Amyotrophic lateral sclerosis in Slovenia – analysis of a patient cohort at the Ljubljana Institute of Clinical Neurophysiology

Amiotrofična lateralna skleroza v Sloveniji – analiza bolnikov Kliničnega inštituta za klinično nevrofiziologijo

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Izvleček

Izhodišča: Podatki o epidemiologiji in značilnostih amiotrofične lateralne skleroze (ALS) so obsežni, a geografsko omejeni. Doslej o ALS v Sloveniji ni bilo sistematično zbranih podatkov, zato smo opravili retrospektivno raziskavo o kliničnih značilnostih in poteku bolezni pri bolnikih, obravnavanih na Kliničnem inštitutu za klinično nevrofiziologijo UKC Ljubljana (IKN) po ustanovitvi specializirane skupine za ALS.

Metode: V raziskavo smo zajeli vseh 271 bolnikov, ki so bili na IKN obravnavani med letoma 2003 in 2012. Zbrali smo podatke o demografskih značilnostih, fenotipu bolezni, preživetju, družinski anamnezi, uporabi perkutane gastrostome, podpornih načinih predihavanja ter zdravljenju z riluzolom.

Rezultati: Povprečna starost bolnikov ob prvih simptomih je bila 62,7 ± 11,4 leta, mediana diagnostičnega zaostanka 11 mescev (interkvartilni razpon 7–19 mesecev), povprečno preživetje od začetka obravnave v skupini za ALS pa 16,4 ± 15,1 meseca. Obliko bolezni s spinalnim začetkom je imelo 179 (66,1 %) bolnikov, z bulbarnim pa 71 (26,2 %) bolnikov. Dejavniki, povezani z daljšim preživetjem, so bili nižja starost, daljši diagnostični zaostanek in raba perkutane gastrostome. Delež bolnikov, ki so uporabljali neinvazivno podporno predihavanje, je z leti naraščal.

Zaključki: Značilnosti bolezni in preživetje bolnikov v naši raziskavi so primerljivi s podatki drugih terciarnih središč. Potreba po neinvazivnem podpornem predihavanju bolnikov z ALS narašča.

Abstract

Backgorund: Data on the epidemiology and phenotype of amyotrophic lateral sclerosis (ALS) are geographically limited and no data have been systematically collected for patients in Slovenia. We performed a retrospective descriptive study on clinical features and disease course of patients with ALS treated by a specialised ALS group at the Institute of Clinical Neurophysiology (ICN), University Medical Centre Ljubljana.

Methods: Data of all 271 patients treated at ICN in the 10-year period between 2003 and 2012 were analysed: basic demographic characteristics, phenotype of disease onset, diagnostic delay, survival, family history, use of percutaneous gastrostomy (PEG), of non-invasive ventilation and riluzole treatment.

Results: Mean age at the onset of symptoms was 62.7 ± 11.4 years, median diagnostic delay 11 (IQ range 7–19) months and mean survival from time of enrolment 16.4 ± 15.1 months. 179 (66.1 %) patients had spinal and 71 (26.2 %) bulbar disease onset. Factors associated with longer survival were lower age at enrolment, longer diagnostic delay and use of PEG. The proportion of patients using non-invasive ventilatory support was increasing with years of analysis.

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Conclusions: Disease characteristics and survival in our series are similar to data from other tertiary care centres. The need for non-invasive ventilatory support in ALS patients is increasing.

Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder that primarily affects the motor system and is characterised by dysfunction of both lower (weakness, muscle atrophy and fasciculations) and upper motor neurons (weakness, spasticity and brisk reflexes). Presentation of ALS is highly variable regarding age, affected body part, degree of upper/lower motor neuron impairment and rate of deterioration. The onset of weakness is typically focal and later it spreads to the adjacent body parts and eventually results in quadriplegia with respiratory insufficiency and weakness of bulbar muscles.[1,2] Most patients die of respiratory failure.[3]

Within ALS, several disease phenotypes are recognised based on the initial signs.[2,4,5] The most prevalent is spinal onset of the disease where weakness first manifests in the limb or trunk muscles; it is found in around 70 % of patients. The second most common form, affecting 25 % – 30 % of patients, is bulbar onset ALS with initial weakness of bulbar muscles; speech and swallowing are predominantly affected. Some 1–3 % of patients present with respiratory insufficiency due to diaphragm weakness. In rare forms of motor neuron disease there is selective involvement of only upper motor neurons (primary lateral sclerosis) or lower motor neurons (progressive muscular atrophy). The incidence rate in the majority of European series ranges between 1.5 and 3.0 per 100,000, while the prevalence rate is between 5 and 8 per 100,000.[6] The incidence peaks in the 6th and 7th decades.[6,7]

