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ORIGINAL ARTICLE

ALS Cognitive Behavioral Screen (ALS-CBS): normative values for the Italian population and clinical usability

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Abstract

Amyotrophic lateral sclerosis (ALS) patients often express cognitive and behavioral dysfunctions within the so-called "frontotemporal spectrum disorders." Guidelines recommend screening of such dysfunctions, albeit only ALS dedicated tools are eventually suitable, due to the profound motor limitations induced by the disease. ALS Cognitive Behavioral Screen (ALS-CBS) is such a screening tool but normative data are not available, limiting its widespread implementation. Our aim consisted in producing normative data for the Italian version of the ALS-CBS. The scale was administered to $n = 458$ healthy controls with different age and education. Following translation and back translation of the original version of the test, normative data and correction scores for the ALS-CBS cognitive subtest (ALS-CBSci) were generated. Furthermore, $n = 100$ ALS consecutive outpatients with a wide range of cognitive and motor severity underwent to the ALS-CBS, besides FAB and Weigl sorting test (WST), in order to check its usability. Completion rate was 100% for ALS-CBS and WST, and 68% for the FAB. Corrected ALS-CBS scores showed 12% detection rate of significant cognitive dysfunction with a moderate kappa with FAB and WST. For the ALS-CBS behavioral subtest (ALS-CBSbi), a caregiver was available for $n = 81$ ALS patients and asked to complete the subset. The detection rate for behavioral dysfunction was 55.5%, and a mild correlation between with the Caregiver Burden Inventory was present ($r = -0.26$, $p = 0.04$). In conclusion, we offer here normative data for the ALS-CBS, a handy tool for screening frontotemporal spectrum dysfunctions in ALS patients, and confirm its usability and validity in an outpatient setting.

Keywords ALS · ALS-CBS · Screening test · Cognitive · Normative · Italian

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Introduction

Current concepts regard cognitive impairment as one major phenotypic feature of amyotrophic lateral sclerosis (ALS) [1]. In fact, albeit full-blown dementia patients represent a minority of ALS subjects, this is not the case for mild cognitive and mild behavioral impairments (ALSci and ALSbi, respectively), whose combined prevalence goes up above 50% in various patient case series [2, 3]. Identifying such deficits in ALS patients, even when expressed at low degrees of severity, is pivotal, since there is consistent evidence that relevant prognostic issues are implied [4, 5]. According to the recently revised ALS diagnostic criteria [6], cognitive and behavioral impairments in ALS patients lie on the Axis II (being Axis I the motor neuron disease [MND] variant, and Axis III the additional non-motor disease features), and the assessment of their presence and severity is strongly recommended even in routine clinical settings. The authors propose the term "frontotemporal spectrum disorders" (FTSD), encompassing most of the cognitive and behavioral dysfunctions expressed by ALS patients, albeit recognizing that dementia not typical of FTSD can also develop [6].

This need for screening ALS patients with reliable neuropsychological tools has to confront firstly with motor limitations induced by the MND itself that hinder most cognitive tasks, for example, the Luria sequence and question the validity of most tests developed in the typical dementia setting [7]. ALS dedicated screening tools have been recently developed, and the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) has been also validated in the Italian population [8, 9], offering the opportunity for a fast screening of ALS subjects even in the usually limited amount of time of the outpatient setting. Another ALS-dedicated screening tool is the Amyotrophic Lateral Sclerosis Cognitive Behavioral Screen (ALS-CBS), specifically referenced in the recent diagnostic criteria for FTSD detection in ALS [6]. As for the ECAS, the ALS-CBS is composed by two components, namely a cognitive and the behavioral subscale (here indicated as ALS-CBSci and ALS-CBSbi, respectively). The ALS-CBSci includes four sections (attention, concentration, mental tracking and monitoring, word initiation and retrieval) with eight different tasks in total. This scale is completed by ALS patients and is feasible even in those subjects presenting with profound motor limitations, being the only low boundary the impossibility of communicating [10]. The behavioral component (ALS-CBSbi) is administered to caregivers and includes 15 items exploring those behavioral changes that may have been developed after ALS onset [10].

