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Original Article

Clinical outcomes and serum uric acid levels in elderly patients with amyotrophic lateral sclerosis aged ≥ 70 years

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Abstract: Background: Amyotrophic lateral sclerosis is a slowly progressive fetal neurodegenerative disease in which clinical phenotype and nutritional status are considered prognostic factors. Advanced age has also been reported to carry a poor prognosis in amyotrophic lateral sclerosis. The elderly population is expected to increase in Japan, as well as in other countries in the near future. Whether late-onset amyotrophic lateral sclerosis affects the average lifespan or survival of patients and the nutritional status was related to survival remains an open question. Methods: We studied the survival of elderly 34 patients with clinically definite amyotrophic lateral sclerosis aged ≥ 70 years and investigated serum triglycerides, cholesterol, LDL/HDL ratio, and glucose. Serum uric acid was examined. Results: The average age at respiratory disorders or death as a whole was 77.5 ± 4.3 years. Survival did not differ significantly between different clinical phenotypes or between patients with and those without riluzole usage. Survival differed significantly between patients with and those without other complications. No biochemical parameter is correlated with outcome in this series, including elevated triglyceride or cholesterol levels and an increased LDL/HDL ratio. The survival correlated with the serum uric acid level ($r = 0.407$, $p = 0.017$). Conclusions: The onset of amyotrophic lateral sclerosis at ≥ 70 years of age might not be the key determinant of survival in patients with amyotrophic lateral sclerosis.

Keywords: Amyotrophic lateral sclerosis, elderly amyotrophic lateral sclerosis, survival, nutritional status, uric acid

Introduction

Amyotrophic lateral sclerosis (ALS) is a slowly progressive fetal neurodegenerative disease in which clinical phenotype and nutritional status are considered prognostic factors [1]. Advanced age has also been reported to carry a poor prognosis in ALS [1]. The elderly population is expected to increase in Japan, as well as in other countries in the near future. Whether late-onset ALS affects the average lifespan or survival of patients and the nutritional status was related to survival remains an open question. We studied the survival of elderly patients with ALS.

Subjects and methods

The subjects were 34 Japanese patients aged ≥ 70 years (17 men and 17 women, age at disease onset 75.2 ± 3.9 years, range 70 to 83 years) who were given a diagnosis of clinically definite ALS according to the El Escorial revised criteria [2]. All patients fulfilled the following criteria: 1) limb weakness and wasting developing naturally during the disease course; 2) ultimately, respiratory function was affected, or the patient died of a respiratory disorder characterized by restrictive dysfunction requiring mechanical ventilation or non-invasive positive pressure ventilation in the absence of other accidental causes of respiratory dysfunction, such as pulmonary embolism; and 3) bulbar symptoms requiring a dysphagia diet, tube feeding, or a gastrostomy during the disease course. Patients were excluded if they had 1) radiating pain, and other neurologic deficits, such as extrapyramidal signs, limited ocular movements, or ataxia; and 2) monomeric weakness or amyotrophy at presentation; or 3) evi-

