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ORIGINAL ARTICLE

Prevalence and determinants of language impairment in non-demented amyotrophic lateral sclerosis patients

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Abstract

Background and purpose: This study aimed at estimating the prevalence of language impairment (LI) in a large, clinic-based cohort of non-demented amyotrophic lateral sclerosis (ALS) patients and assessing its underpinnings at motor and non-motor levels.

Methods: Non-demented ALS patients (N = 348) underwent the Edinburgh Cognitive and Behavioural ALS Screen (ECAS), as well as an assessment of behavioural/psychiatric and motor-functional features. The prevalence of LI was estimated based on the proportion of patients showing a performance below the age- and education-adjusted cut-off on the ECAS-Language. Multiple regression models were run to assess the determinants of language functioning and impairment.

Results: The prevalence of LI was 22.7%. 46.6% of the variance of ECAS-Language scores remained unexplained, with only the ECAS-Executive positively predicting them ($p < 0.001$; $\eta^2 = 0.07$). Similarly, only a lower score on the ECAS-Executive predicted a higher probability of a below cut-off ECAS-Language performance ($p < 0.001$). Spelling and Naming tasks were the major drivers of ECAS-Language performance.

Conclusions: This study suggests that, in non-demented ALS patients, LI occurs in ≈23% of cases, is significantly driven by executive dysfunction but, at the same time, partially independent of it and is not associated with other motor or non-motor features.

KEYWORDS
amyotrophic lateral sclerosis, Edinburgh Cognitive and Behavioural ALS Screen, frontotemporal degeneration, language, primary progressive aphasia

BACKGROUND

Language impairment (LI) within the spectrum of primary progressive aphasia (PPA) is typical of non-demented amyotrophic lateral sclerosis (ALS) patients' cognitive profile [1], including phonological, lexical-semantic and morpho-syntactic deficits, alterations in connected speech and pragmatics [2,3], as well as dysgraphic features [4].

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The occurrence of LI in this population conveys relevant clinical entailments, as (i) currently allowing patients to be classified as cognitively impaired according to Strong et al.'s [1] revised criteria and (ii) negatively impacting on their prognosis [5]. Furthermore, in ALS patients, language has been shown to worsen longitudinally to a greater extent compared to other cognitive domains [6].

However, despite much being known on the semiology of LI in non-demented ALS patients [2-4], its epidemiology in this population is still largely obscure. Indeed, the currently accepted prevalence estimate of LI in non-demented ALS patients (i.e., ≈35%–40%) [1,7] relies on the 2013 pioneering study by Taylor et al. [8], which, however, (i) addressed a relatively small sample size (N = 50) and (ii) did not include ALS-specific language measures. Furthermore, motor and non-motor determinants of LI in this population have been only partially explored to this day, outside of its association with dysexecutive features [8,9] and bulbar involvement [10,11].

Thus, the present study aims (i) to estimate the prevalence of LI in a large, clinic-based cohort of non-demented ALS patients as yielded by the dedicated subscale of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) and (ii) to assess its underpinnings at cognitive, behavioural/psychiatric and motor levels.

METHODS

Participants

Consecutive ALS patients (N = 348) [12] referred to the IRCCS Istituto Auxologico Italiano, Milano, Italy, between 2016 and 2022 were recruited. No patient met either Rascovsky et al.'s [13] or Gorno-Tempini et al.'s [14] criteria for behavioural variant frontotemporal dementia and progressive non-fluent aphasia/semantic dementia, respectively. Moreover, patients did not present with (i) ALS-unrelated neurological/psychiatric diagnoses, (ii) ALS-unrelated severe general-medical conditions possibly entailing encephalopathic features (i.e., system/organ failures or severe, uncompensated metabolic/internal disease) or (iii) severe and/or uncorrected hearing/vision deficits. No exclusion criterion related to the severity of motor disabilities was applied.

The study was approved by the Ethics Committee of the IRCCS Istituto Auxologico Italiano (I.D.: 2013_06_25). Participants provided informed consent and data were treated according to current regulations.