One limitation to a more widespread use of the ALS-CBS is the lack of normative data in healthy controls. Thus, the primary aim of this work consisted in devising normative corrections for the ALS-CBSci subscale in a population of Italian healthy subjects. This will undoubtedly improve the usability of the test in populations different from those in whom it was originally devised, characterized by a high level of education. A secondary aim consisted in exploring the usability of the translated ALS-CBS version in an ALS outpatient setting, in order to test its real-word performances.

Subjects and methods

Recruited samples and collected variables

This study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. We planned to enroll at least 222 participants on the basis of a priori power analysis for multiple regressions [11], as in previous regression-based Italian normative studies (e.g., [12]). Power analysis was performed by G*Power 3.1 with the following parameters: probability level (α) 0.05, desired statistical power (1-β) 0.80, effect size (Cohen's f^2) 0.05, number of linear predictors 3. Eventually, the initial investigation for normative purposes was carried out on $n = 458$ healthy subjects (193 M, 265 F) who varied widely in age and education, in order to sample a consistent number of subjects for each group of age × education (see Table 1). Subjects were recruited in different districts of three provinces of Milan (northern Italy), Naples, and Messina (southern Italy), both in rural or suburban areas and in city centers. Mean age ± SD for the whole sample was 56.4 ± 16.8 years (range 20–89), and mean education was 11.4 ± 4.7 years (range 2–27). All participants were community dwelling individuals who lived independently and were either working or otherwise engaged in activities in the community. Individuals were excluded if they had a current or past history of alcohol or drug abuse, current depression or major psychiatric diseases, a history of brain injury, stroke, dementia, or any other neurological illness detected on a semi-structured clinical interview. Subjects were excluded if they had either (1) age- and education-adjusted Mini Mental State Examination (MMSE) score < 23.8 out of 30 [13], or adjusted Frontal Assessment Battery (FAB) score < 13.5 out of 18 [14]. Based on these criteria, (a) $n = 179$ subjects had both tests available (mean ± SD adjusted MMSE score 28.3 ± 1.5, range 23.9–30; adjusted FAB score 16.6 ± 1.2, range 13.6–18), (b) $n = 244$ subjects had only MMSE available (28.0 ± 1.1, range 23.9–30), and (c) $n = 35$ subjects had only FAB available (15.7 ± 1.2, range 13.5–18).

Subjects had also to be in good general health: endocrine disorders (particularly of the thyroid gland) or any systemic failure of clinical relevance were considered exclusion criteria; however, the inclusion criteria were not too selective, in order to avoid the sampling of a "hyper-normal" group; thus, individuals with mild hypertension or type II diabetes

Table 1 Mean ± standard deviation of ALSCBSci total score by age and educational level

Education (years of schooling)	Age, years 20–29	30–39	40–49	50–59	60–69	70–79	80–89	Total sample
≤ 5	-	-	11.62 ± 2.82 (8)	10.88 ± 3.85 (9)	11.73 ± 3.91 (19)	11.40 ± 2.50 (22)	8.71 ± 2.61 (14)	10.93 ± 3.27 (72)
6–8	15.37 ± 3.66 (8)	15.45 ± 2.69 (11)	15.06 ± 2.41 (16)	15.27 ± 2.31 (22)	14.29 ± 2.47 (27)	13.00 ± 3.00 (17)	11.90 ± 3.60 (10)	14.37 ± 2.86 (111)
9–13	17.50 ± 1.97 (12)	16.46 ± 2.40 (13)	17.45 ± 2.38 (24)	16.26 ± 2.29 (42)	14.87 ± 2.66 (33)	14.52 ± 3.80 (17)	14.00 ± 3.57 (6)	15.97 ± 2.79 (147)
≥ 14	18.70 ± 1.55 (20)	18.64 ± 1.41 (17)	17.50 ± 1.96 (16)	17.10 ± 1.94 (19)	17.03 ± 1.76 (31)	15.30 ± 3.34 (20)	15.00 ± 3.67 (5)	17.22 ± 2.41 (128)
Total sample	17.67 ± 2.51 (40)	17.09 ± 2.49 (41)	16.14 ± 3.15 (64)	15.67 ± 2.92 (92)	14.80 ± 3.17 (110)	13.48 ± 3.46 (76)	11.42 ± 3.95 (35)	15.14 ± 3.48 (458)

