Original Article
Yonsei Med J 2021 Apr;62(4):338-343
https://doi.org/10.3349/ymj.2021.62.4.338
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

# Clinical Course of Amyotrophic Lateral Sclerosis according to Initial Symptoms: An Analysis of 500 Cases

Jang Woo Lee[1,2], Seong-Woong Kang[2,3,4], and Won Ah Choi[3,4]

[1]Department of Physical Medicine and Rehabilitation, National Health Insurance Service Ilsan Hospital, Goyang;
[2]Yonsei University Graduate School of Medicine, Seoul;
[3]Rehabilitation Institute of Neuromuscular Disease, Yonsei University College of Medicine, Seoul;
[4]Department of Rehabilitation Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea.

**Purpose:** One obstacle in early diagnosis of amyotrophic lateral sclerosis (ALS) is its vague initial presentation, which is generally classified into limb- and bulbar-dominant types and may be mistaken for other musculoskeletal conditions. We analyzed clinical data from patients in relation to their initial presentation and prognosis from symptom onset to diagnosis.

**Materials and Methods:** We retrospectively analyzed the medical records of patients with ALS who were admitted for pulmonary rehabilitation between January 2007 and December 2019. We collected data on time of onset, initial presenting symptoms, unnecessary operations due to misdiagnosis, and the time between symptom onset and final diagnosis of ALS.

**Results:** Among 500 patients, unnecessary operations were performed in 43 patients. The median durations between symptom onset and ALS diagnosis for patients with and without operations were 11 and 9 months, respectively ($p$=0.008). 67.0%, 28.8%, and 4.2% of the patients presented with limb-, bulbar-, and respiratory-dominant symptoms, respectively, as initial presentations. The median ages at symptom onset were significantly different for limb-, bulbar-, and respiratory-dominant onset (57.5, 60.6, and 66.7 years, respectively; $p$<0.001). Compared to the other two types, patients with the respiratory-dominant onset were all male and showed higher rate of emergent endotracheal intubation before ALS diagnosis.

**Conclusion:** Inappropriate operations significantly delayed the diagnosis of ALS. Respiratory difficulty can account for a significant proportion among initial presentations in ALS. Compared to limb- and bulbar-dominant types, respiratory-dominant onset appears to show male predominance, older age at symptom onset, and poor respiratory prognosis.

**Key Words:** Amyotrophic lateral sclerosis, early diagnosis, surgical procedures, respiratory symptoms

## INTRODUCTION

Vague initial presentations and ambiguous laboratory findings often make it difficult to diagnose amyotrophic lateral sclerosis (ALS) at an early stage. Although 70% of familial ALS and 10% of sporadic ALS cases are confirmed genetically, familial ALS accounts for only 5–10% of all cases of ALS, and the testable genes may vary according to laboratory settings.[1,2] Therefore, ALS is often misdiagnosed as other diseases and treated inappropriately at the initial stage. Further, unnecessary treatments are likely to further delay the diagnosis of ALS.[3,4]

Various initial presenting symptoms of ALS are generally classified into limb- and bulbar-dominant types. Less than 5% of the patients are known to have trunk or respiratory involvement at the initial stage.[5] However, actual clinical data on these initial presentations are currently insufficient. Here, we analyze the clinical data of a large cohort of ALS patients with respect to initial symptoms and progress from symptom onset to diagnosis to provide useful insights for clinical practice.

**Received:** October 29, 2020 **Revised:** January 11, 2021
**Accepted:** February 2, 2021
**Corresponding author:** Won Ah Choi, MD, PhD, Department of Rehabilitation Medicine, Gangnam Severance Hospital, Rehabilitation Institute of Neuromuscular Disease, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea.
Tel: 82-2-2019-3698, Fax: 82-2-3463-7585, E-mail: reedlove37@yuhs.ac

•The authors have no potential conflicts of interest to disclose.

