AMYOTROPHIC LATERAL SCLEROSIS PATIENTS IN OTORHINOLARYNGOLOGY: A RETROSPECTIVE STUDY

Jesper Rautiola[1], Hannu Laaksovirta[1], Ahmed Geneid[1], Taru Ilmarinen[1], Petra Pietarinen[1], and Teemu Kinnari[1]

[1]Helsinki University Central Hospital

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Abstract

Abstract OBJECTIVES Given its rarity and the lack of clear clinical markers, amyotrophic lateral sclerosis (ALS) remains a diagnostic challenge. Since bulbar-onset ALS (buALS) presents with impaired speech or swallowing, patients are often primarily referred to an otolaryngologist (ORL) or phoniatrician. We analyzed the role of such specialists in ALS diagnostics and treatment. PARTICIPANTS We reviewed data for all 327 patients treated for ALS through the Hospital District of Helsinki and Uusimaa (HUS) between 2010 and 2014, focusing specifically on 110 (34%) patients presenting with bulbar nerve onset (buALS). MAIN OUTCOME MEASURES The presenting symptoms, referral to specialized care, and to a neurology clinic were assessed. Indications and findings from swallowing studies were reviewed as well as the incidence of percutaneous endoscopic gastrostomy (PEG) and tracheostomy. RESULTS Among the 110 patients with buALS, 64 (58%) were primarily referred to a neurologist, 28 (25%) to an ORL, and 5 (5%) to a phoniatrician. The most common presenting symptom was dysarthria in 89 patients, (81%), followed by dysphagia in 26 (24%). In most cases, an ORL or phoniatrician suspected a neuromuscular disease; however, in 8 (24%) cases, the neurological etiology of symptoms was missed. Overall, 49 (45%) patients underwent a swallowing study and 86 (78%) patients underwent PEG placement. CONCLUSIONS Among buALS patients, 30% initially consulted an ORL or phoniatrician and 45% underwent a swallowing study. Based on our results, swallowing studies rarely lead to immediate PEG placement. An initial visit to other specialists had no impact on diagnostic delays or survival. Five keypoints Amyotrophic lateral sclerosis (or ALS) Motor neuron disease Dysphagia Fiberoptic Endoscopic Examination of Swallowing (or FEES) Percutaneous Endoscopic Gastrostomy (or PEG) Level of Evidence: 3

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MAIN OUTCOME MEASURES

The presenting symptoms, referral to specialized care, and to a neurology clinic were assessed. Indications and findings from swallowing studies were reviewed as well as the incidence of percutaneous endoscopic gastrostomy (PEG) and tracheostomy.

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CONCLUSIONS

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Five keypoints

Amyotrophic lateral sclerosis (or ALS)

Motor neuron disease

Dysphagia

Fiberoptic Endoscopic Examination of Swallowing (or FEES)

Percutaneous Endoscopic Gastrostomy (or PEG)

Level of Evidence: 3

Introduction

Amyotrophic lateral sclerosis (ALS), a progressive, neurodegenerative disease, affects the motor neurons in the cerebral cortex, brainstem, and spinal cord, resulting in weakness, spasticity, and the progressive loss of muscular control and function.[1] In Europe, the estimated annual incidence of ALS is 2.1–3.8 with a prevalence of 4.1–8.4 per 100 000 person-years.[2]

Up to 70% of ALS patients experience spinal nerve onset affecting the extremities (extALS).[1] By contrast, 25–30% of ALS patients present with impaired speech and/or swallowing, or bulbar nerve onset ALS (buALS).[1,3–6] The clinical presentation, disease course, and prognosis in these subtypes differ. ALS patients with no evident family history of motor neuron disease, referred to as "Sporadic ALS", make up 90–95% of all ALS patients.[1,3–6]