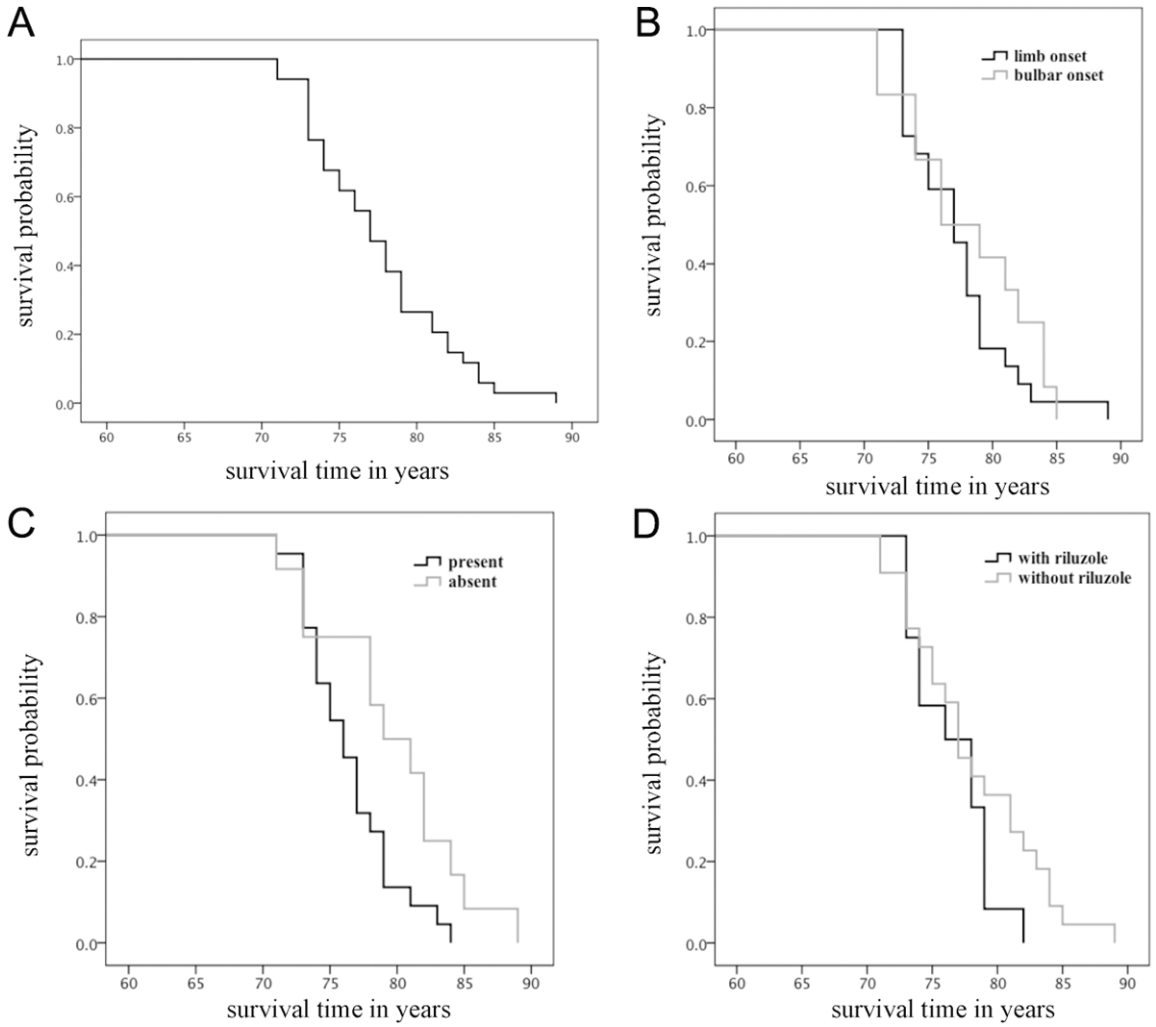

Figure 1. The interval from disease onset to respiratory disorders or death in 34 patients with ALS aged ≥ 70 years (panel A). Survival did not differ significantly according to clinical phenotype (limb onset vs. bulbar onset; 77.2 ± 4.0 vs. 79.5 ± 5.3 years, p = 0.443) (panel B) or whether patients received riluzole (n = 12) or did not receive riluzole (n = 22) (76.5 ± 3.6 vs. 78.0 ± 4.1 years, p = 0.204) (panel D). Survival differed significantly between patients with other complications (n = 22) and those without other complications (n = 12) (76.4 ± 3.5 vs. 79.2 ± 5.0 years, p = 0.028) (panel C).

dence of a mass lesion, inflammation, major vessel disease, or multiple infarcts on cranial magnetic resonance imaging (MRI). All patients were evaluated by at least two experienced neurologists.

In this retrospective database study, we investigated serum triglycerides, cholesterol, LDL/HDL ratio [1], and glucose. Serum uric acid was also examined. These variables were measured in the absence of tube feeding, intravenous nutrition, mechanical ventilation, and oxygen supplementation after the diagnosis of ALS. Correlations between outcomes and these values were evaluated performed with SPSS software (version 18). The primary endpoint was defined as death due to respiratory disorder or respiratory restrictive dysfunction requiring mechanical ventilation or non-invasive positive pressure. Survival was examined with the use of Kaplan-Meier curves, and differences were analyzed with the log-rank test.

Results

Among the 34 subjects, 22 had a history of systemic illness (hypertension in 16, diabetes mellitus in 3, hyperlipidemia in 2, gout in 1, chronic hepatitis in 1, cardiac disease in 4, renal disease in 1, and history of surgery for cancer in