## MATERIALS AND METHODS

### Subject enrolment

As of December 2019, the medical records of 500 consecutive patients with ALS who were hospitalized at the Pulmonary Rehabilitation Center of Gangnam Severance Hospital from January 2007 were retrospectively analyzed. Diagnosis of ALS was essentially based on the revised El Escorial criteria, and the patients who fit the criteria for definite and probable ALS were included in this study. When the diagnosis was uncertain, diagnostic evaluations were repeated during the follow-up period in consultation with an experienced neurologist, if necessary. Patients with motor neuron diseases whose diagnoses were not confirmed as ALS were excluded. Patients with inaccurate data on initial presenting symptoms, onset time, or time of diagnostic confirmation were also excluded from the analysis. During that period, a total of 519 patients were admitted, but the medical records of 500 patients were used for analysis because 19 patients had insufficient medical information. The patients who were included in this study were all native Korean people.

### Collected information of the patients

We collected information on onset time, symptoms of initial presentation, time of diagnosis, and surgical treatments performed in relation to the presenting symptoms between the time of symptom development and diagnosis. The initial presenting symptoms were classified into three types according to the major symptoms at the initial presentation: 1) limb-dominant onset, 2) bulbar-dominant onset, and 3) respiratory-dominant onset. Limb-dominant symptoms included weakness and/or fatigue of the upper or lower extremities and loss of hand dexterity. Bulbar-dominant symptoms included dysphagia, dysarthria, drooling, and chewing difficulty. Symptoms of dyspnea, exertional dyspnea, and orthopnea were regarded as respiratory-dominant symptoms. We also collected data on surgical interventions received by the patients. No operations have been proven to be treatments for ALS until recently. However, some patients with ALS-related symptoms received surgical treatments prior to confirmation of ALS or after misdiagnosis. We defined these interventions as inappropriate operations. This study was approved by the Institutional Review Board of Gangnam Severance Hospital (3-2017-0393).

### Statistical analysis

For comparison of the frequency of each study group, a chi-square test was used. To compare median and mean values between two groups, Mann-Whitney (for non-normal distribution) and independent t-tests (for normal distribution) were performed, respectively. Because the number of subjects with respiratory-dominant onset was relatively low, the Kruskal-Wallis test was performed to compare the three types of initial presentations, and Bonferroni correction was used for post hoc analysis. All statistical analyses were performed using IBM SPSS Statistics 23 (IBM Corp., Armonk, NY, USA).

## RESULTS

The demographic characteristics of 500 patients are shown in Table 1. The average age at symptom onset was 57.9±11.9 years, and the mean duration from symptom onset to diagnosis of ALS was 12.7±11.9 months. Of the patients, 314 (62.8%) were male. Furthermore, 335 (67.0%) patients showed limb-dominant onset, 144 (28.8%) patients had bulbar-dominant onset, and 21 (4.2%) patients had respiratory-dominant onset according to the classification of initial presentation. Overall, 43 (8.6%) patients received inappropriate surgical treatment in

**Table 1.** Characteristics of the Study Subjects

| | Number (%) | Onset age (ys)* | *p* value | Onset to diagnosis (months)* | *p* value |
|---|---|---|---|---|---|
| Overall | 500 | 57.9±11.9 | | 12.7±11.9 | |
| Sex | | | 0.593† | | 0.004† |
| Male | 314 (62.8) | 58.1±11.6 | | 11.5±10.3 | |
| Female | 186 (37.2) | 57.5±12.6 | | 14.9±14.0 | |
| Age (yr) | | | | | 0.985† |
| <60 | 266 (53.2) | | | 12.7±12.5 | |
| ≥60 | 234 (46.8) | | | 12.7±11.2 | |
| Onset type | | | <0.001‡ | | 0.005‡ |
| Limb | 335 (67.0) | 57.5 (15.9) | | 10.0 (13.0) | |
| Bulbar | 144 (28.8) | 60.6 (14.1) | | 8.5 (10.0) | |
| Respiratory | 21 (4.2) | 66.7 (14.0) | | 6.0 (7.0) | |
| Operation | | | 0.053§ | | 0.008§ |
| With operation | 43 (8.6) | 61.8 (12.8) | | 11 (17) | |
| Without operation | 457 (91.4) | 58.3 (16.3) | | 9 (12) | |