Materials

Patients were administered the Italian version of the ECAS [15], whose Language subscale (range 0–28) comprises three tasks: Naming (range 0–8), Comprehension (range 0–8) and Spelling (range 0–12). Response modality (i.e., written or oral) was adjusted based on the presence and severity of upper-limb deficits and/or dysarthric features. Furthermore, patients underwent a behavioural assessment via the ECAS Carer Interview [15,16], Beck Depression Inventory [17] and State and Trait Anxiety Inventory Y (STAI-Y1, trait anxiety; STAI-Y2, state anxiety) [18], as well as a motor-functional evaluation via the ALS Functional Rating Scale Revised (ALSFRS-R) [19]. Disease staging was retrieved via both King's [20] and Milano–Torino systems [21], whereas progression rate (ΔFS) was computed as follows: (48 − ALSFRS-R score)/disease duration in months [22].

Statistics

The prevalence of LI was estimated based on the proportion of patients showing a performance below the age- and education-adjusted cut-off on the ECAS-Language [15].

Determinants of language functioning were explored, by addressing ECAS-Language scores as the outcome, through a multiple linear regression model that simultaneously encompassed as predictors demographic (i.e., age, education, sex and handedness) and motor-functional features (i.e., bulbar, spinal and respiratory ALSFRS-R subscores, disease duration and ΔFS values), the presence/absence of *C9orf72* hexanucleotide repeat expansion, ECAS-Executive, ECAS-Fluency, ECAS-Visuo-spatial and ECAS-Memory subscores and behavioural/psychiatric measures (i.e., ECAS Carer Interview, Beck Depression Inventory, STAI-Y1 and STAI-Y2 scores). Response modality (oral vs. written) was also covaried in order to control for potential differences (since language tasks were untimed).

Determinants of LI were examined by simultaneously entering the same set of predictors, except for age and education, into a multiple logistic regression model that addressed a below versus above cut-off performance on the ECAS-Language [15] as the outcome. The same model, but including also Naming, Comprehension and Spelling scores, was run in order to assess the extent to which each language task contributed to the occurrence of LI.

Within the linear regression model, normality and heteroscedasticity assumptions were checked descriptively (i.e., by evaluating residual skewness and kurtosis values, judged as abnormal if >|1| and |3|, respectively) [23], graphically (i.e., by inspecting residual histogram and Q–Q plots, as well as the predicted residual scatterplot) and inferentially (i.e., via Kolmogorov–Smirnov's test).

Collinearity was diagnosed, within all the above models, in the presence of a variance inflation factor >10 and of a tolerance index <0.1 [24].

When selecting significant predictors within the above models, the significance threshold (α = 0.05) was Bonferroni-corrected as follows: $\alpha_{adjusted}$ = 0.05/numbers of target predictors (i.e., excluding response modality as a covariate). Missing data were excluded pairwise. Analyses were run via jamovi 2.3 (jamovi project, 2022).

RESULTS

Table 1 summarizes patients' background and clinical variables, whereas Table 2 gives their ECAS performances. The prevalence of

TABLE 1 Patients' background and clinical features

N	348
Age (years)	63.3 ± 11.4 (20–88)
Sex (M/F)	60.6%/39.4%
Education (years)	11.6 ± 4.4 (5–24)
Handedness (right/left)	94.5%/5.5%
Disease duration (months)	18.8 ± 21.1 (2–264)
ALSFRS-R	
Total	38 ± 6.8 (12–48)
Bulbar	10.2 ± 2.4 (1–12)
Spinal	16.6 ± 5.9 (0–24)
Respiratory	11.2 ± 1.7 (0–12)
ΔFS	0.8 ± 0.9 (0–6.3)
KSS	
Stage 0/1/2/3/4	1.6%/34.2%/31.9%/26.5%/5.8%
MiToS	
Stage 0/1/2	70.6%/25.5%/3.9%
PEG	0.3%
NIV	5.2%
Genetics	
C9orf72	6.6%
SOD1	2.6%
TARDBP	3.4%
FUS	0.3%
ECAS-CI	0.7 ± 1 (0–5)
STAI-Y1	51.3 ± 10.3 (33–87)
STAI-Y2	49.8 ± 9.9 (30–80)
BDI	13.5 ± 8.8 (0–58)