As yet, no curative treatment for ALS is available. Assisted ventilation is used by a minority of patients. [7] In Finland from 2017 to 2020, the incidence of tracheostomy-assisted ventilation seems to have decreased.[8,9] Prognosis remains poor, with an expected 3-year survival of 40% and an 8-year survival of 10%.[1,3–6] The progression of symptoms ultimately leads to respiratory failure, the leading cause of death among ALS patients.[5] Survival can vary, partly depending on the genotype, from less than 1 year to decades.[10] BuALS is associated with higher all-cause mortality, greater co-morbidities, and a lower quality of life.[1,2,4]

Given the rarity and the lack of clear clinical markers, ALS and buALS specifically represent diagnostic challenges. Since buALS presents with dysarthria and dysphagia,[3] patients may be primarily referred to an otorhinolaryngologist (ORL) or a phoniatrician. Furthermore, referral to an ORL, phoniatrician, or a speech-language pathologist (SLP) is often crucial in order to provide recommendations for dietary changes, compensatory maneuvers, and supplemental forms of feeding such as a percutaneous endoscopic gastrostomy (PEG) tube. A videofluoroscopic swallow study (VFSS) and a fiberoptic endoscopic examination of swallowing (FEES) are often employed.

This retrospective study aims to characterize ALS patients treated in the Helsinki metropolitan region during a five-year period (2010–2014). Specifically, we focused on patients with buALS, their presenting symptoms,

diagnostic delays, and referrals to specialized care. We analyzed the feasibility of VFSS and FEES in patients with buALS, as well as the number of patients undergoing PEG and tracheostomy.

Materials and Methods

Patients

We included all patients treated for ALS in the 1.7 million people Hospital District of Helsinki and Uusimaa (HUS) between 2010 and 2014. ALS diagnosis was confirmed by a senior neurologist (HL), using the El Escorial revised version.[11] Among 388 patients for whom data were available, 9 (2.3%) patients were lost to follow-up and 52 (13.4%) had been erroneously diagnosed with ALS. Thus, our cohort included a total of 327 patients.

Hospital patient records were reviewed for age at which the first symptoms of motor dysfunction appeared, gender, time from the presentation of first symptoms until death, and the incidence of tracheostomy and PEG. In buALS, we also reported the date of the first visit to a healthcare provider, to any medical doctor, to specialized healthcare, and to a neurologist. The presenting symptoms (dysarthria, dysphagia, breathing symptoms) and findings during clinical and endoscopic examination (presence of vocal nasality, hoarseness, dysphagia, and/or fasciculations of the tongue and laryngeal findings assessed by either ORL, phoniatrician, or SLP) were reported. The first specialty a patient was referred to (neurology, otolaryngology, phoniatrics, or internal medicine), referrals to these specialties later during follow-up, and the date of onset of dysphagia and breathing symptoms were also reported. Furthermore, we collected the incidence of instrumental swallowing tests, FEES, or VFSS, as well as their indications, findings, and conclusions.

Statistical analysis

We performed all statistical analyses using the SPSS statistical software package version 27.0 (IBM Corp., Armonk, NY, USA). Correlations were calculated using Pearson's correlation analysis, survival rates were assessed using the Kaplan–Meier method with the log-rank test, and means were compared using the independent t-test and two-way analysis of variance (ANOVA), where applicable. We report two-tailed p values whenever possible, and present our findings with 95% confidence intervals (CIs) when applicable. The homogeneity and normality of data between groups were assessed with the Levene's test and the Shapiro–Wilk's test, respectively.

This study is reported according to the STROBE guidelines.

Results

Demographic data and clinical characteristics

From 327 study patients, 217 (66.4%) had extALS and 110 (33.6%) buALS. We observed a female predominance among ALS patients (189/327, 58%). The proportion of women with buALS (73/110, 66%; $p < 0.005$) was significantly higher than for extALS (116/217, 53%; $p< 0.005$). Among all 327 ALS patients, 296 (91%) had died by the time of data retrieval. In the buALS group, 106 of 110 (96%) patients had died, compared to 190 of 217 (88%) patients in the extALS group. A total of 176 new ALS diagnoses were made during the 5-year study period.

