% were progressive muscular atrophy (PMA). Overall median survival was 44.9 ± 5.8 months. Ethnic Indians had shorter interval from symptom onset to diagnosis and shorter median survival compared to non-Indians. On Cox proportional hazards analysis, poor prognostic factors were bulbar onset, shorter interval from symptom onset to diagnosis and worse functional score at presentation. In conclusion, age of onset and median survival duration are similar to previous reports in Asians. Clinical features and prognostic factors are similar to other populations. In our cohort, ethnic Indians had more rapid disease course accounting for their shorter survival.

Key words: Survival, prognostic factors, motor neuron disease, multi-ethnic, Asian

Introduction
Motor neuron disease (MND) is a degenerative disease of the motor neurons. In its most severe form, amyotrophic lateral sclerosis (ALS), which has both upper and lower motor neuron involvement, there is progressive limb, bulbar and respiratory paralysis and it is uniformly fatal. The incidence of ALS in predominantly Caucasian populations has had a stable or increasing trend and ranges from about 1.5 to 3.3 cases per 100,000 per year (1–5). Median survival of patients from symptom onset is from 20 to 48 months (6). Reported poor prognostic factors include older age of onset, bulbar symptoms at onset, shorter interval from symptom onset to diagnosis, poorer functional and nutritional status, more rapid disease progression and occasionally psychosocial factors (6–9). However, there are ethnic differences in ALS (10). Incidence and mortality in non-Caucasian ALS populations are reported to be lower, although this may partially be the result of incomplete case ascertainment (9). In addition, studies in mixed populations have shown differences in mortality and survival between groups of different ethnic origins, suggesting that genetic factors may influence the predisposition and expression of the disease (11,12).

Apart from the previous two geographic clusters of ALS in the Asia-Pacific region, Guam and the Kii Peninsula in Japan (13–15), incidence and mortality rates of ALS in Asians have been regarded as lower than Caucasians although there have been relatively few studies (10). The incidence of ALS in these two clusters, where environmental causes were suspected to play a role, is also decreasing (14,15). The annual incidence rate between 1998 and 2002 in Japanese
patients from Wakayama Prefecture in the Kii Peninsula was 2.5 per 100,000 compared with 14.4 per 100,000 in the 1960s (15). Reports from elsewhere in Japan (Hokkaido), Hong Kong and Taiwan have described an annual incidence ranging from 0.6 to 1.05 per 100,000 population (16–19). In comparison, another study from the Asia-Pacific region, in a predominantly Caucasian population in Canterbury, New Zealand, reported a high incidence of 3.3 per 100,000 per year (5). Mortality rates are also thought to be lower (10,20) and median survival has been variable, ranging from about 27 to 115 months in the few Asian studies (20–23).

Malaysia is a South-east Asian country with an ethnically mixed population. The main ethnic groups are the Malays and other indigenous groups, Chinese, Indians and other races and their overall proportions are 65.7%, 25.4%, 7.6% and 1.3%, respectively (24). However, there are higher proportions of Chinese and Indians in urban areas (24). Chinese and Indian Malaysians are descendants of immigrants to the Malay Peninsula and Borneo from the 18th century to the early 1900s and have lived in the country for several generations. While there have been studies on MND in the Chinese from China, Taiwan, Hong Kong as well as the Indian population from India (17–19,22,23), there may be differences in the immigrant populations. In this study we describe a cohort of Malaysian patients with MND in terms of their clinical presentation, survival and prognostic factors.

Patients and methods

Subjects

All patients diagnosed to have MND at the University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia, over a 10-year period between 2000 and 2009 were included in the study. The UMMC is a major tertiary neurology centre in Malaysia and its referral base, although primarily from Kuala Lumpur and its surrounding areas, also includes other parts of the country. As a government owned university hospital, it is part of the public health care system that has wide coverage. Public health care services in Malaysia are highly subsidised by the government and patients are seen based on needs, regardless of their ability to pay or other socioeconomic factors. The study was approved by the UMMC Medical Ethics Committee.

