The capacity to consent to treatment in amyotrophic lateral sclerosis: a preliminary report

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Received: 23 April 2020 / Revised: 28 July 2020 / Accepted: 30 July 2020 / Published online: 6 August 2020
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Abstract
Background Facing the relentless worsening of their condition, ALS patients are required to make decisions on treatments and end-of-life care. A cognitive impairment showed to be a negative prognostic factor in ALS patients, perhaps affecting the ability to make informed decisions. Notwithstanding its crucial role, the capacity to consent to treatment (CCT) has never been evaluated in these patients.

Objectives To assess the CCT in an ALS cohort in comparison to a control group, and to study the effects of demographic and clinical variables on this high-level cognitive function.

Methods 102 ALS patients and 106 healthy controls (HC) were enrolled. CCT was assessed using the MacArthur Competence Assessment Tool for Treatment (MAC-CAT-T) and the performance was classified into the three CCT outcomes (full credit, partial credit, no credit). Cognitive and psychological variables were assessed by MMSE, phonemic fluencies, Frontal System Behavioural Scale (FrSBe), and ALS Depression Inventory (ADI). Clinical and demographic variables were analyzed as possible predictors of the MAC-CAT-T outcomes. After a 1-year follow-up, CCT and neuropsychological assessments were repeated.

Results Most ALS patients (i.e., from 75 to 83% according to the different sub-items) retain full CCT. However, a subpopulation of the ALS patients showed a reduced CCT with respect to the HC. Age, education, phonemic fluency, and depression appeared related to the CCT outcomes. After 1 year, only the reasoning items worsened.

Conclusions This is a preliminary report suggesting that the large majority of ALS patients can retain full ability to choose between treatment options. However, demographic and neuropsychological variables may affect CCT, pointing to the need for special attention to the consent disclosure in this disease.

Keywords Amyotrophic lateral sclerosis · Cognitive impairment · Decision-making

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder leading to progressive paralysis and death within 3–5 years from the clinical onset.

Going beyond the classical clinical description by Jean-Martin Charcot [1], which excluded any extra-motor impairment in ALS, there is now evidence that fronto-lobe-related cognitive and behavioural impairment is a common feature of the disease [2–5]. The occurrence of frontotemporal degeneration in ALS has been associated with a shorter survival [3] and, among the non-demented patients, both cognitive (e.g., executive dysfunction) and behavioural impairments seem to be significant negative prognostic indicators [4–6].

Due to the relentless clinical progression, ALS patients need to make ongoing decisions about treatments affecting survival and quality of life (such as mechanical ventilation and gastric tube feeding), as well as to give their informed consent to clinical trials. It is not known whether cognitive and behavioural impairments affect the process of making such complex medical decisions, which have implications for personal values, familial burden, and socio-economic costs.
The capacity to consent to treatment (CCT [7, 8]) is a high-order cognitive function involved in the appreciation of benefits and risks of medical choices and ability to make rational decisions about treatments. Impairment of CCT has been demonstrated in patients affected by MCI and Alzheimer disease (AD [9–13]), Parkinson disease (PD [13–15]) and non-neurodegenerative disorders such as traumatic brain injury [16, 17] and malignant tumors [18–20]. Data on CCT in ALS are still missing, although they appear to have strong clinical and ethical relevance.

This study aims to assess CCT longitudinally in a relatively large ALS cohort from a single Tertiary Clinical Research Center in comparison with a healthy control group and to explore its putative relationship to several clinical, cognitive, and behavioural variables.

Methods

Participants

From 2010 through 2017, we screened 115 consecutive probable or definite ALS patients according to El Escorial-WFN Revised diagnostic criteria [21], followed-up a the Tertiary ALS Center of the University of Palermo, Italy. As controls, we screened a cohort of 113 healthy subjects recruited among friends or relatives of the ALS patients involved in this study.

Inclusion criteria were no previous/current diagnosis of relevant psychiatric or cognitive disorders.

