Late-onset Patients with Sporadic Amyotrophic Lateral Sclerosis in Japan have a Higher Progression Rate of ALSFRS-R at the Time of Diagnosis

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Abstract

Objective The population in Japan is aging at a faster rate than in other countries in the world. It is speculated that the number of patients with late-onset amyotrophic lateral sclerosis (ALS) will increase even more in the future. However, few studies have been undertaken on the characteristics of patients with late-onset ALS in Japan. This study sought to investigate the clinical features of patients with late-onset ALS compared with those with early-onset ALS using the progression rate (ΔFS).

Methods Forty-five patients with sporadic ALS were divided into 2 groups: 23 patients with early-onset of ALS (<65 years; early onset) and 22 patients with late-onset ALS (≥65 years; late onset). Every patient was followed up from the time of initial diagnosis to the primary endpoint (death or time culminating in death without tracheostomy or ventilation assistance including noninvasive positive pressure ventilation) or for at least 48 months after initial diagnosis.

Results ΔFS in the patient group with late onset was significantly higher than that of the group with early onset (p=0.010). Survival of patients with late onset was significantly decreased compared to that of patients with early onset (p=0.031).

Conclusion Our finding suggested that patients with late-onset ALS showed more rapid disease progression than those with early-onset ALS using ΔFS.

Key words: amyotrophic lateral sclerosis, late onset, progression rate, rapidly progression


Introduction

Amyotrophic lateral sclerosis (ALS) is the most common and best recognized form of motor neuron diseases. ALS is a degeneration of both upper and lower motor neurons leading to progressive muscular paralysis with death usually within 1 to 5 years after the onset (1).

The incidence rate of ALS varies with the age at onset. Some studies have reported that the age at onset of ALS is higher now compared to 2 or 3 decades ago (2-6). Previous reports described that late onset of ALS was a risk factor for poor prognosis (7-10).

The population in Japan is aging at a faster rate than in other countries in the world (11). It is speculated that the number of patients with late-onset ALS will increase even more in the future. However, few studies have been undertaken on the characteristics of patients with late-onset ALS in Japan. It is important to study the characteristics of this disease because the aging population is increasing worldwide.

Recently, the progression rate (ΔFS) of the revised ALS functional rating scale (ALSFRS-R) (12) at the time of diagnosis was reported to be useful for the quantitative assessment of patients with ALS (13). Subsequently, to our knowledge, this is the first report of clinical features associated with ΔFS. Herein, we describe the clinical features of patients with late-onset ALS and compare them with those of
Table 1. Summary of Clinical Characteristics between Early- and Late-onset Amyotrophic Lateral Sclerosis Patient Groups

<table>
<thead>
<tr>
<th></th>
<th>Early-onset ALS patients group (n=23)</th>
<th>Late-onset ALS patients group (n=22)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.0 (30-64)</td>
<td>76.5 (66-89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>16/7</td>
<td>15/7</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Onset</td>
<td>Bulbar onset</td>
<td>Limb onset</td>
<td>0.215</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>41.0 (2-48)</td>
<td>35.5 (5-46)</td>
<td>0.075</td>
</tr>
<tr>
<td>Duration (m)</td>
<td>17.0 (3-68)</td>
<td>12.5 (3-134)</td>
<td>0.225</td>
</tr>
<tr>
<td>Progression rate</td>
<td>0.57 (0.04-2.71)</td>
<td>1.01 (0.15-4.00)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Variables are expressed as median (range). Medians were compared using the Mann-Whitney U test. Categorical variables were compared using Fisher exact probability test. ALSFRS-R: revised Amyotrophic lateral sclerosis Functional Rating Scale at initial diagnosis. Duration: from the time when the initial symptoms were noted to diagnosis (months), progression rate (ΔFS); 48-ALSFRS-R at time of diagnosis/duration from the time when the initial symptoms were noted to diagnosis (months).