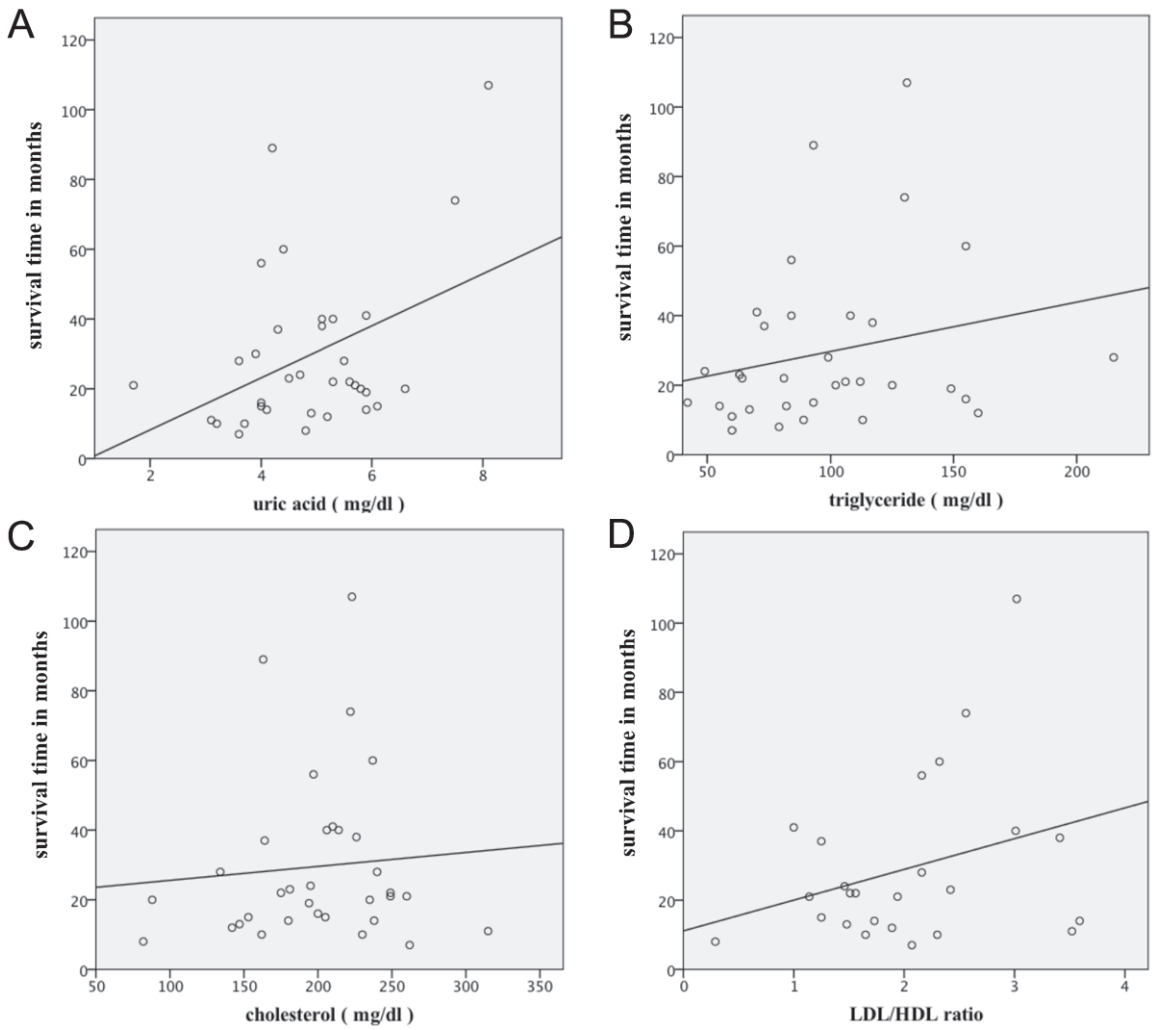

Figure 2. Correlation between nutritional status and the interval from disease onset to respiratory disorders or death. The interval from disease onset to respiratory disorders or death correlated with the serum uric acid level ($r = 0.407$, $p = 0.017$) (panel A), but did not correlate with the serum level of triglycerides ($r = 0.224$, $p = 0.202$) (panel B) or cholesterol ($r = 0.082$, $p = 0.644$) (panel C) or with the LDL/HDL ratio ($r = 0.308$, $p = 0.126$) (panel D).

3). None had vascular events. One patient had previously undergone neurosurgery (cervical laminectomy). No patient had a family history of suspected neurodegenerative diseases, expect for one patient with negative results on FUS and SOD gene analysis.

Initial neurologic assessment (on average onset 12.1 ± 8.3 months from neurologic evaluation, range 3 to 23 months)

Clinical phenotype was characterized by limb onset in 22 patients and bulbar onset in 12. Fasciculations in the tongue or limbs were evident in 29 patients. Among the 5 patients without physical fasciculations at diagnosis, 2 showed fasciculations on electromyography, and 4 subsequently presented with physical fasciculations. In 32 patients, electromyography showed chronic, active denervation as defined previously [1] in widespread areas, involving at least three or more different nerve territories; the other 2 patients did not undergo electromyography. Five patients showed signal changes involving the pyramidal tract on MRI. Compression with abnormal high lesions of the spinal cord was assessed on cervical MRI in 29 patients, but was found in only 1 patient with bulbar onset.