Due to variable clinical presentation, the diagnosis of ALS is challenging and the average reported diagnostic delay is approximately 1 year.[4,8] ALS is relentlessly progressive with survival estimates ranging between 24 and 36 months from the onset of symptoms and 14–19 months from diagnosis, with survivals for a decade or longer possible.[7,9] The most consistently reported negative prognostic factors for survival are older age, shorter diagnostic delay and reduced vital capacity, less often bulbar onset of the disease, lower body mass index, neck muscle weakness and female gender.[5,7,10-13]

ALS is increasingly being recognised as a multisystem disease that affects multiple body functions not necessarily related to muscle weakness. The patients' quality of life is diminished by impairment of swallowing, cachexia, sleep disorders, excessive salivation, bulbar affect, pain etc. An important proportion of patients suffers from fronto--temporal cognitive impairment.[14,15] Such heterogeneous and progressive symptoms require experienced, rapidly responsive medical personnel and this has led to the development of specialised multidisciplinary ALS teams.[16] These are especially important for an early recognition of speech, swallowing or breathing problems and in offering timely social support and palliative care. In addition to improving care, organised ALS teams facilitate systematic follow up of ALS patients, which is a prerequisite for aetiological research.[9,17] For these reasons a dedicated group of healthcare professionals has been formed at the Institute of Clinical Neurophysiology, University Medical Centre Ljubljana (ICN)–the main tertiary centre for neuromuscular diseases in the Republic of Slovenia – under the name of *ALS Group*.

Published data on ALS epidemiology and course of the disease is ample though geographically limited; data on patients in Slovenia have as yet not been systematically collected. We therefore performed a retrospective descriptive study on clinical features and prognosis of patients with ALS treated at the ICN, with the secondary aim to assist in planning future needs of the ALS Group.

Patients and methods

The ALS group

The ALS Group as a specialised team of healthcare professionals was established in October 2002. Its core members are neurologists, nurses, clinical psychologists, speech therapists, respiratory therapists and a social worker. The Group regularly cooperates with other specialties and hospice personnel. ALS Group treats all patients who have been diagnosed with ALS at the ICN and those referred to the ICN with an established diagnosis. As a rule, all patients from Ljubljana region and a great majority of patients from the western parts of Slovenia (Goriška, Koprska, Gorenjska and Dolenjska regions) are followed up regularly at the ICN, while those from eastern Slovenia (Štajerska and Pomurska regions) are mainly referred to ICN for non-invasive ventilation.

Patients

Patients enlisted in the ALS group at the ICN between the 1st of January 2003 and the 31st of December 2012 were included in the study. Data were acquired retrospectively from the ALS Group database and the ICN medical records. Data acquisition was finished in March 2014, 15 months after last enrolment. We collected basic demographic data, phenotype of disease onset, patient-assessed time of symptom onset, date of enrolment into ALS group, family history of ALS, use of percutaneous gastrostomy (PEG), non-invasive ventilation, riluzole treatment and date of death of the deceased patients. Phenotype of disease onset was divided into spinal ons et (first symptoms in limb, trunk or respiratory muscles) and bulbar onset. For patients diagnosed at the ICN, the date of enrolment is the date at which the diagnosis was communicated to them, while for those diagnosed elsewhere, this is the date of their first visit at the ALS Group. Familial ALS was defined as the presence of disease in either a first- or second-degree relative.

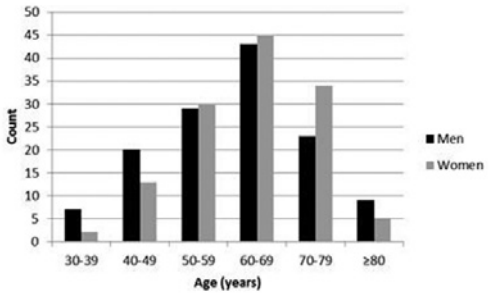

Figure 1: Distribution fo age at sympton onset by gender.