*Onset age and the period between onset to diagnosis are presented as means±standard deviations or medians (interquartile rage), †Independent t-test, ‡Kruskal-Wallis test, §Mann-Whitney U test.

relation to the initial presenting symptoms after a misdiagnosis. A significant difference in onset age was not observed between male and female patients; however, the duration from symptom onset to ALS diagnosis was shorter for male patients than for female patients. There was no significant difference in the time from onset to diagnosis between patients who were aged <60 years and patients who were ≥60 years. No significant correlation was observed between onset age and diagnostic duration (correlation coefficient, -0.044; $p$=0.328; not shown in the table).

Furthermore, 62.7% (n=210) of the patients with limb-dominant onset and 57.6% (n=83) of the patients with bulbar-dominant onset were male; however, all 21 patients with respiratory-dominant onset were male, which was statistically significant ($p$=0.001). Although only 1.5% of the patients with limb-dominant onset and 4.9% of the patients with bulbar-dominant onset received emergent endotracheal intubation caused by acute ventilatory deterioration before ALS diagnosis, 15 of the 21 patients (71.4%) with respiratory-dominant onset underwent emergency endotracheal intubation before the diagnosis of ALS, which was significantly different ($p$<0.001). The median ages at symptom onset were 57.5 years for patients with limb-dominant onset, 60.6 years for patients with bulbar-dominant onset, and 66.7 years for patients with respiratory-dominant onset. The limb-dominant group showed significant earlier onset than the other two groups. The duration between symptom onset and diagnosis was significantly shorter in patients with respiratory-dominant onset, compared to patients with limb-dominant onset (Table 2).

The duration from symptom onset to diagnosis differed between the sexes depending on whether the patients with respiratory-dominant onset were included or not. If the 21 patients with respiratory-dominant onset were excluded from the analysis, the duration from symptom onset to diagnosis in the other 479 patients would be 12.7±12.4 months in male patients and 13.1±11.5 months in female patients; this difference was not statistically significant (independent t-test; $p$=0.220, not shown in the table).

The operation sites of the 43 patients who received inappropriate surgical intervention in relation to the initial symptoms before the diagnosis of ALS are described in Table 3. Thirty-eight patients underwent spinal surgeries, and four of them had multiple operations. Five patients received a carpal tunnel release operation, and one of them received a subsequent operation at the cervical spine. Cubital tunnel release was performed in one patient. None of the 43 patients showed any improvement in their relevant symptoms despite undergoing surgical treatments. Among the 43 patients, 41 patients had limb-dominant onset (12.3% of all patients with limb-dominant onset), and the other 2 patients had bulbar-dominant onset (1.4% of all patients with bulbar-dominant onset), a statistically significant difference ($p$<0.001). The two patients with bulbar-dominant onset received an operation at the cervical spine. No patients with respiratory-dominant onset underwent surgical treatment in relation to their initial presenting symptoms.

## DISCUSSION

The U.S. Food and Drug Administration has approved riluzole and edaravone for the treatment of ALS. Although these drugs cannot change the final outcome of ALS, they are known to slow the progress of the disease[6] and to increase tracheostomy-free survival.[7,8] For better prognosis and response, medication should be administered as early as possible.[9] Therefore, an accurate diagnostic evaluation is required at an early stage of the disease during which symptoms are ambiguous and vague.[10] If asymmetric distal limb weakness occurs in middle age, during which ALS develops frequently, differential diagnosis for various musculoskeletal conditions, including degenerative spinal diseases, is needed. Especially, cautious evaluation including electrodiagnosis should be considered in patients presenting with painless weakness. We have previously published a study showing that 34 (10.3%) of 331 patients with ALS underwent unnecessary surgery due to a misdiagnosis.[11] Another