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; BDI, Beck Depression Inventory; ECAS-CI, Edinburgh Cognitive and Behavioural ALS Screen Carer Interview; F, female; KSS, King's staging system; M, male; MiToS, Milano–Torino staging system; NIV, non-invasive ventilation; PEG, percutaneous endoscopic gastrostomy; STAI-Y1, State and Trait Anxiety Inventory, Form Y State Anxiety; STAI-Y2, State and Trait Anxiety Inventory, Form Y Trait Anxiety; ΔFS, progression rate.

LI as yielded by a below cut-off ECAS-Language performance was 22.7% (79 patients out of 348).

Normality and heteroscedasticity assumptions were fully met for the linear regression model; no collinearity was diagnosed for any of the predictors of each model. $N = 238$ patients were addressed within such models after pairwise exclusion of missing data.

The linear regression model explained 54.4% of the variance of ECAS-Language scores ($F_{(19, 219)} = 13.77$; $p < 0.001$), with only the ECAS-Executive positively predicting them at $\alpha_{adjusted} = 0.0028$ ($\beta = 0.46$; $t(219) = 5.97$; $p < 0.001$; $\eta^2 = 0.07$), and a similar, although marginally significant, effect being found for ECAS-Visuo-spatial ($\beta = 0.15$; $t(219) = 2.78$; $p = 0.006$; $\eta^2 = 0.02$).

Similarly, within the logistic regression model (Akaike Information Criterion =238; $\chi^2(17) = 69.2$; $p < 0.001$), only a lower score on the ECAS-Executive predicted, at $\alpha_{adjusted} = 0.003$, a higher probability of a below cut-off performance on the ECAS-Language ($\beta = -0.11$; $z = -3.32$; $p < 0.001$). When entering into the same model Naming, Comprehension and Spelling scores (Akaike Information Criterion =102; $\chi^2(20) = 205$; $p < 0.001$), only a lower score on the Naming ($\beta = -1.83$; $z = -4.22$; $p < 0.001$) and Spelling tasks ($\beta = -1.33$; $z = -5.24$; $p < 0.001$) predicted, at $\alpha_{adjusted} = 0.0026$, a higher probability of a below cut-off performance on the ECAS-Language subscale as a whole, with the Comprehension task not surviving the Bonferroni correction ($\beta = -1.44$; $z = -2.56$; $p = 0.011$) and no other predictors yielding significance.

TABLE 2 Patients' ECAS performances

ECAS	Raw scores	Below cut-off[a] (%)
Total	99.7 ± 18.8 (31–129)	33.6%
ALS-specific	73.7 ± 15.3 (21–97)	31.3%
ALS-nonspecific	26.1 ± 5.1 (9–34)	23.3%
Language	23.4 ± 4 (9–28)	22.7%
Naming	6.8 ± 1.4 (0–8)	–
Comprehension	7.6 ± 0.7 (4–8)	–
Spelling	9 ± 2.9 (0–12)	–
Fluency	16.3 ± 5.6 (0–24)	20.7%
Executive	33.9 ± 7.8 (7–48)	22.4%
Memory	14.7 ± 4.7 (1–22)	21%
Visuo-spatial	11.3 ± 1.1 (6–12)	8.3%

Abbreviations: ALS, amyotrophic lateral sclerosis; ECAS, Edinburgh Cognitive and Behavioural ALS Screen.

[a]Poletti et al. [12]. 91.7% of patients provided oral responses.

DISCUSSION

The present study provides relevant insights regarding the prevalence and determinants of LI, as yielded by the ECAS, in a large, clinic-based cohort of non-demented ALS patients. To this day, this is the largest-sized investigation on the topic, as well as the one including the highest number of both motor and non-motor variables.

Findings reported here suggest that up to ≈23% of non-demented ALS patients can present with impairments of language functioning, as assessed by the dedicated ECAS subscale. Despite being lower than the currently accepted estimate (≈35%–40%) [1,7,8], the present estimate aligns to those yielded by recent, and up-to-now largest-sized, studies assessing language in non-demented ALS patients via either a second-level battery ($N = 117$) [9] (i.e., up to 23%) or the ECAS-Language itself ($N = 215$) (i.e., 25%) [25].