Statistical analysis

Demographics and disease characteristics were analysed using descriptive methods: mean, range, standard deviation (SD) and frequencies. Median with interquartile (IQ) range was used for the diagnostic delay because of its skewed distribution; diagnostic delay was calculated as the difference between the time of enrolment into the ALS Group and the time of symptom onset, as assessed by the patient. Subgroup comparisons were done by independent t-test for continuous and χ^2 test for categorical variables. Variables independently associated with survival were identified using a multiple linear regression model. Kaplan-Meier survival analysis was then used to estimate survival depending on these factors; the Breslow (Generalized Wilcoxon) χ^2 statistics was used to test for difference between groups. P value of 0.05 was set as the limit of statistical significance. SPSS Statistics 20.0 (IBM®) was used for statistical analysis.

The study is part of a wider study on epidemiology and pathogenesis of ALS, which has been approved by the National Medical Ethics Committee of the Republic of Slovenia.

Results

In the described 10-year period, our ALS Group treated 271 patients (137 men, 50.6 %). The average number of annually enrolled patients was 19 and 35 in the first and in the last three analysed years, respectively. The number of patients in the ALS Group care at any one time grew from approximately 20 in the year 2003 to between 75 and 85 in the year 2012.

The mean age at symptom onset was 62.7 years (range 32–90 years), while the mean age at enrolment was 64.0 years (range 35–91 years). Age distribution by gender is shown

in Figure 1. It illustrates male predominance in the younger age groups and female predominance among older patients. Median diagnostic delay between symptom onset and enrolment was 11 (IQ 7–19) months. Phenotype was characterised as bulbar onset in 71 (26.2 %) and as spinal onset in 179 (66.1 %) patients. Of the latter, three had diaphragmatic weakness with respiratory insufficiency as the first disease sign, four were initially diagnosed with progressive muscular atrophy, and one with primary lateral sclerosis. In 21 (7.7 %) patients disease phenotype could not be reliably established due to insufficient medical records. Altogether nine (3.3 %) patients had a familial form of the disease. Characteristics of patient subgroups based on disease phenotype, age and diagnostic delay are presented in Table 1. Comparisons of subgroups showed younger age at diagnosis in spinal onset patients, longer average survival in younger patients and in those with longer diagnostic delay (Table 1). Male patients significantly outnumbered females in the spinal onset subgroup, but the opposite was true in the bulbar onset subgroup. When stratified for age at onset, the male to female ratio was 1.8 for those aged < 50 years, 1.0 for those at an age between 50–64 years, and 0.83 for those aged ≥ 65 years. Patients with bulbar onset were more frequently treated with PEG compared to spinal onset ones, while there was no statistically significant difference in the use of ventilatory support, diagnostic delay or survival between spinal and bulbar onset subgroups (Table 1).

In the whole sample, mean survival from symptom onset was 29.6 ± 18.1 months and from time of enrolment 16.4 ± 15.1 months. One-year survival from symptom onset was 86 %, 2-year survival 50 % and 5-year survival 8 %; for time of enrolment these figures were 50 %, 18 % and 2 %, respectively. In the regression analysis, factors independently associated with longer survival from symptom onset were lower age at enrolment (b = - 0.48), longer diagnostic delay (b = 0.98) and use of PEG (b = 5.31), while gender, use of ventilator support, riluzole and clinical disease type

Table 1: Demographic and clinical characteristics of patients in predefined subgroups.

	Number of male patients	Age at symptom onset (years)	Survival from symptom onset (months)	Diagnostic delay (months)	Number of patients with PEG	Number of patients using ventilatory support
All patients (n = 271)	127 (50.6 %)	62.6 (11.4)	29.6 (18.1)	14.6 (11.9)	93 (34.3 %)	94 (34.7 %)
Spinal onset (n = 171)	96 (56.3 %)*	61.7 (11.5)*	30.0 (19.0)	15.0 (11.2)	41 (24.1 %)*	65 (37.9 %)
Bulbar onset (n = 71)	26 (36.6 %)*	65.5 (10.5)*	28.3 (16.5)	12.0 (10.9)	49 (69.0 %)*	20 (28.2 %)
Age < 65 years (n = 131)	53.4 %	54.1 (7.8)*	33.9 (20.5)*	15.8 (12.2)	34.4 %	41.7 %
Age ≥ 65 years (n = 116)	47.4 %	72.3 (5.5)*	25.8 (14.8)*	13.2 (11.4)	37.9 %	38.2 %
Diagnostic delay < 12 months	45.7 %	63.8 (11.6)	23.4 (17.0)*	6.6 (2.6)*	47.2 %*	35.4 %
Diagnostic delay ≥ 12 months	54.1 %	61.0 (11.3)	39.3 (16.7)*	23.9 (12.0)*	23.4 %*	30.6 %