MND patients were identified from the UMMC Neurology Unit database and their case records were reviewed in detail. Demographic data, clinical onset, function at initial diagnosis and current status, therapy and outcome were recorded using a pre-designed standardized questionnaire. The diagnosis of MND was confirmed based on clinical findings and electromyography that provided electrophysiological confirmation of lower motor neuron involvement. Patients were further classified clinically into subtypes, namely progressive muscular atrophy (PMA), amyotrophic lateral sclerosis (ALS), progressive bulbar palsy and primary lateral sclerosis based on clinical evidence of upper and lower motor neuron involvement. Classification of MND subtypes was based on the El Escorial criteria (25). Clinical onset was divided into bulbar (if the presenting symptom was mainly weakness of the bulbar muscles) or spinal (if the main weakness was initially over the limbs). As patients were reviewed retrospectively; we did not use the ALS functional rating scale (ALSFRS) to assess patients’ functional status. Function at presentation was assessed using the simpler modified Rankin scale (mRS).

Riluzole has been shown to be effective in delaying disease progression (26). However, due to cost reasons, not all patients were treated with riluzole and some were on the medication for only a few months. Patients were therefore considered as having been on riluzole treatment only if they were treated for at least six months.

Patients who were no longer on regular follow-up were contacted by telephone and information about their status was obtained from the patient or their next of kin. For patients who died but the date of death was unknown, mortality records were traced using individual national identity card (IC) numbers from the national mortality registry kept by the Malaysian National Registration Department.

Statistical analyses

Statistical analysis was carried out using SPSS, version 16.0. Epidemiological data were analysed using standard descriptive methods. Survival duration was defined as time from onset of symptoms until death and was estimated using Kaplan-Meier survival analyses and survival distributions were compared using the Breslow method. Cox proportional hazards model was used to identify the independent predictors of survival.

Results

Patient characteristics

There was a total of 73 patients, of which 43 (58.9%) were men and 30 (41.1%) were women, giving a male: female ratio of 1.43: 1. The ethnic breakdown was as follows: Chinese, 47 (64.4%); Malay, 14 (19.2%); and Indian, 12 (16.4%). During the same period the ethnic distribution of all adult patients seen at UMMC was Malays, 36.4%; Chinese, 34.4%; Indians, 24.4%; and other races, 4.8%. The mean age of onset of symptoms was 51.5 years (SD, 11.3; range 17.5–74.9 years). Only nine (12.3%) patients had an onset before 40 years of age. Mean age of onset did not differ significantly between the sexes (males, 50.8 ± 11.5 years; females, 52.6 ± 10.2 years). Mean age of onset for the different ethnic groups was as follows: Malay, 46.1 ± 11.9 years; Chinese, 45.8 ± 12.3 years; Indian, 44.4 ± 13.8 years.
Indian, 50.4 ± 10.5 years; and Chinese, 53.4 ± 11 years. Malays had a younger mean age of onset than non-Malays (46.1 vs. 52.8 years) but this was not statistically significant (p = 0.072). None of the patients had a positive family history of ALS.

Clinical presentation

Mean duration of symptoms prior to diagnosis of MND was 11.7 ± 9.8 months. There was no significant gender difference. However, Indians had a much shorter interval from symptom onset to diagnosis compared to non-Indians (5.1 vs. 13.0 months, p = 0.01).

Fifty-five (75.3%) patients had spinal symptoms while 18 (24.7%) had bulbar symptoms at the onset of disease. More women than men had bulbar onset (61.1% vs. 38.9%, p = 0.05). There were no statistically significant differences between bulbar and spinal onset patients in terms of mean age of onset and mean duration from symptom onset to diagnosis. Although there was a higher frequency of bulbar onset patients among Indians (33.3%) compared to Malays (21.4%) and Chinese (23.4%), this was also not statistically significant (p = 0.47). All 18 bulbar onset patients complained of dysarthria while 14 (77.8%) also had dysphagia. Associated limb weakness was seen in 10 (56.6%) patients and one patient also complained of dyspnoea. In those with spinal onset, 25 (45.5%) presented with upper limb weakness, 22 (40%) with lower limb weakness and eight (14.5%) with both upper and lower limb weakness. Weakness involved both distal and proximal muscles in 26 (47.2%), distal muscles only in 20 (36.4%), and proximal muscles only in eight (14.5%) patients. The pattern of weakness was asymmetrical in all.

Spinal onset patients had associated dysarthria in 12 (21.8%) and dysphagia in six (10.9%). Table I lists the presenting symptoms of our patients.