with a satisfactory drug treatment were not excluded. No further instrumental or laboratory tests were carried out.

Subsequently, the usability and validity of the Italian version of the ALS-CBS were explored on $n = 100$ (67 M/33 F) consecutive ALS non-demented outpatients without tracheostomy, recruited at the NEMO Milano Center (Italy). Probable and definite ALS according to current clinical criteria [15] was required for inclusion, while the impossibility to communicate was an exclusion criterion. Each ALS patient underwent to the following: ALS-CBS cognitive subscale (ALS-CBSci), FAB, Weigl's Sorting Test (WST; [16]). FAB was pro-rated when patients could not complete it due to disease-induced physical limitation [7]. Finally, a main caregiver was present in $n = 81$ cases and was asked to complete the behavioral subscale of the ALS-CBS (ALS-CBSbi) and the Caregiver Burden Inventory (CBI; [17]. C9ORF72 expansions were always < 30, with the exception of two patients.

Test procedures

The original English versions of the ALS-CBS [10] were translated into Italian by two bilingual neurologists, blinded to each other. The two translations were subsequently compared and minor inconsistencies found and solved. Blind back translation was then performed by a third bilingual neurologist.

The ALS-CBSci includes four sections, each scoring from 0 to 5: (a) attention (including commands, mental addition, and saccades/anti-saccades); (b) concentration (digit span backwards); (c) mental tracking and monitoring (months of the year backwards, alphabet recitation, number-letter alternating task); (d) word initiation and retrieval (verbal fluency). None of the recruited subjects (both patients and controls) performed the written version of the ALS-CBSci. Total ALS-CBSci score may range from 0 to 20 and the administration of the Italian version required approximately 5–10 min and little training. The subsequent analysis and scoring of subject's performance take 1–2 min. The originally proposed cutoff values were ≤ 10 and < 17, respectively, for significant and mild cognitive impairment [10]. Following the ALS-CBSci completion, each subject was, in fact, asked to complete the FAB. Control subjects then completed also the MMSE for normative purposes, while ALS outpatient ended the session with the WST. All tests were administered in a noise-free room with no distractions, according to the appropriate specific procedures, and each subject was tested alone. Finally, in the outpatient setting, main caregivers were asked to complete the ALS-CBSbi and the CBI during the testing session of each corresponding patient: a short briefing with the examiner was performed at the end. For the ALS-CBSbi subscale, the original cutoff scores of ≤ 36 and ≤ 32 for mild and pronounced behavioral impairment were, respectively, applied.

Statistical analysis

Data are shown as mean ± standard deviation (SD). Simple linear regression (SLR) and multiple linear regression (MLR) analyses were used to examine the relation between ALS-CBSci total score and age (in years), education (years of schooling), and sex. Several age and education transformations were considered to linearize their relation with ALS-CBSci total raw score and to identify the MLR model accounting for the greatest proportion of the total variance, as measured by the R^2 statistic. Finally, according to the procedure described by Spinnler and Tognoni [18], a non-parametric technique was applied to the adjusted scores with the purpose of estimating tolerance limits cutting the general population from which the sample was drawn into defined proportions (i.e., cut-off scores), with a fixed risk of error (i.e., confidence level).

In the second part of the statistical analysis (scale usability in ALS outpatients), Cohen's kappa and two-tailed Pearson's r were used for assessing concordance and correlations between the collected variables, respectively.