Four ALS patients fulfilling both the Neary clinical criteria for frontotemporal dementia [22] and the revised diagnostic criteria for ALS-FTD spectrum disorder [23] were excluded. Five ALS patients and seven healthy controls with a personal history of psychiatric disorders (i.e., major depression; schizoaffective disorder; obsessive–compulsive personality disorder) were also excluded. Four ALS patients declined to be enrolled in the study (Fig. 1).

We finally enrolled 102 (M/F: 1.48) consecutive non-demented patients and 106 healthy controls recruited among the relatives/friends of the patients. Demographic variables for ALS and controls were the age at onset (years), education (years), and sex (M/F). For the ALS group, clinical variables included the score at the ALS Functional Rating Scale (ALSFRS-R [24]), expressing the degree of disability; the ΔFS (i.e., interval [months] from clinical onset to diagnosis/48—ALSFRS-R score at diagnosis), a rating score of the disease progression [25]; the forced vital capacity (FVC%), as a measure of respiratory dysfunction.

Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained from the ALS patients and controls. The Ethics Committee of the former DiNeC, now Department of Biomedicine, Neuroscience and Advanced Diagnostics of the University of Palermo, approved the study protocol (n. 12; May 12, 2009).

Measures

Neuropsychological evaluations (NPS)

Both groups of ALS patients and controls underwent a neuropsychological assessment including the following tools:

(i) The phonemic fluency task, a quick and useful test for the identification of frontal lobe dysfunction, with particular reference to executive functions [26–28]. In particular, participants were asked to generate as many words as possible, beginning with a given letter, in a time range of 60 s. We performed three trials with the letters F, A, S.

None of the ALS patients at entry was severely dysarthric, all subjects scoring 4 or 3 in the first item of the ALSFRS-R scale. However, dysarthric patients were allowed an extra time of 30 s to perform the test. Scores were calculated according to the published normative data [26].

(ii) The Frontal System Behavioural Scale (FrSBe), a 46-item rating scale mainly exploring the frontal-lobe-related behavioral impairment. It consists of three sub-scales: apathy (14 items); disinhibition (15 items); executive dysfunction (17 items). A total score of 65 or greater is associated with a clinically significant frontal-lobe-mediated dysfunction [29].

To explore depressive symptoms, we administered the ALS Depression Inventory (ADI-12 [30]). It is a validated
self-reported questionnaire which includes 12 statements, each with 4 possible answers: “I fully agree”; “I agree”; “I don’t agree”; “I do not agree at all”. Scores range from 12 (best total score, no depression at all) to 48 (worst total score, severe depression). Scores above 28/48 (optimal cutoff) indicate a clinically relevant depression.

The global cognitive status was evaluated with the screening test Mini-Mental State Examination (MMSE; scores range from 0 to 30, with lower scores indicating poorer cognitive performance [31]; range indicating a mild cognitive impairment is between 24/30 and 27/30, after correction for age and education according to the normative data of the Italian population [32].

Consent capacity measures

The CCT was assessed with the Mac Arthur Competence Assessment Tool for Treatment (MacCAT-T [33]), a semi-structured interview based on a real consent disclosure on the eventuality of a respiratory failure and the invasive mechanical ventilation options.

MacCAT-T explores four main decision-making abilities: understanding (subsections: disorder, treatment and benefit/risks), appreciation (disorder, treatment), reasoning (consequential, comparative, generating consequences, logical consistency) and expressing a choice. We used in these experiments the Italian version of the MacCAT-T tool [34].

The understanding section explores the subject’s ability to comprehend a clinical diagnosis and the therapeutic options. The appreciation section evaluates the subjective estimation of the value of the information. The reasoning section allows the subject to compare alternatives. Finally, expressing a choice section evaluates the ability to choose between treatment options.

For each item, a scoring of 2 refers to a full credit (capable), 1 refers to partial credit (marginally capable), whereas 0 refers to no credit (incapable).

All the recruited subjects participated in the MacCAT-T interview after a disclosure session on respiratory dysfunction in ALS and invasive and non-invasive ventilatory support treatments.