**Table 3.** Operation Sites before Diagnosis of Amyotrophic Lateral Sclerosis

| Operation site | Number of patients (n=43) | Notes |
|---|---|---|
| Cervical spine | 17 | Twice in one patient, and three times in one patient |
| Cervical and lumbar spine | 1 | |
| Lumbar spine | 20 | Twice in one patient, and three times in one patient |
| Carpal tunnel release | 5 | Cervical spinal operation after carpal tunnel release in one patient |
| Cubital tunnel release | 1 | |

**Table 2.** Comparison of Onset Age and Time between Onset and Diagnosis among Limb-, Bulbar-, and Respiratory-Dominant Onset Groups

| | Limb (n=335)* | Bulbar (n=144)* | Respiratory (n=21)* | Limb vs. Bulbar† | Bulbar vs. Respiratory† | Respiratory vs. Limb† | Among 3 groups† |
|---|---|---|---|---|---|---|---|
| Age of symptom onset (yr) | 57.5 (15.9) | 60.6 (14.1) | 66.7 (14.0) | 0.012 | 0.159 | 0.006 | <0.001 |
| Time between symptom onset and diagnosis (months) | 10.0 (13.0) | 8.5 (10.0) | 6.0 (7.0) | 0.105 | 0.204 | 0.018 | 0.005 |

*Median (interquartile range), †$p$ values from Kruskal-Wallis test with Bonferroni correction.


https://doi.org/10.3349/ymj.2021.62.4.338

study using data from the Korean National Health Insurance Service revealed that 41.8% of patients with ALS were misdiagnosed with myelopathy and that 5.78% received inappropriate spinal surgery.[12] Unlike these previous studies, the present study derived the time of symptom development through medical records and consequently revealed that inappropriate surgical treatments based on misdiagnosis significantly increased the time from symptom onset to diagnosis of ALS. Kraemer, et al.[4] also reported that improper operations delayed the diagnosis of ALS in a study of 100 patients. Misdiagnosis of other musculoskeletal diseases at the beginning of ALS and inappropriate surgical treatments may lead to suffering, unnecessary medical expenses, and delays in ALS diagnosis, which may prevent indispensable initial treatments and affect long-term prognosis.[13,14] Because ALS is very rare, symptoms of ALS may be difficult to recognize unless the physician is familiar or experienced with neuromuscular diseases. The characteristics of limb-dominant ALS most commonly involving middle-aged people and presenting as focal asymmetric limb weakness at an initial stage can often be confused with degenerative spinal diseases.[15,16] The bulbar-dominant type is known to be related to a shorter duration between onset and diagnosis, compared to the limb-dominant type.[4,17,18] Generally, it is hard to suspect musculoskeletal disorders, including spinal diseases, which require surgical treatment, as a cause of bulbar symptoms.[3] In this study, 95.3% of the patients who received inappropriate operations also had limb-dominant onset. In fact, musculoskeletal diseases have been considered as a priority in many patients with initial presentation of limb-related symptoms. Nzwalo, et al.[3] reported that the diagnosis of ALS was faster when the initial consultation doctor was a neurologist, compared with other specialist doctors. Based on these results, diagnostic evaluations, such as imaging studies, electrodiagnosis, and genetic tests, are required in patients with suspected symptoms of ALS, so that the diagnosis of ALS can be accelerated and unnecessary treatments can be avoided.