Materials and Methods

Patients

The present study population consisted of 45 patients with sporadic ALS. On the basis of the El Escorial/Airlie House criteria (14), the diagnosis of clinically definite or clinically probable ALS was made between 1999 and 2005. All ALS patients were consecutively consulted at our hospital and interviewed by neurologists. Every patient underwent serum and cerebrospinal fluid examination, cranial and spinal cord magnetic resonance imaging, evoked motor and sensory potential examinations, electromyogram, and functional respiratory tests. Patients with clinically probable ALS were later confirmed as having definite ALS. The onset of illness was the time of progressive weakness in any body part ascertained by multiple family and patient interviews and consultation with the first visited physicians. Each patient was followed up from the time of initial diagnosis to the primary endpoint (death or time culminating in death without tracheostomy or ventilatory assistance including noninvasive positive pressure ventilation) or for at least 48 months after initial diagnosis.

Patients were divided into 2 groups: 23 patients with early-onset ALS (<65 years; early onset; 16 men, 7 women; median age, 55.3 years; range, 30-64 years) and 22 patients with late-onset ALS (≥65 years; late onset; 15 men, 7 women; median age, 75.6 years; range, 66-89 years). The 2 groups were compared for initial symptoms, ALSFRS-R score at the time of initial diagnosis, duration (from the time when the initial symptoms were noted to diagnosis) and ΔFS (13). ΔFS was calculated as ΔFS=(48-ALSFRS-R score at time of diagnosis/duration from the time when the initial symptoms were noted to diagnosis (months) (13). The time of initial onset was determined on the basis of subjective complaints and information confirmed from family members. Data for ΔFS represented a fixed covariate at the baseline of diagnosis (13).

Statistical analysis

Categorical variables were compared using the Fisher exact probability test. Other variables are expressed as median (range). Medians were compared using the Mann-Whitney U test. The association between age categories and post-diagnosis period until primary endpoint were examined using the Kaplan-Meier curve, and differences were analyzed using the log-rank test and Cox proportional hazards model. All analyses were carried out using StatView statistical software, version 5.0 (Abacus Concepts, Inc., Berkeley, CA). Values for p less than 0.05 were considered significant.

Results

The clinical features of the patients with ALS are summarized in Table 1. In the ALS patient group with early onset, 6 patients were bulbar onset and 16 patients were limb onset. In those with late onset, 11 patients were bulbar onset and 10 patients were limb onset. There was no significant difference between ALS patients with bulbar onset and limb onset in each group (p=0.215). The ALSFRS-R score at the time of initial diagnosis was not significantly different in patients with early onset (median, 41.0 points; range; 2-48
The clinical features of the ALS patients with limb onset are summarized in Table 3. The ALSFRS-R score at the time of initial diagnosis was not significantly different in early onset patients with limb onset (median, 39.5 points; range, 4-48 points) compared with late onset patients with limb onset (median, 36.0 points; range, 14-45 points; p = 0.349). The duration was not significantly different in early onset patients with limb onset (median, 21.0 months; range, 3-68 months) compared with late onset patients with limb onset (median, 13.0 months; range, 7-134 months; p = 0.505). ΔFS was significantly different in early onset patients with limb onset (median, 0.54; range, 0.04-0.91) compared with late onset patients with limb onset (median, 0.76; range, 0.18-1.71; p = 0.046) (Fig. 5). Using simple, nominal variables in the Cox proportional hazards model, survival was found to differ between early onset patients and late onset patients with bulbar onset. Survival of patients with late onset was significantly decreased compared with patients with early onset (p = 0.034) (Fig. 6).

Discussion

In this study, we demonstrated that ΔFS of the late-onset ALS group was significantly higher than that of the early-onset ALS group. Moreover, even in both groups with bulbar and limb onset, we demonstrated that ΔFS of the late-onset ALS group was significantly higher than that of the early-onset ALS group. These results showed that ALS in the group with late onset was rapidly progressing. In addition, the survival of patients with late onset was significantly decreased compared with that of patients with early onset.