Vital capacity was < 80% (range 24.6 to 78.5%) in 15 of 26 patients. Of 31 patients who underwent arterial blood gas analysis, 26 had decreased oxygen levels (< 90 mmHg; range

35.7 to 89.2 mmHg), and 8 had increased carbon dioxide levels (≥ 50 mmHg; range 50.7 to 95.1 mmHg). In another patient, arterial blood gas analysis was performed at the time of cardiopulmonary arrest (oxygen and carbon dioxide levels were 47.9 and 172.3 mmHg, respectively). The diagnosis according to the revised El Escorial criteria [2] was clinically definite ALS in 23 patients, clinically probable ALS in 6, clinically probable-laboratory supported ALS in 4, and clinically possible ALS in 1.

Outcomes of patients with ALS

During the disease course, all patients were given a diagnosis of clinically definite ALS according to the revised El Escorial criteria [2]. The interval from disease onset to respiratory disorders or death in the study group as a whole was 29.5 ± 23.3 months (median 21 months, range 7 to 107 months). The average age at respiratory disorders (n = 3) or death (n = 31) was 77.5 ± 4.3 years (median 77 years, range 71 to 89 years) (**Figure 1**). Survival did not differ significantly between different clinical phenotypes (limb onset vs. bulbar onset: 77.2 ± 4.0 vs. 79.5 ± 5.3 years, p = 0.443) or between patients with (n = 12) and those without riluzole usage (n = 22) (76.5 ± 3.6 vs. 78.0 ± 4.1 years, p = 0.204) (**Figure 1**). Survival differed significantly between patients with (n = 22) and those without other complications (n = 12) (76.4 ± 3.5 vs. 79.2 ± 5.0 years, p = 0.028).

Nutritional status of patients with ALS

The interval from disease onset to respiratory disorders or death correlated with the serum uric acid level (r = 0.407, p = 0.017) (**Figure 2**). The interval from disease onset to respiratory disorders or death did not correlate with serum levels of triglycerides (r = 0.224, p = 0.202), cholesterol (r = 0.082, p = 0.644), or glucose (r = 0.063, p = 0.724) or with the LDL/HDL ratio (r = 0.308, p = 0.126).

Discussion

Recently, in 2010, the incidence of ALS was reported to increase with advancing age [3, 4]. In classic ALS, median survival from disease onset to death ranges from 20 to 48 months [1], and advanced age at disease onset is a risk factor for poor survival [1]. For example, the survival of patients aged ≥ 80 years with ALS/MND in Scotland was reported to be 1.69 years, and the disease duration of ALS/MND was 5 to 6 months shorter than the average value [5]. A study done in Minnesota reported that the survival of patients aged > 60 years was 11 months shorter than that of patients aged ≤ 60 years [6]. In Japanese patients aged ≥ 65 years with ALS, the survival was shorter than that of patients aged < 65 years [7]. Survival in our cohort aged ≥ 70 years was not shorter than the 20 months generally considered the minimal survival in classic ALS [1]. One reason for this outcome was attributed to the fact that our definition of late onset differed from that in previous reports; however, the 70 years in our definition was consistent with the findings of recent studies reporting that the peak incidence of ALS occurs at 70 to 74 years in men [3] and women [4]. Motor neuron degeneration might be less frequent in elderly patients with ALS as reported in a previous study of 70 patients with ALS who were older than 80 years [3]. Survival in ALS might be also affected by other coexisting conditions such as cardiac or pulmonary disease or the clinical phenotype of ALS, especially in patients with bulbar onset, increasing in incidence after 65 years of age [5, 8]. In our subjects, survival did not differ between different clinical phenotypes, but the survival of patients without complications was longer than that of patients with complications.

In our study, elevated triglyceride or cholesterol levels and an increased LDL/HDL ratio, which has been linked to prolonged survival [1], did not correlate with survival. However, the serum uric acid level was apparently related to survival. Uric acid is considered an important natural antioxidant that may reduce oxidative stress by acting as a scavenger of free radicals [9]. Low uric acid levels have been reported to be a risk factor for Parkinson's disease [10], and a free radical scavenger was found to delay the progression of motor disability in patients with ALS [11]. Whether maintaining a high serum uric acid level during the disease course can prolong survival remains uncertain, but this possibility should be addressed in future studies.

Because the population of Japan is aging at a faster rate than in other countries, epidemiologic studies of elderly patients will become more important in the future. Survival in our cohort was not shorter than the generally considered the minimal survival in classic ALS [1].

Disclosure of conflict of interest

No potential conflicts of interest were disclosed.

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