Longitudinal evaluation

The neuropsychological assessment and the Mac-CAT-T interview were carried out in the ALS group at the enrolment (T0, n = 102) and 12 months later (T12, n = 72). Of the thirty patients that were not re-evaluated, seven were lost at follow-up, ten became home bound, eight were severely dysarthric/anarthric and could not perform the phonemic fluency test, and five have deceased.

Data analysis

All analyses were performed using IBM® SPSS® Statistics 21. Non-parametric data comparisons were made with the Mann–Whitney rank-sum test. Differences between groups were evaluated with the Chi-square test. To compare data of multiple groups, a Kruskal–Wallis ANOVA on ranks was applied.

Multinomial regression analysis was performed to assess which variables are likely to be independently associated with MacCAT-T subscores. Wilcoxon matched-pairs test was used to compare differences between CCT outcomes at baseline and 1-year follow-up.

For all analyses, p values < 0.05 were considered significant.

Results

Baseline demographic and neuropsychological variables

Demographic, clinical, and neuropsychological characteristics of patients and controls are shown in Table 1.

Onset was spinal in 70 patients (68.6%), whereas it was bulbar in 32 (31.4%). Median age at onset was 62 years (IQR = 54–68). At the time of the enrollment, the median disease duration from the clinical onset was 22.5 months (IQR = 13–40). Median ΔFS was 0.53 (IQR 0.28–0.88), indicating a slow/intermediate rate of progression. Median education level was 8 years (IQR 5–13), indicating a slow/intermediate rate of progression. Median education level was 8 years (IQR 5–13). The median age of the control group was 65 years (IQR = 60–68), with a male-to-female ratio of 1.71. The controls also had a median education of 8 years (IQR = 6–13).

ALS patients, therefore, did not significantly differ from HC in the main demographic variables, i.e. the age at the enrollment, M/F ratio and education. However, patients performed significantly below HC on the phonemic fluencies and the FrSBe battery, two neuropsychological measures for frontotemporal cognitive/behavioral impairment [28, 29].

In particular, at baseline, 16% of the patients performed below cut-off on the verbal fluency test (ALSci), and 18% of the patients provided a pathological performance of the FrSBe battery (ALSbi), indicating that in our non-demented ALS cohort at least one-third of the patients show frontal-lobe-related cognitive/behavioral impairment [23]. These data further confirm the widely reported evidence of a cognitive/behavioral impairment in a sizable number of non-demented ALS patients [2, 28, 35, 36].

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Measures of depression (i.e., ADI-12) and global cognitive functioning (i.e., MMSE) were not significantly different between the two groups.
Groups performance on the MAC-CAT-T standards

Table 2 shows the CCT outcomes by domains for the ALS patients and controls. The large majority of ALS patients performed as capable (i.e., full credit) in all the MAC-CAT-T subscales. However, 10–17% of the patients received a partial credit score (i.e., marginally capable) in the different subscales, and a smaller proportion (i.e., 4–10%) scored as incapable of appropriately giving informed consent. None of the HC scored as incapable, but 5–22% of this group showed to be marginally capable in different subscales.

Considering the specific CCT items, those ALS patients who performed as marginally capable or incapable, therefore, with scores significantly lower that controls, did so at all Understanding subscales (i.e., disorder, treatment, benefit/risks), at both the Appreciation subscales (i.e., disorder and treatment), and at expressing a choice subscale.

Demographic, clinical and neuropsychological predictors of CCT outcome in ALS patients

Table 3 shows the results of the multiple logistic regression analysis of the effects of demographic, clinical, and neuropsychological variables on the different MacCAT-T domains. For this analysis, all subscales of each MacCAT-T domain were combined.

Age seems to be related to lower performance at the understanding and reasoning domains. Of the other variables tested, low level of education and low scores at the phonemic fluency appeared to be significantly related only to low performance at the understanding disorder domain. Thus, in our ALS population, older age, a low education and a pathological phonemic fluency might represent risk factors that may lead to an incorrect comprehension (i.e., understanding domain of the MacCAT-T) of a clinical diagnosis and its therapeutic options; therefore, predicting a marginally capable or incapable performance at the MacCAT-T.