Generally, patients with ALS are classified into limb-dominant and bulbar-dominant types according to the initial presentation, and limb-dominant onset is known to be more common than bulbar-dominant onset.[19] In addition, in this study, limb-dominant onset was about 2.3 times more frequent than bulbar-dominant onset. However, respiratory-dominant onset accounted for a non-negligible rate of 4.2%, in addition to limb- and bulbar-dominant onset. Although dyspnea can be an initial presenting symptom in patients with ALS, ventilatory insufficiency is known to be very rare.[20,21] In a small group of patients, trunk or respiratory involvement may occur early in the disease,[22] although there is insufficient clinical data on this: a few studies have reported on the actual rate of initial respiratory involvement among all patients. In the studies by Paganoni, et al.[23] and Gautier, et al.,[24] 1.6% (5 of 304 patients) and 3.0% (17 of 573 patients) showed respiratory symptoms as initial symptoms of ALS, respectively. Shoesmith, et al.[25] reported that 2.7% (21 of 791 patients) had initial respiratory symptoms in their retrospective chart review. Among 21 patients with respiratory-dominant onset, 76% were male. and the median age of symptom onset was relatively higher at 68.5 years, similar to that in our study. de Cavalho, et al.[26] analyzed 29 patients presenting with initial ventilatory insufficiency, comprising four of their cases and 25 patients from 16 previous case reports. The average age of these patients was 62.7 years, which was younger than that in studies by our group and Shoesmith, et al.,[25] and 86.2% (n=25) of them were male. In a study by Gautier, et al.,[24] all 17 patients with respiratory-dominant onset were male as well. Our study differs from previous studies in that we directly compared the clinical demographics of different clinical types with patients with initial respiratory symptoms. Although the reason remains unknown, it is believed that there is a male predominance for respiratory-dominant onset, and the onset age tends to be relatively higher, compared to the other types. In addition, in 71.4% of patients with respiratory-dominant onset in our study, emergent placement of endotracheal intubation was required. This is different from the study of Shoesmith, et al.,[25] in which only 14.3% (3 of 21) of the patients needed endotracheal intubation. However, in many case reports, mechanical ventilatory support was required in the early stages of the disease in patients who presented with initial respiration-related symptoms,[26] and emergent endotracheal intubation was also needed prior to the diagnosis of ALS, as in our study.[27,28] In a large-scale study, it was reported that the period from symptom onset to non-invasive ventilation was shorter in patients with respiratory onset, compared to that in other types.[24] Therefore, it is considered that prognosis related to the ventilation is poor in patients with early respiratory symptoms.

If a patient complains of respiratory difficulty, generally the physician considers cardiologic or pulmonary problems first. Dyspnea is also likely to be regarded as a kind of aging process, like distal limb weakness derived from a degenerative spinal disease. Furthermore, because the onset age of the respiratory-dominant type is relatively higher than that of other types, it is possible that ALS might not be considered at the initial presentation in many cases. However, the diagnosis of ALS may be accelerated during the course of various treatments and diagnostic evaluations: indeed, the disease progressed quickly in 15 of 21 (71.4%) patients who showed rapid deterioration of respiratory function requiring emergent endotracheal intubation in our study. The patients with respiratory-dominant onset were all male and had exceptionally short durations from symptom onset to diagnosis. When male patients with respiratory-dominant onset were excluded, however, there was no longer a difference between sexes in the time between symptom onset to diagnosis. The disease had progressed rapidly in this patient group, and during the treatment for rapid deterioration of ventilatory insufficiency, various tests might have been performed resulting in a quicker diagnosis. Although the

diagnosis was significantly faster in patients with respiratory-dominant onset than patients with other types, considering the occurrence of sudden ventilatory failure and consequent emergent intubation, it is thought that earlier diagnosis is needed in these patients. Therefore, attention needs to be paid to respiratory symptoms, of which the causes are unknown. Detailed history taking and a meticulous physical examination are also required. Because medical information is deficient and the reasons for male predominance and older age of respiratory-dominant onset are still unclear, epidemiological studies and further investigations are required.

A few limitations warrant consideration. Recall bias may have occurred because the information of onset time and symptoms depended heavily on the patients' memories. Even though medical data were gathered at a single institution, the initial evaluation and treatments were carried out at different hospitals, and medical staff at the patients' first visits also varied. Therefore, the treatments and diagnostic workups would have differed depending on the medical institution and doctors that the patients visited. Furthermore, because access was limited, progress of diagnostic evaluation, especially related to operations in other hospitals, could not be verified. Since only the time from symptom onset to diagnosis was analyzed, a follow-up study on the long-term outcomes of patients with different clinical types is needed.

