ORIGINAL

Increase in the amyotrophic lateral sclerosis age of onset : Analysis of cases originating in 2011-2020

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Abstract : The onset age of amyotrophic lateral sclerosis (ALS) has been increasing, but recent trends remain unclear. This study examined changes in ALS onset age over the past decade. We analyzed 233 ALS patients diagnosed from 2011 to 2020 at Tokushima University Hospital. The Jonckheere–Terpstra test assessed the trend in onset age. We compared onset age between 2011–2015 (Group A) and 2016–2020 (Group B) using the Mann–Whitney U test. We also analyzed the annual proportion of patients with onset age ≥80 using Spearman's rank correlation. In Tokushima Prefecture, we evaluated annual increase rates of individuals aged ≥80 and ALS patients with onset age ≥80, using 2011 as baseline. Regression slopes were compared using a t test. Onset age showed a significant positive trend ($p = 0.04$), and Group B had older onset age than Group A ($p = 0.048$). The proportion of patients with onset age ≥80 increased significantly ($\rho = 0.69$, $p = 0.03$). No significant difference was found between regression slopes for the general elderly population and ALS patients with onset age ≥80 ($p = 0.49$). These findings suggest that the onset age of ALS at Tokushima University Hospital has increased over the past decade. J. Med. Invest. 72 : 286-289, August, 2025

Keywords **:** *Amyotrophic lateral sclerosis, Aging*

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive degeneration and loss of upper and lower motor neurons and typically manifests after middle age. It is speculated that the number of ALS cases will increase worldwide in the future (1). Aging has been identified as a risk factor for ALS onset (2). Epidemiological studies have reported an increase in age of onset of ALS (3-6). The number of ALS patients in Japan has been increasing, with approximately 9,600 reported cases in 2017 (7). In Japan, a study involving 280 ALS patients diagnosed between 1965 and 2003 reported an increase in age of onset of ALS (4). Although the age of onset in ALS patients has increased in recent years, little is known about the last decade in Japan. As Japan anticipates a heightened proportion of older individuals in its demographic landscape, persistent exploration into the advancing age of ALS onset becomes imperative. Considering that older-onset patients with ALS tend to have a shorter survival period from disease onset, early diagnosis is important (8, 9). Additionally, older-onset patients often have bulbar palsy (4), so prompt management of dysphagia and communication disorders is important. Given the necessity of nutritional intervention, dysphagia treatment strategies, and overall patient care, elucidating the proportion of older-onset ALS patients becomes essential. Therefore, the aim of this retrospective study was to investigate changes in the age of onset and the increase in the proportion of ALS patients who developed the disease at age ≥80 years.

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METHODS

Participants

We retrospectively analyzed data from patients with ALS who presented to the Department of Neurology, Tokushima University Hospital, with disease onset during a 10-year period from January 2011 to December 2020. Patient data, including age, sex, age of ALS onset, address, and upper and lower motor neuron signs, were retrieved from medical records. The inclusion criteria were defined as patients who met the definite, probable, or probable laboratory-supported ALS criteria on the basis of the updated Awaji criteria (10). We checked whether patients had undergone genetic analysis, and excluded those with known pathogenic ALS gene variants, regardless of family history (11, 12). Genetic analysis included screening for the following ALS-associated genes : *ANG*, *C9orf72*, *DAO*, *DCTN1*, *FUS*, *OPTN*, *PFN1*, *SOD1*, *SQSTM1*, *TARDBP*, *UBQLN2*, *VAPB*, *VCP*, and *TBK1*.

Statistical analyses

We performed statistical analyses to evaluate temporal trends and group differences in ALS onset age, to assess changes in the proportion of patients aged ≥80 years, and to examine whether demographic aging in Tokushima Prefecture contributes to the increase in older-onset ALS cases.

First, patients were classified by the calendar year of disease onset. The trends in onset year and age of onset were evaluated via the Jonckheere–Terpstra test.

Next, patients were divided into two groups : those with onset before December 31, 2015 (Group A), and those with onset after January 1, 2016 (Group B). Differences in the age of onset between the two groups were compared using the Mann–Whitney

U test.

We also calculated the annual proportion of ALS patients who developed the disease at age ≥80 years from 2011 to 2020. To assess whether there was a significant increasing trend in the proportion of older-onset ALS patients, we performed a Spearman's rank correlation analysis between calendar year and the proportion of patients aged ≥80 years.

Finally, we conducted a regional analysis focusing on patients residing in Tokushima Prefecture. To investigate whether the increasing number of ALS patients who developed the disease at age ≥80 years reflects population aging, we compared the annual increase in the number of ALS cases aged ≥80 years to the annual increase in the general population aged ≥80 years in the same region. Using 2011 as the baseline year, linear regression slopes were calculated for both groups and compared using a t test. This analysis included only ALS patients residing in Tokushima Prefecture.