Four (5.5%) spinal onset patients had no clinical evidence of upper motor neuron involvement at follow-up and were classified as progressive muscular atrophy (PMA). All were men, two were Chinese, one Malay and one Indian. The rest were classified as ALS. There were no significant differences in the mean age of onset and duration of symptoms prior to diagnosis between the two subtypes. Mean mRS at presentation was 1.9 (range 1–4). This was not significantly influenced by sex, ethnicity, age of onset, duration of disease prior to diagnosis, clinical onset (bulbar vs. spinal) and subtype. Table II lists the clinical characteristics overall and for the different ethnic groups.

Twenty (27.4%) patients were started on riluzole. However, only 11 (15.1%) and five (6.8%) patients were on riluzole for more than six months and 18 months, respectively. Eleven (15.1%) had percutaneous gastrostomy (PEG) inserted during the course of their disease. Four patients were ventilated on a respirator at the terminal phase of their disease and all subsequently died. Owing to financial constraints and the lack of resources, non-invasive positive pressure ventilation was not a treatment option for our patients.

Survival

Forty-two (57.5%) patients had died at the end of the study period. The two-year and five-year survival rates were 54% and 35%, respectively. The overall median survival duration was 44 ± 5.8 months since onset of symptoms. Median survival was shorter in Indians compared to non-Indians (27 ± 9.9 vs. 44 ± 12.2 months, p = 0.045), but there was no significant gender difference in median survival (44 months for both) (Figure 1).

Significantly shorter median survival was seen in bulbar onset (28 ± 3.8 months) compared to spinal onset (50 ± 13.8 months) patients, p = 0.043, and in patients with symptom onset to diagnosis interval of 12 months or less (32 ± 4.2 months) compared to longer than 12 months (66 ± 25.7 months) (p = 0.002). A non-significant trend to shorter survival was also seen patients with mRS of 3 or more at presentation (26 ± 7.4 vs. 50 ± 13.3 months, p = 0.078), age of onset 65 years or older (28 ± 4.1 vs. 44 ± 6.7 months, p = 0.69) and PMA patients compared to ALS patients (15 ± 5.0 vs. 44 ± 7.4 months, p = 0.101). No survival differences were seen in patients who had PEG tube insertion and who were on riluzole treatment.

Using Cox regression analysis, bulbar onset symptoms, duration from symptom onset to diagnosis and mRS at presentation were found to be independent predictors of poor survival in our MND patients. There was significant interaction between being of Indian ethnicity and having a shorter interval from symptom onset to diagnosis.

Discussion

There is now increasing evidence that there are differences between populations in motor neuron disease (10–12). In this study, we described the clinical features and survival of MND in a multi-ethnic Asian patient cohort, comprising Malays, Chinese...
and Indians. There are similarities between our MND patients and those of other populations in terms of having a male predominance and similar spinal-to-bulbar-onset ratio (5,22,23,27). The mean age of onset in Malaysian MND patients was comparable to the Chinese population from China, Hong Kong and Taiwan, which ranged from 50.9 to 58.8 years (18,19,23) and older than that reported in Indians, 46.2 years (22). There was no significant difference in the age of onset between Chinese, Indian or Malay Malaysians. This further emphasizes the fact that Asian patients are younger compared to Caucasians whose mean age of onset was about a decade older (3–5,7). Interestingly, mean age of onset has progressively increased in Japanese patients from the Wakayama Prefecture, rising from 53.4 years in patients whose onset was before 1990 to 64.8 years in those after (21). This was attributed to the increasing aging of the overall population as well as changes in socioeconomic and environmental

Table II. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Chinese</th>
<th>Malays</th>
<th>Indians</th>
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<tbody>
<tr>
<td>n (%)</td>
<td>73 (100)</td>
<td>47 (64.4)</td>
<td>13 (17.8)</td>
<td>12 (16.4)</td>
</tr>
<tr>
<td>Males (%)</td>
<td>43 (58.9)</td>
<td>24 (51.1)</td>
<td>11 (78.6)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>Bulbar onset (%)</td>
<td>18 (24.7)</td>
<td>11 (23.4)</td>
<td>3 (21.4)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Mean age at onset (years ± SD)</td>
<td>51.5 ± 11.3</td>
<td>53.4 ± 11.0</td>
<td>46.1 ± 11.9</td>
<td>50.4 ± 10.5</td>
</tr>
<tr>
<td>Duration from onset to diagnosis (months ± SD)</td>
<td>11.7 ± 9.8</td>
<td>13.3 ± 10.7</td>
<td>12 ± 7.5</td>
<td>5.1 ± 3.9</td>
</tr>
<tr>
<td>Mean modified Rankin score at presentation</td>
<td>1.9 (1–4)</td>
<td>1.89 (1–4)</td>
<td>1.85 (1–3)</td>
<td>1.75 (1–4)</td>
</tr>
</tbody>
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Figure 1. Kaplan-Meier survival plots for a) ethnicity b) site of onset c) duration of symptoms to diagnosis d) function at presentation (modified Rankin score).
Survival and prognostic factors of MND in Malaysians