Data are presented as average (standard deviation) for numeric and as number (percentage) for categorial variables.
**statistically significant difference between subgroups (p < 0.01)*
PEG = percutaneous gastrostomy

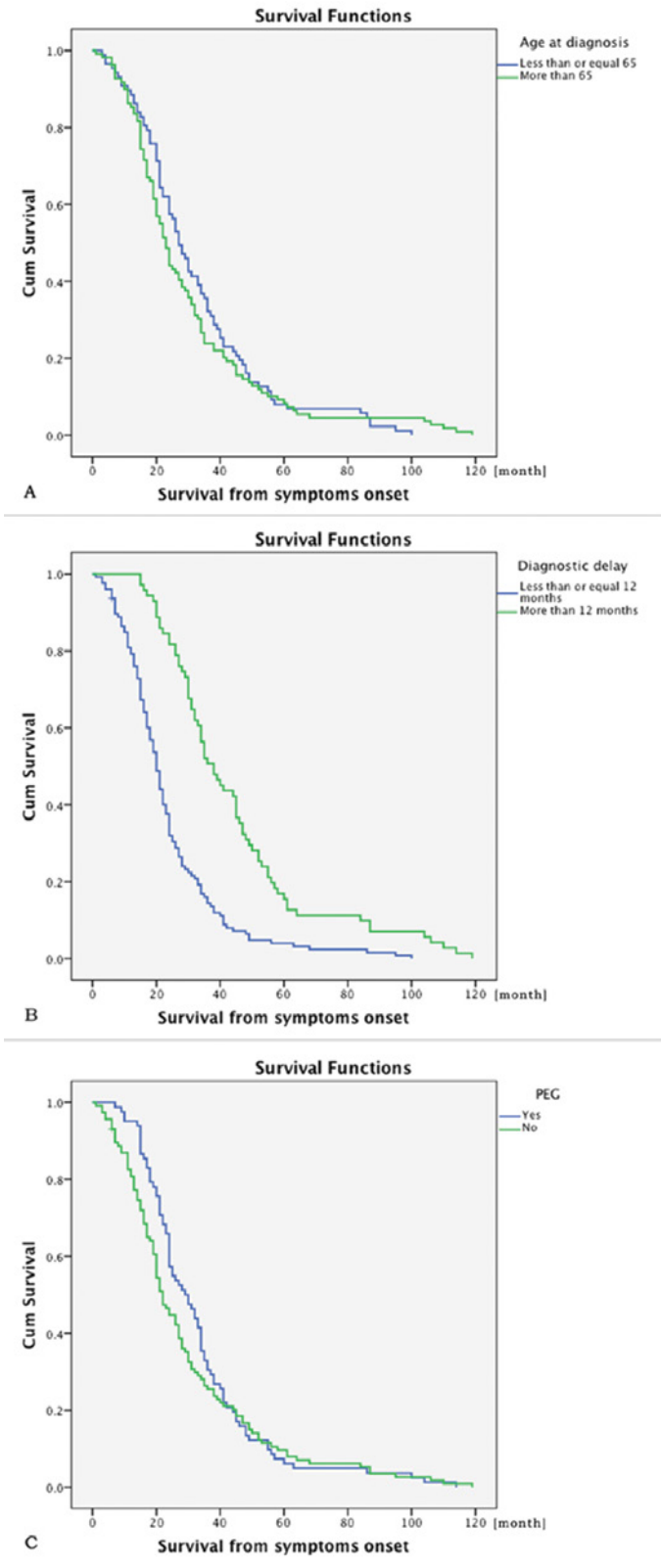

Figure 2: Kaplan-Meier survival curves based on variables independently associated with survival.
a. Survival by age at symptom onset (≤ 65 years and > 65 years)
b. Survival by diagnostic delay (≤ 12 months and > 12 months)
c. Survival by use of percutaneous gastrostomy
Legend: PEG = percutaneous gastrostomy