In the control group, no significant correlation between age, education and CCT outcomes emerged, although these factors tended to predict low scores at appreciation of disease and treatment items and final choice (data not shown).

Longitudinal analysis of NPS and CCT in ALS

We could repeat FrSBe, phonemic fluencies, MMSE, ADI and CCT after 1 year in 72 patients. Table 4 shows the
clinical and neuropsychological evaluations in the ALS group at baseline and 12 months later. As the number of ALS subjects that could be evaluated decreased at T12, we compared the demographic, clinical and neuropsychological characteristics of this latter group with the whole ALS cohort when both at baseline and we found no significant differences (data not shown).

As expected, the number of patients undergoing non-invasive ventilation and/or submitted to a percutaneous gastrostomy increased, as did the functional disability measured with the ALSFRS-R. Concerning the neuropsychological tests, 1 year after the basal evaluations the proportion of patients with pathological performances in the phonemic fluencies and FrSBe battery increased significantly, suggesting that the specific frontal-lobe-related cognitive/behavioural functions may impair with the disease progression (Fig. 2 [37, 38]). Interestingly, no significant changes were observed in the measure of depression (ADI-12) and general cognition (MMSE).

With regard to the MacCAT-T assessment at 1-year follow-up, Wilcoxon matched-pairs tests showed that only the items related to reasoning and expressing a choice worsened after 1 year, whereas the other (understanding and appreciation disease, treatment and benefit/risks) did not show significant changes (Table 2).

### Table 2  CCT Outcomes by domains for ALS patients and controls

| MacCAT-T domain (bold) | Capable | Marginally capable | Incapable | p       |
|------------------------|---------|--------------------|-----------|---------|
| Understanding subscales |         |                    |           |         |
| Disorder               | 83 (78.3) | 23 (21.7) | 0 (0) | 0.034* |
| ALS                    | 82 (80.5) | 14 (13.7) | 6 (5.8) |         |
| ALS (1-year follow-up) | 58 (80.5) | 10 (13.8) | 4 (2) | n.s.† |
| Treatment              | 82 (77.4) | 24 (22.6) | 0 (0) | 0.001† |
| ALS                    | 82 (80.4) | 10 (9.8) | 10 (9.8) |         |
| ALS (1-year follow-up) | 57 (79) | 7 (9.7) | 8 (11) | n.s.† |
| Benefit/risks          | 82 (77.4) | 24 (22.6) | 0 (0) | 0.001† |
| ALS                    | 77 (75.4) | 17 (16.6) | 8 (8) |         |
| ALS (1-year follow-up) | 57 (79) | 7 (9.7) | 8 (11) | n.s.† |
| Appreciation subscales |         |                    |           |         |
| Disorder               | 100 (94.3) | 6 (5.7) | 0 (0) | 0.017* |
| ALS                    | 85 (83.3) | 12 (11.8) | 5 (4.9) |         |
| ALS (1-year follow-up) | 64 (88.8) | 7 (9.7) | 1 (1.3) | n.s.† |
| Treatment              | 100 (94.3) | 6 (5.7) | 0 (0) | 0.014* |
| ALS                    | 84 (82.3) | 14 (13.7) | 4 (4) |         |
| ALS (1-year follow-up) | 60 (83.3) | 11 (15.2) | 1 (1.3) | n.s.† |
| Reasoning subscales    |         |                    |           |         |
| Consequential          | 90 (84.9) | 16 (15.1) | 0 (0) | 0.11† |
| ALS                    | 85 (83.3) | 13 (12.7) | 4 (4) |         |
| ALS (1-year follow-up) | 59 (81.9) | 11 (15.2) | 2 (2.7) | n.s.† |
| Comparative            | 92 (86.8) | 14 (13.2) | 0 (0) | 0.12† |
| ALS                    | 85 (83.3) | 13 (12.7) | 4 (4) |         |
| ALS (1-year follow-up) | 58 (80.5) | 12 (16.6) | 2 (2.7) | n.s.† |
| Gener. conseq          | 96 (90.5) | 9 (8.5) | 1 (1) | 0.09† |
| ALS                    | 83 (81.4) | 14 (13.7) | 5 (4.9) |         |
| ALS (1-year follow-up) | 57 (79.1) | 8 (11.1) | 4 (2) | 0.02† |
| Logical                | 99 (93.4) | 6 (5.6) | 0 (0) | 0.011† |
| ALS                    | 85 (83.3) | 10 (9.8) | 7 (6.9) |         |
| ALS (1-year follow-up) | 61 (84.7) | 8 (11.1) | 3 (4.1) | 0.01† |
| Expressing a choice    | 100 (94.4) | 6 (5.6) | 0 (0) | 0.005† |
| ALS                    | 83 (81.4) | 12 (11.8) | 7 (6.8) |         |
| ALS (1-year follow-up) | 60 (83.3) | 11 (15.2) | 1 (1.3) | 0.01† |