Results

ALS-CBS cognitive subscale: normative data for the Italian population

The mean and standard deviation of ALS-CBSci total score for the observed sample, divided by age and educational level, is shown in Table 1. SLR showed that ALS-CBSci was significantly and inversely associated with age ($\beta = -0.09$; $p < 0.0001$), significantly and positively associated with education ($\beta = 0.42$; $p < 0.0001$), and females had a significantly higher ALS-CBSci total score than males ($\beta = 0.99$; $p = 0.003$). In order to obtain a statistical model able to predict, on the basis of the demographic features, the ALS-CBSci total score, these three variables were entered in a MLR model to examine their individual contribution to the total ALS-CBSci score and to develop an equation to predict ALS-CBSci total score. After having studied the independent effects of age, education, and sex on ALS-CBSci, and using additional transformations (exponential, quadratic, reciprocal, logarithmic, and power model) to find the model that accounted for the greatest proportion of total variance, the final regression model excluded sex that was not independently significantly associated with ALS-CBSci total score, whereas included age and the logarithmic transformation of education. This model accounted for the 45% of the total variance (adjusted $R^2 = 0.45$). Regression coefficients from this model were used as the basis for ALS-CBSci adjustment. The obtained ALS-CBSci score was adjusted with the difference between the predicted score based upon the subject's actual age and education and the predicted score given by 2.34 years of education and 56.41 years of age using the following formula: ALS-CBSciadj = raw ALS-CBSci–(3.98 × (Ln(Education) − 2.34)) + (0.06×(Age − 56.41)). The values of 2.34 and 56.41 represent the mean years of logarithmic transformation of education and age of our sample, respectively. An adjusted score was calculated for each subject of the sample by adding or subtracting the contribution of the concomitant variables from the original score, and a correction grid was then derived to allow immediate adjustment of the raw performances of newly tested individuals according to age and education (Table 2). Due to fixed scale limits of ALS-CBSci, no adjustment was made for raw scores corresponding to the scale ends (6.33% of subjects achieved the top score, no subjects had a raw score equal to zero).

After ranking the adjusted scores from the worst to the best performance, we also computed cut-off scores, which represent the lowest adjusted scores exceeded by given proportions of the population, with specific confidence levels. In line with previous Italian normative studies [12, 14], we suggest to use a score ≤ 9.87 (see Table 3) as cut-off score for cognitive dysfunctions.

ALS-CBS usability and validity in ALS outpatients

Demographic and clinical characteristics of the recruited ALS outpatients are shown in Table 4. The completion rate and the obtained scores of the administered tools are shown in Table 5 and Supplementary Table 1. Completion rate was 100% for ALS-CBSci and WST; on the other hand, as previously reported, FAB was pro-rated in $n = 32$ (32%) ALS patients due to disease induced physical limitations. A total of $n = 14$ (14%) patients obtained a raw score under the cut-off ≤ 9.87 at the ALS-CBSci; following adjustment, ALS patients with impaired ALS-CBSci were $n = 12$ (12%). On the other hand, $n = 21$ (21%) patients were impaired at the FAB and $n = 21$ (21%) at the WST. Cohen's kappa between adjusted FAB scores and the ALS-CBSci was 0.55 and 0.53, for the raw and adjusted scores, respectively. Analogously, Cohen's kappa between adjusted WST and the ALS-CBSci was 0.60 and 0.35, for the raw and adjusted scores, respectively. These levels of agreement were similar to higher with respect to the one calculated between adjusted FAB and WST (0.39). In addition, it should be noted that FAB scores were pro-rated in a high proportion of ALS patients (see Supplementary Table 1), introducing a potential bias source and that the WST explores a single function within the frontal domain. In any case, positive correlations were found between the ALS-CBSci adjusted scores and both, FAB ($r = 0.60$ $p < 0.0001$) and WST ($r = 0.59$ $p < 0.0001$) scores.

When using the proposed ALS-CBSci cutoff for milder cognitive impairment (< 17), $n = 75$ (75%) patients were screened positive at the adjusted ALS-CBSci.