were not; adjusted R^2 0.355. Survival curves based on variables independently associated with survival are presented in Figure 2. Survival in patients with PEG (mean 33.3 months, *SE* 2.2) was significantly higher than in patients without PEG (mean 29.5 months, *SE* 2.2; $\chi^2(1) = 5.85$, $p = 0.016$). The survival was significantly shorter in patients with a diagnostic delay of ≤ 12 months (mean 23.6 months, *SE* 1.5), compared to those with a diagnostic delay of > 12 months (mean 44.2 months, *SE* 2.3; $\chi^2(1) = 49.48$, $p < 0.01$). While older age at diagnosis as a continuous variable was negatively associated with survival, subgroups arbitrarily divided at 65 years did not differ in survival according to the Kaplan-Meier analysis (mean survival for age at diagnosis ≤ 65 years 32.5 months, SE 2.2, mean survival for > 65 years 29.9 months, SE 2.2; $\chi^2(1) = 2.34$, $p = 0.126$).

In total, 34.3 % of all patients had a PEG placed and 34.7 % used non-invasive assisted ventilation. With regard to the year of enrolment, the proportion of patients who decided for TEG was stable, while the proportion of those using non-invasive ventilatory support was rising ($p < 0.01$, $r^2 = 0.748$, linear regression analysis; Figure 3). Four patients had a tracheostomy done solely for airway hygiene. Six patients opted for invasive ventilation; two of them had started using it before the diagnosis of ALS was established. Average survival after PEG placement was 9.0 ± 11.6 months and survival after institution of non-invasive ventilation was 7.8 ± 7.3 months. Approximately one half (54.6 %) decided for riluzole treatment and this remained constant throughout the analysed period.

Discussion

Referral of patients with motor neuron disease from across Slovenia to the ICN ALS Group is neither mandatory nor systematic, so our data cannot be used as population statistics, although the majority of Slovenian patients are referred to the ICN at some point. Using our data, the lower estimate of ALS incidence in Slovenia would be 1.8/100,000 and prevalence 4.3/100,000 which is comparable to other European countries.[6] The stu-