In conclusion, unnecessary surgical treatments due to misdiagnosis at an early disease stage significantly delay the diagnosis of ALS. In particular, because limb-dominant onset is often misdiagnosed as a musculoskeletal disease, especially of spinal origin in many cases, detailed surveillance, including close history taking, physical examination, and diagnostic evaluations, such as electrodiagnosis, is required. Respiratory difficulty can be another initial presentation of ALS accounting for an appreciable number of cases, in addition to the limb- and bulbar-dominant types. Finally, compared to the limb- or bulbar-dominant type, the respiratory-dominant onset type showed male predominance, older age at onset of symptoms, and poor prognosis.

## ACKNOWLEDGEMENTS

This study was supported by an SRC research grant from Yonsei University College of Medicine for 3-2015-0264.

## AUTHOR CONTRIBUTIONS

Conceptualization: Seong-Woong Kang. Data curation: Won Ah Choi. Formal analysis: Jang Woo Lee. Funding acquisition: Seong-Woong Kang. Investigation: Won Ah Choi. Methodology: Won Ah Choi. Project administration: Seong-Woong Kang. Resources: Won Ah Choi. Software: Jang Woo Lee. Supervision: Seong-Woong Kang. Validation: Jang Woo Lee. Visualization: Jang Woo Lee. Writing—original draft: Jang Woo Lee. Writing—review & editing: Won Ah Choi. Approval of final manuscript: all authors.

## ORCID iDs

Jang Woo Lee https://orcid.org/0000-0002-2634-0375
Seong-Woong Kang https://orcid.org/0000-0002-7279-3893
Won Ah Choi https://orcid.org/0000-0003-0403-8869

## REFERENCES

1. Joyce NC, Tolchin DW, Howard IM, Paganoni S. Motor neuron disease. In: Frontera WR, Delisa JA, Basford JR, Bockenek WL, Chae J, Robinson LR, editors. Delisa's physical medicine and rehabilitation: principles and practice. 6th ed. Philadelphia (PA): Lippincott Williams & Wilkins Health; 2019. p.501-19.
2. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. N Engl J Med 2017;377:162-72.
3. Nzwalo H, de Abreu D, Swash M, Pinto S, de Carvalho M. Delayed diagnosis in ALS: the problem continues. J Neurol Sci 2014;343:173-5.
4. Kraemer M, Buerger M, Berlit P. Diagnostic problems and delay of diagnosis in amyotrophic lateral sclerosis. Clin Neurol Neurosurg 2010;112:103-5.
5. Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, et al. Amyotrophic lateral sclerosis. Lancet 2011;377:942-55.
6. Sawada H. Clinical efficacy of edaravone for the treatment of amyotrophic lateral sclerosis. Expert Opin Pharmacother 2017;18:735-8.
7. Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev 2012;2012:CD001447.
8. Okada M, Yamashita S, Ueyama H, Ishizaki M, Maeda Y, Ando Y. Long-term effects of edaravone on survival of patients with amyotrophic lateral sclerosis. eNeurologicalSci 2018;11:11-4.
9. Yoshino H. Edaravone for the treatment of amyotrophic lateral sclerosis. Expert Rev Neurother 2019;19:185-93.
10. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis: Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, van Damme P, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force. Eur J Neurol 2012;19:360-75.
11. Kim S, Kang SW, Choi W, Park JH, Lee Y, Yu SJ. Survey on the diagnostic process of amyotrophic lateral sclerosis. J Korean Acad Rehabil Med 2011;35:110-4.
12. Kim JM, Park JH, Kim HS, Lee JW, Lim HS, Choi WA, et al. Epidemiology and diagnostic process of amyotrophic lateral sclerosis as distinct from myelopathy: 5-year cohort study of whole-population in South Korea. Amyotroph Lateral Scler Frontotemporal Degener 2018;19:547-54.
13. Bakola E, Kokotis P, Zambelis T, Karandreas N. Inappropriate surgeries in amyotrophic lateral sclerosis: a still considerable issue. Amyotroph Lateral Scler Frontotemporal Degener 2014;15:315-7.
14. Onder H, Yildiz FG. Cervical spondylotic myelopathy mimicking amyotrophic lateral sclerosis. J Neurol Res 2016;6:89-90.
15. Srinivasan J, Scala S, Jones HR, Saleh F, Russell JA. Inappropriate surgeries resulting from misdiagnosis of early amyotrophic lateral sclerosis. Muscle Nerve 2006;34:359-60.
16. Yoshor D, Klugh A 3rd, Appel SH, Haverkamp LJ. Incidence and characteristics of spinal decompression surgery after the onset of symptoms of amyotrophic lateral sclerosis. Neurosurgery 2005;57:984-9.
17. Khishchenko N, Allen KD, Coffman CJ, Kasarskis EJ, Lindquist JH, Morgenlander JC, et al. Time to diagnosis in the National Registry of Veterans with amyotrophic lateral sclerosis. Amyotroph Lateral Scler 2010;11:125-32.