*Baseline MacCAT-T in ALS vs controls, Chi-square analysis
†MacCAT-T in ALS: baseline vs 1-year follow-up, Chi-square analysis
Discussion

In this work, we explored the decision-making capacities in a cohort of non-demented ALS patients from a single Tertiary ALS Center. The study sample included patients in different stages of the disease, including some one-fifth of subjects already receiving non-invasive respiratory support and/or enteral nutrition.

Among the different specific tools for assessment of capacity to consent [39], the MacCAT test has the advantage that it allows a customised disclosure of the diagnosis and the possible therapeutic approaches. Specifically, we focused on a semi-structured interview on the eventuality of respiratory failure and the invasive mechanical ventilation options.
Tracheostomy and the invasive ventilation are the most effective life-prolonging treatments in ALS [40]. This modality of respiratory support determines a variable gain of survival without affecting the disease progression towards a locked-in state. The consent disclosure on respiratory management is a crucial and ethically relevant step of ALS care and it should be proposed to the patients in advance, allowing a thoughtful decision [41].

We observed that, in comparison to the healthy controls, some thirty percent of the ALS patients scored pathologically at the cognitive and behavioural tests, which supports the appreciative presence of ALS. In the ALS patients in a random ALS population [23, 42, 43].

Most of ALS patients (80–83%) showed to be “Fully Capable” of facing all the aspects of a consent disclosure (understanding, appreciation, reasoning and expressing a choice). A smaller number of patients was “Marginally Capable”, meaning the emergence of ambivalence, vagueness or the need for supplemental clarifications or support for the decision.

Finally, a minority group of ALS patients was scored as “Incapable”, which refers to inadequate high-level cognitive abilities for facing a medical choice consciously. The whole ALS group showed a less satisfactory performance at CCT as compared to the control group, even if, interestingly, up to 23% of healthy subjects showed a partial credit in one or more CCT items.

Impaired capacity to consent-to-treatment showed to be predicted by older age and low education. A link between low educational attainment and decision-making has been already demonstrated in healthy subjects [43, 44] and suggests the need for special prudence in consent disclosure with patients with limited cultural resources. An impairment of the phonemic fluency is related to most the CCT items, whereas no significant relationship emerged with the FrSBe scores. This evidence suggests that an impaired language processing undermines per se the participation to a consent disclosure, irrespective of the executive functioning [42, 45].

At 1-year follow-up, notwithstanding the whole worsening of the cognitive functioning, the performance at the CCT interview didn’t change for most items, excepting them related to the reasoning and expressing a choice.

This study has limitations. The putative presence of language problems, in terms of expression or comprehension, was not systematically evaluated. The cognitive and behavioural evaluations were limited to two main tests, verbal fluency and the FrSBe battery. Therefore, in an extension of this study, other relevant cognitive and behavioral tests to expose more thoroughly the frontal-lobe-related dysfunctions will be warranted.