The mean age at symptom onset in the buALS group (66 years) was significantly higher compared with the extALS group (59 years; $p< 0.001$), however in neither group was it associated with gender. A higher age significantly associated with a shorter overall survival time (r = -0.333; $p < 0.001$). Mean survival was 47 months among all patients (95% CI 41.5–53.3), 55 months (95% CI 46.5–63.7) in the extALS group, and 34 months (95% CI 28.9–38.7) in the buALS group. Thus, survival in the extALS group was significantly longer ($p < 0.005$; *Figure 1)*. The clinical characteristics for all study patients as well as a comparison of buALS and extALS patients appear in Table 1.

Presenting symptoms and referral to specialized healthcare among patients with bulbar-onset ALS

Among the 110 patients with buALS, 64 (58%) were primarily referred to a neurologist, 28 (25%) to an ORL, 12 (11%) to internal medicine, and 5 (5%) to a phoniatrician. Among the 33 patients initially examined by an ORL or phoniatrician, the mean delay in referral to an academic neurology center was 56 days (median 26, standard deviation (SD) ± 78, range 0–337). In 25 (76%) patients, a clear suspicion of a neuromuscular disease existed and patients were referred to a neurologist primarily within one month. Among the remaining 8 (24%) patients, the neuromuscular etiology was missed and referral was delayed for up to 1 year. Several reasons explain these difficulties in understanding the neurological nature of the disease symptoms and signs. A tumor was suspected in two patients presenting with constant supraglottic spasticity, obstruction, and a tense voice. In six patients, mild symptoms were linked to misleading findings such as a loose denture, Reinke's edema, vocal fold atrophy, or laryngeal reflux, while the incipient dysarthria or dysphagia was ignored. In several of these patients, examination was completed by a less experienced specialist, including two co-authors, 10 years ago.

Among all buALS patients, the most common presenting symptom was dysarthria, observed in 89 (81 %) patients, followed by dysphagia in 26 (24%) patients, and respiratory difficulties in 7 (6.6%) patients. A combination of symptoms was reported in a total of 12 (11%) patients.

In buALS, the mean time from symptom onset to the first healthcare provider visit was 4.4 months (range 0–23, SD ± 4.77), 7.1 months (range 0–55, SD ± 8.43) to a specialist visit, and 8.5 months (range 0–56, SD ± 9.73) to a neurologist referral. In some non-sporadic ALS patients, disease progression was extremely slow resulting in a long diagnostic delay. In order to capture the typical course of disease for buALS, we omitted from our analysis outliers with a delay exceeding 2 years from symptom onset to the first healthcare provider visit.

At some point during follow-up, 48 of 110 (44%) patients were referred to an ORL, 17 (16%) to a phoniatrician, and 102 (94%) to an SLP. Among all buALS patients, 3 (3%) were not referred to any such specialist. All patients were ultimately referred to an academic neurology center.

The most common finding reported at an ORL, phoniatrician, or SLP consultation was dysarthria in 100 (91%) patients, followed by dysphagia in 94 (85%), fasciculations of the tongue in 77 (70 %), vocal hoarseness in 50 (45%), and vocal nasality in 44 (40%) patients. The most common laryngeal findings were a limitation to the vocal fold abduction movement in 11 (20%) patients, vocal fold atrophy in 8 (7.2%), and laryngeal spasm/vocal cord dysfunction in 2 (1.8%) patients.

Assessment of swallowing in patients with bulbar-onset ALS

Among all buALS patients, 49 (45%) underwent at least one swallowing function test, FEES in 15 patients and VFSS in 39 patients, with 5 (4.5%) patients undergoing both tests, and among them 32 (82%) with VFSS and 9 (60%) with FEES had either a strongly suspected or confirmed ALS at the time of referral. VFSS was indicated by a previous aspiration in 18 (46%) patients and 18 (46%) patients underwent VFSS in order to evaluate the safety of oral nutrition, whereas 10 (26%) procedures served to evaluate an esophageal obstruction. Among patients undergoing FEES, the corresponding figures are 4 (27%), 6 (40%), and 5 (33%). The findings of the swallowing function tests appear in Table 2. (Table 2).