Table 2 Adjustment values for the ALS-CBSci total score, by age and educational level. The values should be added to the observed ALS-CBSci total score of a subject in order to remove the effects of age and education from his or her performance on the test

	Age, years						
Education (years of schooling)	20–29	30–39	40–49	50–59	60–69	70–79	80–89
≤ 5	6.05	6.64	7.25	7.84	8.44	9.03	9.63
6–8	− 0.29	0.30	0.90	1.49	2.09	2.69	3.29
9–13	− 2.09	− 1.49	− 0.89	− 0.30	0.30	0.89	1.49
≥ 14	− 3.47	− 2.88	− 2.28	− 1.68	− 1.09	− 0.49	0.10

Regarding behavioral screening, the completion rate of both the ALS-CBSbi and the CBI was 81%, due to the absence of the main caregivers in the remaining patients. A total of $n = 45$ patients (55.5%) were assigned a score ≤ 36, with a score ≤ 32 in $n = 33$ (40.7%) of them. Interestingly, only a mild correlation was found between the two ALS-CBS subscales (cognitive and behavioral; $r = 0.24$, $p = 0.03$). Furthermore, as previously reported [19], CBI scores mildly negatively correlated with the ALS-CBSbi scores ($r = -0.26$, $p = 0.04$) but not with the ALS-CBSci ones ($p = 0.58$).

Finally, no differences were found when analyzing cognitive and behavioral data with respect to demographic and clinical variables (site of onset, disease duration, ALS-FRS-R score, NIV, and PEG use) (data not shown).

Discussion

Frontotemporal spectrum dysfunction is highly prevalent in ALS patients, and recent guidelines recommend its recognition even in the outpatient setting [6]. This implies the need for suitable and fast screening tools that could be unaffected by ALS-related motor impairments, since previously validated ones may not be appropriate, at least in the more advances stages of the disease [7, 20]. Cognitive screening has profound prognostic implications, since the potential presence of an executive dysfunction is significantly associated with shorter survival, even in the absence of overt dementia [21, 22].

Table 3 Normative values of the ALS-CBSci test. Example of table reading: At least 95% of the population had a ALS-CBSci-adjusted total score higher than 9.87. This sentence has a probability of 95% of being true

	Population proportion		
Confidence level alpha	$p = 0.90$	$p = 0.95$	$p = 0.99$
90%	11.51	10.18	6.46
95%	11.45	9.87*	6.46
99%	11.08	9.65	6.36

* Suggested cut-off score

Recent guidelines recommend the ALS-CBS as one of the two available tools for the screening of cognitive (and behavioral) impairments in ALS patients [6]. As a matter of fact, the administration of the test requires approximately 10 min little training and is generally quite well accepted by the subject. The scale was previously validated for the Spanish [23] and the Brazilian populations [24], besides being revised for telephone-based administration [25]. The aim of the present study was to offer the Italian normative data for the cognitive subtest of the ALS-CBS. In fact, the original population in which the scale was devised had a high level of education (14.5 years on average; [10]) and the usability of the scale might be, consequently, potentially compromised in absence of normative data. As a matter of fact, the average educational level of our ALS population sample was about 4 years lower. Furthermore, the equal distribution of the sample for each combination of age, education, and sex was not always guaranteed (especially as to elderly people with high education level or young people with low education level) because of the following: (1) the current Italian legislation requiring a minimum of 8 years of education (law 1859/62), and (2) the low proportion of elderly Italian people with education level greater than 8 years [26].