https://doi.org/10.3349/ymj.2021.62.4.338

18. Zoccolella S, Beghi E, Palagano G, Fraddosio A, Samarelli V, Lamberti P, et al. Predictors of delay in the diagnosis and clinical trial entry of amyotrophic lateral sclerosis patients: a population-based study. J Neurol Sci 2006;250:45-9.
19. Rothstein JD. Edaravone: a new drug approved for ALS. Cell 2017; 171:725.
20. Jorgensen S, Arnold WD. Motor neuron diseases. In: Cifu DX, editor. Braddom's physical medicine and rehabilitation. 5th ed. Philadelphia (PA): Saunders Elsevier; 2016. p.883-905.
21. Krivickas LS, Carter GT. Adult motor neuron disease. In: Frontera WR, DeLisa JA, Gans BM, Walsh NE, Robinson LR, editors. Delisa's physical medicine and rehabilitation: principles and practice. 5th ed. Philadelphia (PA): Lippincott Williams & Wilkins Health; 2010. p.717-40.
22. Vucic S, Burke D, Kiernan MC. Diagnosis of motor neuron disease. In: Kiernan MC, editor. The motor neuron disease handbook. Sidney: Australasian Medical Publishing Company Limited; 2007. p.89-115.
23. Paganoni S, Macklin EA, Lee A, Murphy A, Chang J, Zipf A, et al. Diagnostic timelines and delays in diagnosing amyotrophic lateral sclerosis (ALS). Amyotroph Lateral Scler Frontotemporal Degener 2014;15:453-6.
24. Gautier G, Verschueren A, Monnier A, Attarian S, Salort-Campana E, Pouget J. ALS with respiratory onset: clinical features and effects of non-invasive ventilation on the prognosis. Amyotroph Lateral Scler 2010;11:379-82.
25. Shoesmith CL, Findlater K, Rowe A, Strong MJ. Prognosis of amyotrophic lateral sclerosis with respiratory onset. J Neurol Neurosurg Psychiatry 2007;78:629-31.
26. de Carvalho M, Matias T, Coelho F, Evangelista T, Pinto A, Luís ML. Motor neuron disease presenting with respiratory failure. J Neurol Sci 1996;139 Suppl:117-22.
27. Sato K, Morimoto N, Deguchi K, Ikeda Y, Matsuura T, Abe K. Seven amyotrophic lateral sclerosis patients diagnosed only after development of respiratory failure. J Clin Neurosci 2014;21:1341-3.
28. Chou CT, Lin CH, Choi WM. Acute respiratory failure as initial presentation of amyotrophic lateral sclerosis onset. Int J Gerontol 2008;2:72-5.