Among the VFSS procedures, 8 (21%) resulted in a recommendation for PEG placement. None of the FEES procedures resulted in an immediate PEG recommendation. Outright swallowing interdictions were not provided based on either test. However, patients undergoing a swallowing function test more often received PEG at some point ($r = 0.207$; $p < 0.05$). The incidence of PEG placement among all buALS patients reached 78% (n = 86): 94% (n = 46) among those who underwent a swallowing function test and 66% (n = 40) among those who did not.

Among all study patients, 192 of 327 (59%) underwent PEG placement, which was more frequent in the buALS group (86/110 patients, 78%; $r = 0.281$; $p < 0.001$) compared to the extALS group (106/217, 49%). PEG was associated with a shorter survival time in the extALS group [53 months with PEG (95% CI 44.1–62.1; $p < 0.001$) vs. 57 months without PEG (95% CI 42.3–72.1;$p < 0.05$) and a longer survival time in the

buALS group [35.6 months (95% CI 29.9–41.4; $p < 0.001$) and 26.8 months (95% CI 18.1–35.5; $p < 0.05$); (*Figures 2 & 3).*

The mean time from symptom onset to death in patients with buALS was not significantly longer among those primarily referred to a neurologist compared to those referred to an ORL or phoniatrician. Mean survival in the buALS patient group was 32 months (95% CI 27.3–36.9) compared to 33 months (95% CI 23.0–44.2) and 37 months (95% CI 25.9–47.4), respectively, among those initially referred to an ORL and a phoniatrician.

Discussion

We characterized 176 newly diagnosed ALS patients in the Helsinki metropolitan region of 1.7 million inhabitants during a 5-year period (2010–2014). The estimated annual ALS incidence of 2.1 per 100 000 mirrored reports from other European countries. Furthermore, the proportion of patients with buALS (34%), the higher mean age at onset in buALS (66 years) compared with extALS (59 years), and the female predominance in buALS (66%) agree with previous studies.[12] The strength of our study setting lies in selecting a retrospective sample, making it possible at the time of data retrieval to trace the complete course of disease for most patients.

In our study, 48 of 110 patients (44%) with buALS were not initially referred to a neurologist. Among 110 patients, 33 (30%) were initially referred to an ORL/phoniatrician, typically because of dysarthria or dysphagia. Practically all patients were referred to a neurologist at some point, however, in 8 (24%) patients, an ORL/phoniatrician had clear difficulties in understanding the nature of the symptoms. The primary reasons for the diagnostic delay appeared to be the early stage and mild symptoms of disease, physician inexperience, and, in two patients, a constant spasticity or hyperfunction in the supraglottic structures leading to a narrowed airway and tumor suspicion.

ORLs require awareness of the potential symptoms and signs of bulbar-onset ALS, often presenting with dysarthria or dysphagia. Clinical findings may include weakness in the facial muscles, palate, or tongue, as well as fasciculations of the tongue, and a hypernasal or breathy voice with incomplete vocal fold closure.[13]Dysarthria should not be regarded as a sign of laryngeal pathology. In general, our study confirms Turner et al.'s[12] findings that, although half of all buALS patients being initially referred to other than neurologists, this did not significantly impact diagnostic delays or survival.

Our study also aimed to evaluate the feasibility of VFSS and FEES in buALS patients. A recent systematic review concluded that several assessment strategies are employed in neuromuscular diseases, depending on the center, the country, and local protocols. In our study, 18 of 39 patients (46%) presented with aspiration in VFSS and 5 of 15 (33%) in FEES.

An obvious advantage of FEES, performed in 14% of buALS patients, is that patients may receive recommendations for modifying food consistency and therapeutic strategies, and compensatory maneuvers can be evaluated during examination with visual feedback. However, a recommendation for complete tube feeding after VFSS or FEES in our study patients remained extremely uncommon. Thus, the usefulness of VFSS, performed on 35% of buALS patients, remains questionable.