Data analysis was performed using R software (version 4.3.0 ; http://www.r-project.org/).

Ethical Considerations

This study was approved by the Ethical Review Committee of the University of Tokushima Hospital for Biomedical Sciences and Medical Research.

RESULTS

Number of patients

A total of 239 patients were included and categorized as having definite, probable, or probable laboratory-supported ALS on the basis of the updated Awaji criteria.

Of these, 215 patients underwent genetic analysis. Six patients were found to have pathogenic ALS gene variants (three with *SOD1* mutations, one with an *OPTN* mutation, one with a *VCP* mutation, and one with a *TBK1* mutation) ; these patients were excluded from the study. The remaining 24 patients did not undergo genetic testing. Among the entire cohort, only two patients had a family history of ALS. Both of these patients had undergone genetic testing and were negative for all known pathogenic variants ; therefore, they were included in the analysis. Consequently, 233 ALS patients without confirmed pathogenic gene variants were included in the final analysis (138 males and 95 females ; mean age : 63.9 ± 12.8 years). The patients were further classified as having definite (n = 49), probable (n = 111), or probable laboratory-supported (n = 73) ALS. The characteristics of the included patients are summarized in Table 1. The number of patients varied from year to year, and no consistent increasing or decreasing trend was observed (Figure 1).

Changes in age of onset

The age of onset increased significantly over time (Jonckheere–Terpstra test, $p = 0.04$). Compared with Group A, Group B had a significantly greater age of onset (Figure 2, median [interquartile range] : Group A, 65.0 [57.0-71.8] ; Group B, 68.0 [55.5-74.5] ; Mann–Whitney U test, $p = 0.048$).

Trend in proportion of ALS patients who developed the disease at age ≥80 years

A significant positive correlation was observed between calendar year and the proportion of ALS patients who developed the disease at age ≥80 years (Spearman's rank correlation coefficient, $\rho = 0.69$, $p = 0.03$), indicating an increasing trend in older-onset cases over the past decade.

Table 1. Characteristics of included cases

Variables	Overall n=233
Age, years	63.9 (12.8)†
Sex	
Male	138 (59.2)‡
Female	95 (40.8)‡
Updated Awaji criteria category	
definite	49 (21.0)‡
probable	111 (47.6)‡
probable-laboratory supported	73 (31.3)‡
Address	
Tokushima	111 (47.6)‡
Others	122 (52.4)‡

†Data represent mean
‡Data represent number (%). Percentages may not total 100% due to rounding.

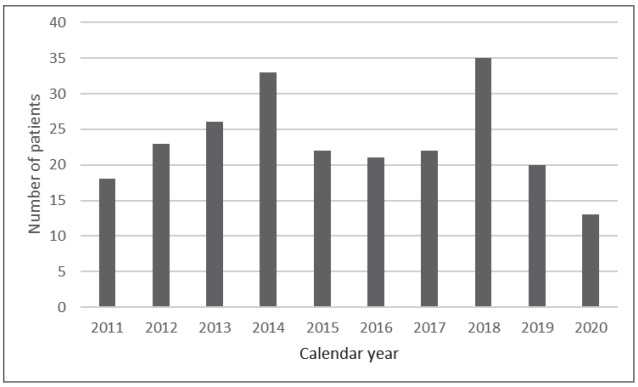

Figure 1. Changes in the number of cases
The number of cases varied annually.

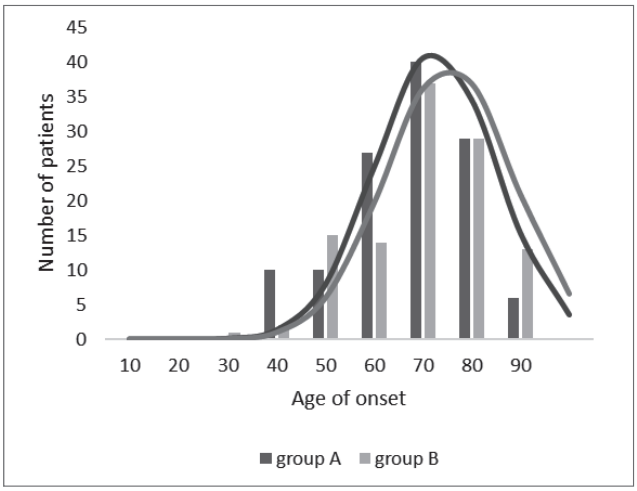

Figure 2. Histogram and normal distribution curve of age at onset of ALS : comparison between Group A (before December 31, 2015) and Group B (after January 1, 2016)
The peak age of Group B shifted to an older age compared to Group A ($p = 0.048$).