As previously shown [7], the ALS-CBSci was completed by all subjects in a consecutive series of 100 ALS patients, whereas 32% could not complete the FAB. The WST obtained a full completion rate as well, but this test explores only the sorting domain, contrarily to ALS-CBSci that is, more

Table 4 Demographic and clinical characteristics of the enrolled ALS outpatients. Mean ± SD (range)

ALS	$n = 100$
Sex, M/F	67/33
Age, years	64.3 ± 10.2 (42–82)
Education, years	10.1 ± 4.2 (3–25)
Onset	81 Spinal 19 Bulbar
Disease duration, months	42 ± 37 (1–175)
ALS-FRS-R	31.2 ± 9.2 (8–47)
Riluzole, Y (%)	80%
PEG, Y (%)	12%
NIV, Y (%)	42%

Table 5 ALS patients: mean ± standard deviation of ALSCBSci total score by age and educational level

Education (years of schooling)	Age, years					
	40–49	50–59	60–69	70–79	80–89	Total sample
≤ 5	---	12.94 (1)	15.08 ± 3.00 (8)	12.52 ± 4.68 (10)	---	13.62 ± 4.01 (19)
6–8	15.64 ± 3.59 (3)	13.94 ± 4.54 (8)	15.68 ± 3.17 (11)	14.69 ± 4.21 (9)	14.45 (1)	14.93 ± 3.72 (32)
9–13	16.15 ± 1.52 (5)	16.37 ± 2.44 (8)	13.34 ± 2.85 (11)	13.74 ± 2.92 (10)	17.64 (1)	14.67 ± 2.87 (35)
≥ 14	15.89 ± 0.16 (2)	13.63 ± 3.25 (6)	15.17 (1)	13.37 ± 2.79 (4)	14.28 (1)	14.03 ± 2.59 (14)
Total sample	15.95 ± 1.99 (10)	14.66 ± 3.54 (23)	14.68 ± 3.04 (31)	13.58 ± 3.80 (33)	15.46 ± 1.89 (3)	14.46 ± 3.36 (100)

properly, a "mini-battery." These data further confirm the idea that cognitive screening tools should be ad hoc designed in ALS, due to the important limitations induced by the disease.

The detection rate for cognitive dysfunction was 12%, somehow low with respect to other series that reported values up to 50% [3], but we decided to consider only the cutoff for full-blown impairment, since the mild cognitive impairment cutoff screened 75% of patients, being—at this moment—less useful for screening purposes, as also previously noted [23]. Perhaps, the fact that 41% of our ALS patients were having NIV could have contributed to overrate mild cognitive impairment in our series. In any case, this is an important limit of the present study that we are trying to carefully address in our ongoing project, characterizing mild cognitive/behavioral impairment ALS patients.

In any case, FAB and WST detection was just moderately higher (for the Z score = 0), and interestingly, kappa was only moderate. This seems to imply that the three tests display differences in sample coverage: in fact, in our series, $n = 31$ patients (31%) were screened positive in at least one of these three tests, obtaining a theoretical prevalence value for cognitive dysfunction that was closer to those previously reported [2]. A possible explanation could perhaps be found in other confounding factors, as, for example, the significantly skewed sex ratio of our working sample. In fact, only 33% of patients were female and according to one recent report, female ALS patients may express increased executive dysfunction with respect to their male counterpart [27], albeit this was not verified in our series. A further potential source of circularity in the analysis could be identified in the fact that both ALS-CBSci and FAB have the same verbal fluency task with the S phonemic cue. The WST was included also for this reason, screening for a different frontal function, and showing with ALS-CBSci both kappa and correlations similar to those obtained with the FAB. Finally, we did not assess the inter-rater variability, planning to address this limit in our future work.

In any case, we conclude confirming that ALS-CBS is as a manageable bedside cognitive and behavioral screening tool able to assess ALS outpatients without being affected by disease-related motor impairment. Further work is needed in order to confirm the validity, specially cross-cultural in the Italian population, of the behavioral subtest of this scale, albeit the reported positivity rate appears here to be similar to what has been previously reported [4, 10].

Our current ongoing projects are now focused on the comparison between the ALS-CBS and the ECAS and on the longitudinal applicability of the instrument in ALS outpatients, as very recently analogously done for the ECAS [28, 29].

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Compliance with ethical standards

Conflict of interest No conflicts of interest were reported by all the Authors.

Ethical approval This study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Statement of informed consent Subjects were recruited following ethical approval and informed consent.

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