Overall, these preliminary results suggest that most ALS patients retain a full or partial capacity to choose between treatment options. Those patients at higher risk for impaired CCT (i.e., incapable, according to the MacCAT-T) were older, less educated, and most probably with cognitive dysfunction. In these subjects, consent disclosure for any procedure should be handled with special attention, considering the need of anticipating possible clinical problems, by spending more time and multiple sessions to a single choice.

Acknowledgements We are grateful to all the participants for their generous contribution to this research study.

Funding This work was supported by an Italian MoH Grant No. GR20091596540 (2009) and by the European Union’s Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 841116 to RS.

Compliance with ethical standards

Conflicts of interest The authors report no conflict of interest.

References

1. Charcot JM (1874) De la sclérose latérale amyotrophique. Prog Med 2:325–327
2. Goldstein LH, Abrahams S (2013) Change in cognition and behaviour in amyotrophic lateral sclerosis: nature of impairment and implications for assessment. Lancet Neurol 12:368–380
3. Robertson ED, Hesse JH, Rose KD et al (2005) Frontotemporal dementia progresses to death faster than Alzheimer disease. Neurology 65:719–725
4. Gordon PH, Goetz RR, Rabkin JG et al (2010) A prospective cohort study of neuropsychological test performance in ALS. Amyotroph Lateral Scler 11:312–320
5. Elamin M, Phukan J, Bede P et al (2011) Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. Neurology 76:1263–1269
6. Chiò A, Iardi A, Cammarosano S et al (2012) Neurobehavioral dysfunction in ALS has a negative effect on outcome and use of PEG and NIV. Neurology 78:1085–1089
7. Appelbaum PS, Grisso P (1988) Assessing patients’ capacity to consent to treatment. N Engl J Med 319:1635–1638
8. Grisso T, Appelbaum PS (1998) Assessing competence to consent to treatment. A guide for physicians and other health professionals. Oxford University Press, New York
9. Marson DC, Schmitt F, Ingram KK et al (1994) Determining the competency of Alzheimer’s patients to consent to treatment and research. Alzheimer Dis Assoc Disord 8(suppl 4):5–18
10. Marson DC, Chatterjee A, Ingram KK et al (1996) Toward a neuropsychological model of competency: cognitive predictors of capacity to consent in Alzheimer’s disease using three different legal standards. Neurology 46:666–672
11. Huthwaite JS, Martin RC, Griffith R et al (2006) Declining medical decision-making capacity in mild AD: a two-year longitudinal study. Behav Sci Law 24:453–463
12. Okonkwo OC, Griffith HR, Copeland JN et al (2008) Medical decision-making capacity in mild cognitive impairment. Neurology 71:1474–1480
13. Griffith HR, Dymek MP, Atchison P et al (2005) Medical decision-making in neurodegenerative disease: mild AD and PD with cognitive impairment. Neurology 65:483–485