Survival duration has been variable in different populations (6). Analyses of patients in the placebo arm of clinical trials over the last decade have shown improved survival (28). Median survival duration in Malaysians was 44 months and this was longer than that reported from south-west China (30.7 months) but shorter than in India (114.8 months) (21–23). On the whole, Asians tended to have longer median survival than Caucasians, which has ranged from 19 to 41 months (2,5,7,8,29). Poor prognostic factors in our patients include bulbar onset, having a poorer functional status at presentation and a shorter interval from symptom onset to diagnosis. These are factors that suggest more aggressive disease or a more rapidly progressive disease leading the patient to seek medical attention more quickly. These findings are consistent with previous studies and further emphasize similarities between ALS populations in Malaysia and other parts of the world (6). While an older age of onset is often considered a poor prognostic factor, this was not seen in our patients. There were also no gender differences. Therapeutic interventions such as insertion of PEG tube for feeding and riluzole therapy were also not significant factors. Insertion of PEG was not always performed in a timely manner as many of our patients were reluctant to start on PEG tube feeding until their dysphagia was quite severe. Riluzole therapy was also not consistently used and few patients were able to afford taking the medication for a long period of time. A Cochrane Collaboration review had shown that riluzole prolonged median survival by two to three months if taken for at least 18 months (30).

Our study showed shorter median survival duration in Malaysians of Indian ethnicity compared to non-Indian Malaysians (27 vs. 44 months). Indian Malaysians had a significantly shorter interval from symptom onset to diagnosis compared to other ethnic groups, suggesting a more rapidly progressive disease. This was in contrast to a large study from India which suggested that Indians had a relatively slower disease course (22). In addition, Indian Malaysians had a higher percentage of bulbar onset patients, a poor prognostic indicator, although this was not statistically significant. While our patient numbers are too few to draw any definite conclusions, ethnic differences in clinical onset have been shown in Europe with a higher occurrence of bulbar onset in the Irish compared to the Italian populations (27). Although the small number of ethnic Indian patients in our cohort may account for the differences seen, the possibility that there may be differences between Indian Malaysians and Indians from India needs to be explored further. Differences in disease pattern between immigrant Indians and Indians in India have been previously described, e.g. it has been shown that ethnic Indian immigrants to South-east Asia as well as other countries have higher cardiovascular disease risk and mortality compared to other ethnic groups and Indians in India (31–33).

Differences between ethnic groups from the same country have been reported previously. In a study from Israel, Jews of North African origin had younger age of onset but shorter survival duration (10). The authors suggested differences in genetic predisposition as a cause for these findings as the exposure to environmental factors is essentially similar for all ethnic groups, as they have been in the country for a long time. Similarly, in Malaysia, all ethnic groups have been resident in the country for several generations, further supporting the suggestion that any ethnic differences may be due to the genetic predisposition of the patients.

There are several limitations to the study. First, this was a retrospective study from a tertiary referral centre and was therefore prone to referral selection bias inherent in such studies. Secondly, the number of patients in our cohort was small and this may due to a number of MND patients not seeking medical attention and not referred for further diagnosis and assessment. In Asian societies, where families may still have a traditional outlook, neurological deficits are often blamed on ‘aging’ and therefore degenerative diseases may not always be brought to medical attention. Finally, assessment of function was by the simpler and less specific mRS instead of the ALSFRS, as this was carried out retrospectively from clinical case records. However, a recent study has suggested that the latter could be accurately scored retrospectively as well (34). Nevertheless, all patients were reviewed and diagnosed by neurologists and many were closely followed up. Survival data were also accurately estimated as mortality data were easily obtainable from the National Registration Department.

In conclusion, this study found an age of onset and median survival duration in Malaysian MND patients comparable to previous reports from Asian populations. Its clinical features and prognostic factors were generally similar to other ALS populations. There was a suggestion that ethnic Indian Malaysians may have more rapid course of disease, accounting for their shorter survival duration, but this will need further investigation.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References