In our study, 86 of 110 patients (78%) with buALS underwent PEG placement, similar to reports from previous studies.[12]PEG associated with a longer survival period among buALS patients in our study, possibly associated with improvement in nutritional status. This finding was reversed in the extALS patient group, possibly related to the fact that among this ALS subtype the swallowing symptoms usually appear late. Those who underwent swallowing studies were also slightly more likely to undergo PEG placement, which may be related to the shared indications in both. However, the driving force in proceeding with PEG placement was rarely a swallowing study. More likely, the decision was forced by increasing aspiration.

Moreover, median survival among our patients, 55 months in extALS versus 34 in buALS, agrees with previous studies.[7,12]Survival in extALS is typically longer, since bulbar affision represents a major cause of morbidity and mortality in ALS patients and occurs fairly late in the limb-onset disease subgroup.

In our study, 8 (2.4%) patients were treated with a tracheostomy. This also agrees with the low overall tracheostomy incidence in Finland.[8] Since invasive mechanical ventilation brings about the risk of entering a complete locked-in state, this option requires a timely consultation with an experienced specialist and a profound consideration of end-of-life treatment options.[1,14,15]

Conclusions

Based on our findings, the diagnosis and treatment of ALS in Finland agree with results from earlier studies. Primary diagnostics are performed quickly and efficiently and do not depend on the specialty of the initial physician a patient consults. Gastric tubes are commonly placed and appear to improve survival among buALS patients. Swallowing studies rarely provided clear recommendations when considering feeding, thereby casting doubt on their usefulness. Invasive ventilation remains a rarity among all ALS patients in Finland.

Authors declare that they have no conflicts of interest.

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The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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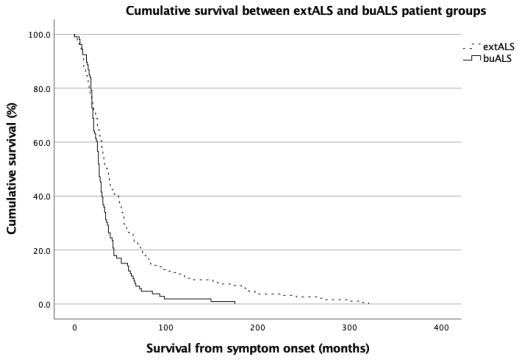
Table 1: Clinical characteristics of study patients, overall and within groups. The p values are provided in the right-hand column for the difference between groups, and in the respective cells for the intragroup difference. P values are provided only for statistically significant differences.

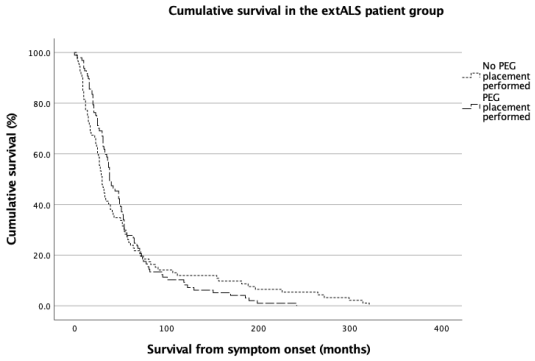
Table 2. Significant findings from the swallowing function tests.

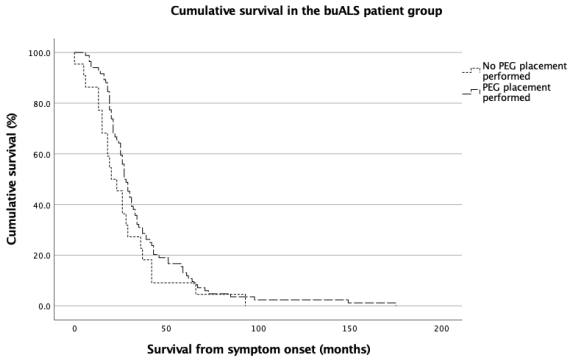
Figure 1. Comparison of survival among extALS and buALS patients($p < 0.005$).

Figure 2. Cumulative survival in the extALS group, depending on whether PEG placement was performed.

Figure 3. Cumulative survival in the buALS group, depending on whether PEG placement was performed.







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