Regional analysis of patients residing in Tokushima Prefecture

Among the 233 ALS patients without confirmed pathogenic gene variants, 111 resided in Tokushima Prefecture (Table 1). These patients were used for the comparison with the general population in the prefecture. In Tokushima Prefecture, when 2011 was the base year, there was no significant difference in the slope of the linear regression between the general population aged ≥80 years and the number of ALS patients who developed the disease at age ≥80 years (Figure 3) (t test, $p = 0.49$) (13).

DISCUSSION

In the present study, we analyzed ALS patients diagnosed at one of the major hospitals in Tokushima Prefecture between 2011 and 2020. The onset age of ALS gradually increased over time, and the proportion of patients who developed the disease at age ≥80 years also increased.

Aging of the general population has been reported to be associated with an older age of onset of ALS (4-6). In our study, the slopes of the linear regressions for the general population aged ≥80 years and the number of ALS patients who developed the disease at age ≥80 years included in our study living in Tokushima Prefecture did not significantly differ when 2011 was used as the base year. Similarly, a study from Italy reported an increase in the mean onset age from 65.0 years from 1995-2004 to 66.3 years from 2005-2014 (6). In Italy, as in Japan, the percentage of people over 65 years of age has continued to increase from 1995 to 2014, and these percentages have been high worldwide (14). These findings support the notion that aging of the general population contributes to an older age of ALS onset.

However, other risk factors may be associated with the older onset of ALS. In addition to age, several risk factors are associated with the development of ALS, including smoking, exposure to lead and heavy metals, exposure to pesticides, low body mass index, and low educational background (15). Notably, older patients with ALS may have fewer risk factors other than age. An epidemiological study in Wakayama Prefecture involving 240 ALS patients revealed a decreased risk of ALS onset with increasing age, highlighting the complex interplay between age and these risk factors (5). This suggests that the observed increase in the age of onset may also be attributable to a reduction in these other risk factors. Therefore, future research should involve a larger number of cases, use multivariate analysis, and analyze existing risk factors collectively.

This study has several limitations. The number of ALS patients included was relatively small. This may be because the study was conducted at a single hospital. Furthermore, similar to other studies, we excluded patients who met the criteria for possible ALS on the basis of the updated Awaji criteria. Therefore, the number of patients included in our study might have been small.

In summary, our findings demonstrate an increasing age of ALS onset and an increase in the proportion of older-onset patients over the past decade. Consequently, considering the possibility of ALS even in older patients and early diagnosis are imperative. Postdiagnosis, it is essential to note that older-onset ALS patients experience rapid symptom progression and a higher prevalence of bulbar palsy.

CONFLICT OF INTEREST

None of the authors have any conflict of interest.

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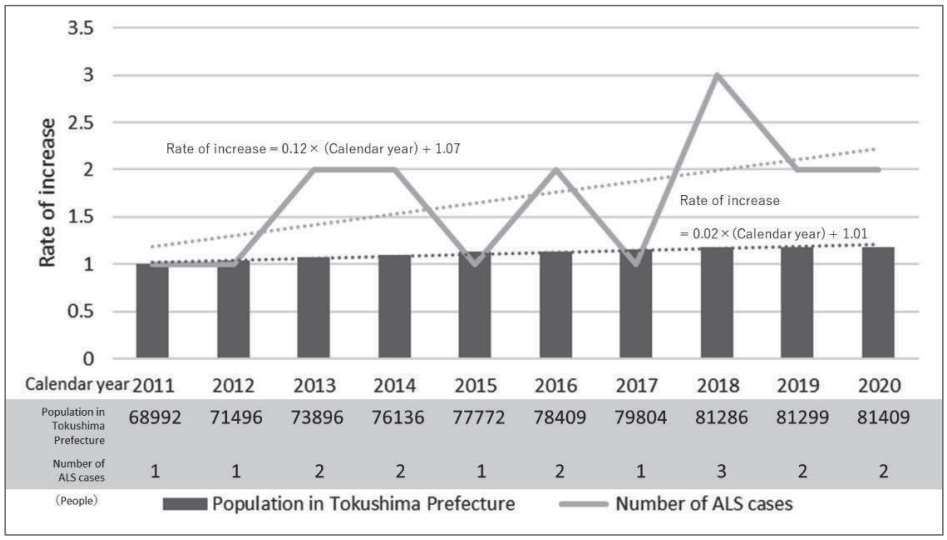

Figure 3. Annual rate of increase in the general population aged ≥80 years and the number of ALS patients who developed the disease at age ≥80 years living in Tokushima Prefecture (13)
There was no significant difference in the rate of increase.

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