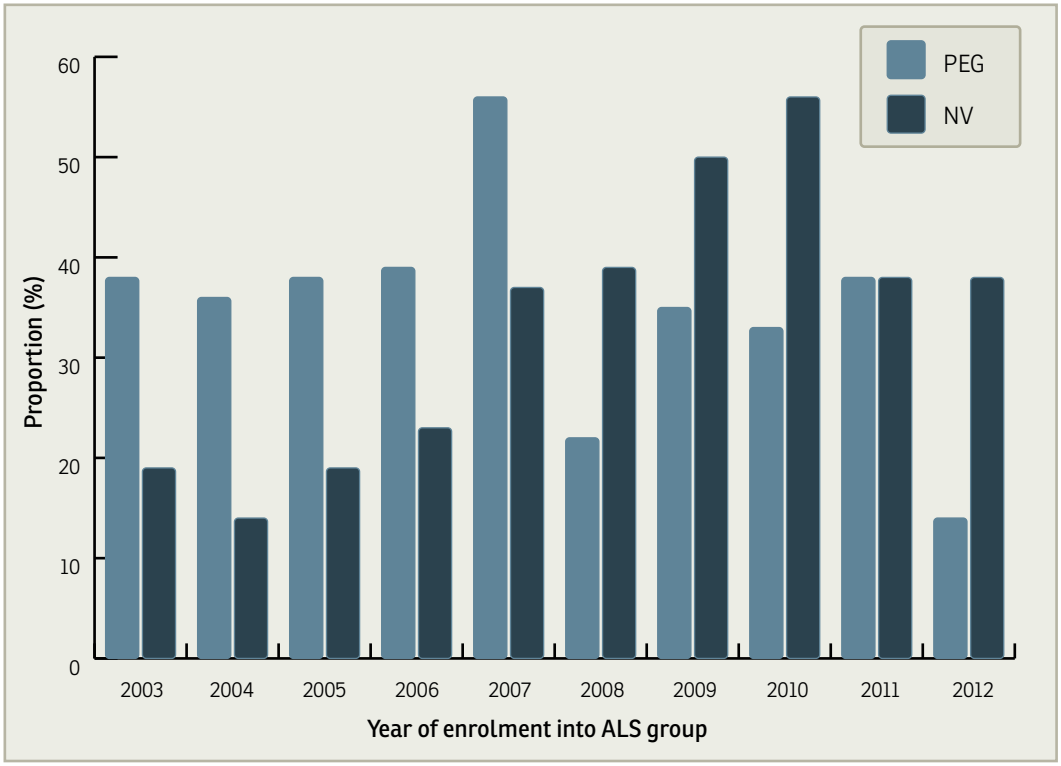

Figure 3: Proportion of patients using a percutaneous gastrostomy tube or ventilatory support at any time during disease course, distributed by year of enrolment into the Amyotrophic Lateral Sclerosis Group.
Legend:
PEG = percutaneous gastrostomy, NV = non-invasive ventilation.

dy thus offers a relevant picture of the epidemiologic and demographic characteristics of ALS in Slovenia and a realistic representation of ALS patients in a tertiary care centre.

Age distribution at symptom onset in our sample was similar to many other series, but we did not find the usually reported predominance of male patients.[5,6,18-20] In younger patients, the male to female ratio was the expected 1.8 : 1, but among older patients females predominated even when the demographic structure of the Slovenian population was taken into account.[7,21,22] Although this trend is rare, it has been found in at least one other recent study.[10]

The median diagnostic delay of 11 months is in line with other international reports, which mostly range between 9 and 13 months.[4-6] The average survival was also similar to that in other systematically studied patient populations.[7,9] In addition to longer diagnostic delay and younger age, which were the expected positive prognostic factors, in our sample use of PEG was the third variable associated with longer survival. The validity of the first two positive prognostic factors has been confirmed repeatedly while the effect of PEG placement on the survival is less clear.[7,13] Longer survival after longer diagnostic delay is usually explained by slower disease progression.[7] Like several other authors, we have not found gender or disease phenotype to be independent predictors of survival.[7,23,24]

The proportion of patients using PEG in our sample has remained similar throughout years, while the number of patients opting for non-invasive ventilation support has been increasing with time and reached approximately 50 %. This rising percentage can be attributed to better organisation and improving expertise of the ALS group itself as well as to increased awareness in regional referring centres. When the ALS group was formed, contrary to PEG, non-invasive ventilation was, not systematically available to ALS patients, and this remains a developing field in terms of education and cooperation with health insurance agency. The lower proportions of patients on non-invasive ventilation or PEG among those enrolled in the last two analysed years is expected as in some of them the disease had not reached its advanced stage by the end of data collection. The survival after PEG placement and initiation of ventilatory support in our sample is comparable to that reported in other studies, indicating timely

referral and quality post-procedural care.[12] The proportion of non-invasively ventilated patients has reached levels reported by other tertiary care centres.[25] The 2.2 % share of invasively ventilated patients in Slovenia is lower than in some other countries.[26] In our study, non-invasive ventilation was not associated with improved survival, but it has to be noted that the care for ventilation might not have been optimal in the first years of the ALS Group; furthermore, data on technical details of ventilation, such as time of ventilation and support pressures, which are known to influence survival and quality of life, were not included in the analysis.[27,28] The influence of noninvasive ventilation on the survival and quality of life thus requires a more detailed study.

ALS is predominantly a sporadic disease. A recent meta-analysis revealed the rate of familial ALS to be 5.1 % in prospective population based registries and 3.7 % in retrospective studies.[29] The rates reported in European countries differ substantially, from e.g. 1.5 % in Greece to 11.6 % in Finland.[29] The proportion of 3.3 % in our study seems relatively low. However, the reported proportions may differ due to the lack of clear definition of familial ALS, differences in data collection protocols or geographic variability.[29] In a genetic study on a different population of 72 Slovenian patients with ALS, mutations in four most common genes causing ALS (*C9ORF72*, *SOD1*, *TARDBP* and *FUS*) were found in 5 patients (6.9 %).[30]

Limitations of our study are its retrospective design with incomplete data for some patients. The numbers on survival, PEG and non-invasive ventilation use are affected by data collection conclusion less than two years after the last enrolment. On the other hand, the overall number of patients included contributes to the reliability of the study.

Conclusions

The demographic and disease characteristics as well as the survival of patients from a Slovenian tertiary ALS centre are similar to those in other published series. The increasing number of patients requiring non-invasive ventilatory support can be attributed to the professional and organisational efforts of the ALS Group and calls for increased resources to ensure further progress of care for ALS patients in Slovenia.

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