Recently, ΔFS of ALS was reported and calculated on the
### Table 2. Summary of Clinical Characteristics between Early- and Late-onset Amyotrophic Lateral Sclerosis Patient Groups with Bulbar Onset

<table>
<thead>
<tr>
<th></th>
<th>Early-onset ALS patients group (n=6)</th>
<th>Late-onset ALS patients group (n=11)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.5 (30-64)</td>
<td>77.0 (66-89)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>4/2</td>
<td>7/4</td>
<td>p&gt;0.999</td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>43.5 (39-46)</td>
<td>35.0 (5-46)</td>
<td>0.057</td>
</tr>
<tr>
<td>Duration (m)</td>
<td>10.5 (3-28)</td>
<td>11.0 (3-27)</td>
<td>0.880</td>
</tr>
<tr>
<td>Progression rate</td>
<td>0.47 (0.14-1.75)</td>
<td>2.00 (0.15-4.00)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Variables are expressed as median (range). Medians were compared using the Mann-Whitney U test. Categorical variables were compared using Fisher exact probability test. ALSFRS-R: revised Amyotrophic lateral sclerosis Functional Rating Scale at initial diagnosis. Duration: from the time when the initial symptoms were noted to diagnosis (months), progression rate (ΔFS); ALSFRS-R at time of diagnosis/duration from the time when the initial symptoms were noted to diagnosis (months).

Figure 3. Comparison between the progression rate of early- and late-onset amyotrophic lateral sclerosis patients groups with bulbar onset. The progression rate (ΔFS) was different in the patient group with early-onset amyotrophic lateral sclerosis (ALS) (median, 0.47; range 0.14-1.75) compared with the group with late-onset ALS (median, 2.00; range, 0.15-4.00). ΔFS of the late-onset ALS group was significantly higher than that of the early-onset ALS group (p=0.044).

Figure 4. Kaplan-Meier survival plots according to the age at onset and of post-diagnosis period until primary endpoint in amyotrophic lateral sclerosis patients with bulbar onset. Kaplan-Meier survival plots according to the age at onset and post-diagnosis period until primary endpoint (death or time culminating in death without tracheostomy or ventilation assistance) in amyotrophic lateral sclerosis patients (n=17) are shown. By using simple, nominal variables in the Cox proportional hazards model, the survival of patients with late onset (n=11) was significantly decreased compared to that of patients with early onset (n=6; p=0.031).

The first report of an association between clinical features and ΔFS.

In the present study, ALSFRS-R score and duration (from the time when the initial symptoms were noted to diagnosis) were not significantly different between ALS patients with early onset and those with late onset. However, ΔFS of late-onset ALS group was significantly higher than that of the early-onset ALS group. Survival of patients with late onset was significantly decreased compared with that of patients with early onset. It was suggested that ΔFS might predict the prognosis more accurately (13).
A previous study had reported that patients with late-onset ALS had a poor prognosis (15). In this regard, it was speculated that the degeneration of motor neurons was relevant in the aging process (15). However, degeneration of motor neurons in ALS was reported to be different from that in the normal aging process. In addition, it was surmised that a poor prognosis was affected by age-related physiological respiratory insufficiency rather than by age-related of motor neurons (16). The age at onset of ALS is higher now compared to the recent 2 or 3 decades (2-6). This might be related to the longer life expectancy of the general population. Although the increase in mortality is restricted to the population aged ≥65 years, it cannot be explained by the increasing age of the general population alone (17). It was formerly reported that elderly people with ALS were less likely to consult a neurologic specialist (18). Recently, it was thought that elderly people consult neurologists more often (19). Thus, it was thought that the clinical features of patients with late-onset ALS were related to pathological, physiological and medical-sociological factors.

The population in Japan is aging at a faster rate than in other countries in the world (11). It is speculated that the
number of patients with late-onset ALS will increase even more in the future. The present study evaluated the clinical features in a small number of patients with ALS in Japan. By using ΔFS, we confirmed the result of previous reports.

In conclusion, by using ΔFS, we found that patients with late-onset ALS showed more rapid disease progression than those with early-onset ALS. We propose that ΔFS may be useful for the assessment of affected patients. A larger population is required to validate our conclusion.

The authors state that they have no Conflict of Interest (COI).

References