In this last respect, it should be noted that prevalence estimates of LI as yielded by the ECAS-Language have been shown to vary considerably depending on which statistical approach has been adopted to derive cut-off values (e.g., regression-based vs. *z*-score-based) [25]. Although those addressed here are *z*-score-based but, at the same time, demographically adjusted [15], thus

warranting a sufficient generalizability of the present results, further investigations should focus on delivering such an estimate through regression-based normative approaches [26].

Relatedly, it has to be mentioned that the present prevalence estimate is measure-dependent, thus coming with the potential biases intrinsic to the ECAS-Language. In this regard, it has been highlighted that, compared to other ECAS subscales, the ECAS-Language might suffer from a slightly poorer sensitivity [27], with such an issue having been attributed to it not optimally covering the full spectrum of LI typical of non-demented ALS patients [2-4,27]. Consistently, the present work highlights that the Naming and, to an even greater extent, Spelling tasks of the ECAS-Language are the major drivers of the performance on this subscale, at variance with the Comprehension task [25]. In fact, the Comprehension task, despite being inherently simpler than the Naming one [28], relies on the same items that are previously primed within the latter [29] —both these factors potentially entering biases related to task-difficulty effects into Comprehension scores. Furthermore, the predominant contribution of the Spelling task to ECAS-Language scores might reflect the confounding effect of attention and executive functions towards its scores—given that such processes highly contribute to oral spelling performances [30]. Notably, this last notion would be supported by the finding that ECAS-Executive scores strongly predict the ECAS-Language. It is thus advisable that, when screening for LI in non-demented ALS patients, the ECAS be complemented with further, domain-specific measures such as the Screening for Aphasia in NeuroDegeneration [31] or the Mini-Linguistic State Examination [32], which have both been developed in order to deliver a first-level estimate of global language functioning by focusing on the semiology of LI typical of neurodegenerative conditions.

Even in the face of the abovementioned considerations on the potential biases of the ECAS-Language, and consistently with earlier reports [8,9], this work appears to confirm that attention and executive functioning are strong determinants of language in non-demented ALS patients—also showing that dysexecutive features are associated with LI in this population. Nevertheless, a notable amount of variance (i.e., 46.6%) in ECAS-Language scores could not be accounted for by either executive performances or other variables, this supporting the previously acknowledged notion of LI being primary, at least to an extent, in this population [8,9] and not merely secondary to executive dysfunction [2-4].

Relatedly, it is worth noting that the ECAS-Fluency was not found to significantly contribute to language functioning, this being to an extent counterintuitive, given that verbal fluency tasks tap on both executive and language components [33-35]. At the same time, such a finding aligns with a recent report that failed to show, within a cohort of non-demented ALS patients, perfectly overlapping associations between in vivo ECAS-Language and ECAS-Fluency scores and the postmortem regional distribution of TDP-43 neuropathology [35], thus suggesting that in this population language and verbal fluency deficits do not necessarily co-occur.

By contrast, the unprecedented finding of visuo-spatial abilities being herewith linked, albeit weakly, to language, might be explained by a mediating role of executive processes, that underpin to similar extents all instrumental domains. Such a hypothesis would be in line with a recent study reporting, in non-demented ALS patients, an association between the Language and Visuo-spatial subscales of the ECAS and its social cognition task [36], which suggests a spurious interplay between non-executive cognitive domains that may indeed be underpinned by executive processes.

Furthermore, the present study does not support a role of either motor (i.e., bulbar involvement, disease severity and progression rate) or genetic features (i.e., *C9orf72* hexanucleotide expansion) towards LI in non-demented ALS patients. Despite being in contrast with previous reports suggesting an association between such features and cognition in this population [37-41], this finding might be accounted for by the fact that, in order to increase the ecological validity of the study, several predictors have been herewith addressed simultaneously—in contrast to earlier investigations, mostly focusing on univariate analyses [37-41]—, as well as by the fact that the abovementioned associations might not evenly apply to all cognitive domains.