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14. Martin RC, Okonkwo OC, Hill J et al (2008) Medical decision-making capacity in cognitively impaired Parkinson’s disease patients without dementia. Mov Disord 23(13):1867–1874
15. Karlawish J, Cary M, Moelter ST et al (2013) Cognitive impairment and PD patients’ capacity to consent to research. Neurology 81:801–807
16. Triebel KL, Martin RC, Novack TA et al (2012) Treatment consent capacity in patients with traumatic brain injury across a range of injury severity. Neurology 78:1472–1478
17. Triebel KL, Martin RC, Novack TA et al (2014) Recovery over 6 months of medical decision-making capacity after traumatic brain injury. Arch Phys Med Rehabil 95:2296–2303
18. Triebel KL, Martin RC, Nabors LB et al (2009) Medical decision-making capacity in patients with malignant glioma. Neurology 73:2086–2092
19. Kim SYH, Marson DC (2014) Assessing decisional capacity in patients with brain tumours. Neurology 83:482–483
20. Kerrigan S, Erridge S, Liaquat I et al (2014) Mental incapacity in patients undergoing neuro-oncologic treatment. Neurology 83:537–541
21. Brooks BR, Miller RG, Swash M et al (2000) El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler 1:293–299
22. Neary D, Snowden JS, Gustafson L et al (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 51:1546–1554
23. Strong MJ, Abrahams S, Goldstein LH et al (2017) Amyotrophic lateral sclerosis—frontotemporal spectrum disorder (ALS-FTSD): revised diagnostic criteria. Amyotroph Lateral Scler Frontotemp Degen 18:153–174
24. Cedarbaum JM, Stambler N, Malta E et al (1999) The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS study group (phase III). J Neurol Sci 169:13–21
25. Kimura F, Fujimura C, Ishida S et al (2006) Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. Neurology 66:265–267
26. Lezak MD (ed) (1995) Neuropsychological assessment, 3rd edn. Oxford University Press, Oxford, pp 544–550
27. Abrahams S, Leigh PN, Harvey A et al (2000) Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). Neuropsychologia 38:734–747
28. Lomen-Hoerth C, Murphy J, Langmore S et al (2003) Are amyotrophic lateral sclerosis patients cognitively normal? Neurology 60:1094–1097
29. Grace J, Malloy P (2001) The frontal systems behavior scale manual. Psychological Assessment Resources, Odessa
30. Hammer EM, Häcker S, Hautzinger M et al (2008) Validity of the ALS-Depression-Inventory (ADI-12)—a new screening instrument for depressive disorders in patients with amyotrophic lateral sclerosis. J Affect Dis 109:213–219
31. Folstein MF, Folstein SE, McHugh PR (1975) “Mini-mental state:” a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198
32. Measso G, Caravanzan F, Zappalà G et al (1993) The Mini-Mental State Examination: normative study of a random Italian population. Dev Neuropsychol 9:77–85
33. Grisso T, Appelbaum P (1997) The MacCAT-T: a clinical tool to assess patients’ capacities to make treatment decisions. Psychiatr Serv 48:1415–1419
34. Grisso T, Appelbaum P (2000) Il consenso alle cure. Guida alla valutazione per medici e altri operatori sanitari. Centro Scientifico Editore, Torino
35. Phukan J, Elamin M, Bede P et al (2012) The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. J Neurol Neurosurg Psychiatry 83:102–108
36. Strong MJ, Grace GM, Freedman M et al (2009) Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. Amyotrophic Lateral Scler 10:131–146
37. Crockford C, Newton J, Lonergan K et al (2018) ALS-specific cognitive and behavior changes associated with advancing disease stage in ALS. Neurology 91:e1370–e1380
38. Benbrika S, Desgranges B, Eustache F et al (2019) Cognitive, Emotional and Psychological Manifestations in Amyotrophic Lateral Sclerosis at Baseline and Overtime: A Review. Front Neurosci 13:951:e1-e22
39. Sturman ED (2005) The capacity to consent to treatment and research: A review of standardised assessment tools. Clin Psychol Rev 25:954–974
40. Spataro R, Bono V, Marchese S et al (2012) Tracheostomy mechanical ventilation in patients with amyotrophic lateral sclerosis: clinical features and survival analysis. J Neurol Sci 323:66–70
41. Spataro R, La Bella V (2012) Ethical issues: invasive ventilation in amyotrophic lateral sclerosis. BMJ Support Palliat Care 2:85–86
42. Phukan J, Pender NP, Hardiman O (2007) Cognitive impairment in amyotrophic lateral sclerosis. Lancet Neurol 6:994–1003
43. Cassimiro L, Fuentes D, Nitrini R et al (2017) Decision-making in cognitively illiterate and low-educated older women: results on the Iowa Gambling Task. Arch Clin Neuropsychol 32(1):71–80. https://doi.org/10.1093/arclin/acw080
44. Tymula A, Rosenberg BL, Rudermanb L et al (2013) Like cognitive function, decision making across the life span shows profound age-related changes. PNAS 42:17143–17148
45. Whiteside DM, Kealey T, Semla M et al (2016) Verbal fluency: language or executive function measure? Appl Neuropsychol Adult 23:29–34.