Moreover, behavioural/psychiatric features did not appear to be linked to language functioning in non-demented ALS patients, thus supporting an independence between these two clusters. However, in this respect, it is worth mentioning that a family history of behavioural/psychiatric disorders has been recently suggested as a risk factor for the development of LI in ALS patients [42]. Therefore, future investigations focusing on LI in this population should also include information on the familiy history for behavioural/psychiatric disorders within the range of its potential predictors.

This study is not of course free of limitations. First, and most importantly, language was assessed only via the dedicated subscale of the ECAS; hence, further studies are needed that adopt, with similar aims, second-level, thorough language tests/batteries, and/or that carry out a qualitative analysis of language errors on the ECAS-Language in order to actually determine whether it is able to capture LI in this population by also disentangling it from dysexecutive features. Relatedly, such findings might not be fully generalizable to languages other than Italian: for instance, a recent report comparing Italian to English patients with progressive non-fluent aphasia—which is a condition pathophysiologically and genetically related to ALS [11]—has shown between-language differences in speech praxis and morpho-syntactic processing [43]. At the same time, it is worth stressing that, as previously mentioned, the prevalence estimate given here is similar overall to those recently reported in non-demented ALS patients speaking other languages, that is, English [9] and German [25].

Secondly, this investigation was cross-sectional and thus neither allowed to estimate the incidence of LI in this population nor explored its motor and non-motor determinants in a longitudinal fashion. Relatedly, although featured by a large sample, this study was clinic-based and thus possibly subject to referral bias.

Thirdly, norms herewith addressed for the ECAS [15] do not come with cut-offs at the single-task level [44]: this did not allow to determine the exact number of patients impaired on each ECAS-Language task (i.e., Naming, Comprehension and Spelling).

Fourthly, no information on the lateralization of motor damage was available, although this could have been informative in light of the fact that such a feature has been proved to affect cognitive phenotypes in ALS [45].

Fifthly, measures neither of baseline cognitive status nor of cognitive reserve (besides education) were herewith addressed, thus not allowing a definite conclusion to be drawn on the potential contribution of premorbid cognitive levels towards LI within the present cohort [46].

Sixthly, the present study does not encompass neuroimaging data and thus does not deliver insights into which perisylvian regions, that is, whether anterior or posterior ones [4], and/or fronto-parietal, executive/attentive circuitries contributed to LI within the cohort addressed here.

Finally, this study solely focused on the occurrence of language dysfunctions in non-demented ALS patients, thus not allowing conclusions to be drawn on the prevalence and determinants of full-blown aphasic syndromes (i.e., progressive non-fluent aphasia or semantic dementia) in this population. Hence, as also highlighted within a recent systematic review on the association between motor neuron diseases and PPA [11], it is advisable that future investigations focus on the epidemiology of such a fronto-temporal dementia phenotype in ALS patients. Indeed, it has been stressed that, whilst a relatively large amount of evidence is available on the epidemiology of ALS-related disorders in PPA patients, the same does not apply to that of PPAs in patients whose primary diagnosis is ALS [11].

In conclusion, this study suggests that LI, as revealed by the language subscale of the ECAS, occurs in ≈23% of non-demented ALS patients. Moreover, although the present work highlights that attention and executive functioning are major drivers of language abilities in this population, it also shows that more than 50% of the variance of ECAS-Language scores are not accountable by either dysexecutive features or other motor/non-motor variables. Therefore, data presented here support the notion of LI being, at least to an extent, primary in non-demented ALS patients. However, in the light of a number of potential biases inherent to the ECAS-Language, it is advisable that further first-level language measures be administered when screening for LI in non-demented ALS patients.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The dataset associated with the present study is available upon reasonable request of interested researchers at the following link: https://zenodo.org/record/7419497#.Y5N4DnbMJPa

ETHICAL APPROVAL

Participants provided informed consent. This study was approved by the Ethics Committee of IRCCS Istituto Auxologico Italiano (I.D.: 2013_06_25).

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