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# Optometric assessment in amyotrophic lateral sclerosis patients: A focus on the relation between ocular motility disturbances and cognitive findings

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**Summary.** — *Background and Purpose* To assess the visual function in a large cohort of Amyotrophic Lateral Sclerosis (ALS) patients in different stages of the disease through optometric assessment, and to evaluate the relation between ocular motility and cognitive data in a subgroup of patients. *Methods* The optometric protocol included ocular motility tests (broad H test and Northeastern State University College of Optometry - NSUCO test), near point of convergence (NPC), refractive error, best corrected visual acuity, binocular visual alignment assessment, and ocular symptoms questionnaire. The functional measure was expressed by ALS Functional Rating Scale-revised (ALSFRS-r) and the cognitive impairment was assessed by the Edinburgh Cognitive and Behavioural ALS Screen (ECAS). Demographic and clinical features were also collected. *Results* Two-hundred consecutive ALS patients (median age: 64; M/F: 118/82) in different stages of disease were recruited. Regarding ocular motility tests, patients with acceptable NSUCO values in both saccades and pursuits performance, obtained a significantly higher ECAS total score and most of the domains. *Conclusions* This study highlights the importance of optometric evaluations in multidisciplinary assessment to take care of ocular impairment early in the disease process. Our results seem to confirm the association between ocular motility disturbances and cognitive dysfunction, consistently with the literature.

 

## 1. – Introduction

In the last decades, considerable knowledge has been obtained about the different features of Amyotrophic Lateral Sclerosis (ALS), highlighting the concept that it is a multisystem disease which culminates in dysfunction of the motor system as its hallmark manifestation [1,2]. In this context, cognitive and behavioral changes suggestive of frontal dysfunction are accepted as part of the disease, as well as some signs of oculomotor abnormalities [3,4]. As far as ocular motility is concerned, several studies reported saccades and pursuits impairments in ALS patients [5-12]. To the best of our knowledge, there have been few reports on the use of comprehensive functional optometric assessments to clarify ocular involvement in ALS [13,14]. For this reason, the overall aim of this study was to perform a comprehensive optometric exam on a large cohort of ALS patients and to focus on the possible cross-sectional relations between ocular motility disturbances detected by optometric tests and cognitive data.

## 2. – Methods

A thorough assessment of ocular functions was performed in ALS patients at Neuromuscular Omnicentre (Fondazione Serena Onlus, Milan, Italy) from 2016 to 2019. Patients with a diagnosis of definite, probable, or laboratory-supported probable ALS according to the Revised El-Escorial Criteria [15] were involved. Patients with severe cognitive dysfunctions and/or behavioural disorders and/or significant psychiatric disorders were excluded, together with patients with diagnosis of any ocular disease. Specific demographic and clinical variables were collected. The optometric tests are listed below:

- Ocular motility evaluation by broad H test: abnormal eye movements were recorded.
- Saccades and pursuits assessment using the Northeastern State University College of Optometry (NSUCO) oculomotor test. Scores were divided into two groups (acceptable scores – unacceptable scores) for the statistical analysis: scores less than or equal to three were not considered acceptable values, corresponding to abnormal movements.
- Binocular visual alignment was assessed by cover test in free space.
- Near point of convergence (NPC) was measured by a Wolff wand; objective break point greater than 15 centimeters was considered unacceptable.
- Monocular and binocular refractive errors were detected.
- Best corrected binocular visual acuity was measured.
- Questionnaire on ocular history and symptoms was administered.

The Amyotrophic Lateral Sclerosis Functional Rating Scale—revised (ALSFRS-r) [16] was used to assess disease severity. To evaluate the relation between the cognitive impairment and the ocular function, the Italian version of the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) [17] was performed. The maximum total score of this scale is 136 and decreasing scores indicate lower cognitive performance. The study design was approved by the institutional ethics committee of Milano Area 3 (No. 353-072017) and all the subjects involved signed the informed consent in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments.

**2**˙1. *Statistical analysis*. – Data were described using a median and interquartile range or frequency and percentage, as appropriate. The associations between ocular assessments and cognitive evaluations were assessed at univariate level using the Mann-Whitney U test. Furthermore, multivariable logistic regression models were used to confirm the significant associations adjusting the analysis for the effect of age at evaluation, sex, site of onset, disease progression rate and disease duration. All tests were two-tailed and the statistical significance was set at $p < 0.05$. All analyses were performed using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

| **Demographic and clinical characteristics** | **Overall cohort (n=200)** | **Analysis cohort (n=71)** |
|---|---|---|
| Age at evaluation (years) | 63.99 [55.26 – 70.71] | 64.39 [55.32 – 70.18] |
| Disease Duration (months) | 42.90 [21.93 – 82.73] | 24.65 [17.73 – 47.53] |
| Disease Progression Rate | 0.50 [0.26 – 0.89] | 0.59 [0.31 – 0.91] |
| Sex, m. n (%) | 118 (59) | 44 (62) |
| C9ORF72 expansion, yes. n (%) | 5 (3) | 1 (2) |
| Site of onset, spinal. n (%) | 162 (84) | 53 (79) |
| Noninvasive ventilation at evaluation, yes. n (%) | 92 (46) | 19 (27) |
| Invasive ventilation at evaluation, yes. n (%) | 9 (5) | 0 (0) |
| Percutaneous endoscopic gastrostomy at evaluation, yes. n (%) | 31 (16) | 3 (4) |
| Eye tracking communication device user, yes. n (%) | 23 (11) | 0 (0) |
| ALSFRSr Total score | 29.00 [18.00 – 36.00] | 32.50 [24.00 – 38.00] |
| **Optometric assessment** | **Overall cohort (n=200)** | **Analysis cohort (n=71)** |
| Saccades unacceptable values (1 – 3), n (%) | | |
| Accuracy | 90 (46) | 29 (41) |
| Head Movement | 79 (42) | 27 (39) |
| Pursuit unacceptable values (1 – 3), n (%) | | |
| Accuracy | 121 (61) | 39 (55) |
| Head Movement | 69 (37) | 27 (39) |
| Broad H test abnormal eye movements (yes), n (%) | 29 (15) | 7 (10) |
| NPC unacceptable values (break point ≥ 15 cm), n (%) | 57 (29) | 12 (17) |
| **Cognitive assessment** | **Overall cohort (n=200)** | **Analysis cohort (n=71)** |
| ECAS ALS specific | - | 77.00 [69.00 – 84.00] |
| Language | - | 25.00 [22.00 – 26.00] |
| Verbal fluency | - | 20.00 [14.00 – 20.00] |
| Executive functions | - | 35.00 [30.00 – 40.00] |
| ECAS ALS nonspecific | - | 28.00 [26.00 – 30.00] |
| Memory | - | 16.00 [14.00 – 19.00] |
| Visuospatial | - | 12.00 [11.00 – 12.00] |
| ECAS Total score | - | 105.00 [92.00 – 115.00] |

Fig. 1. – Descriptive analysis of the sample. Values are represented as median (interquartile range), unless otherwise indicated. Abbreviations: ALSFRSr, Amyotrophic Lateral Sclerosis Functional Rating Scale revised; NPC, Near Point of Convergence; ECAS, Edinburgh Cognitive and Behavioural ALS Screen.

| | Abnormal Saccady Accuracy | Normal Saccady Accuracy | *p-value* | *p-value** |
|---|---|---|---|---|
| ECAS ALS specific | 71.0 [61.0 – 79.0] | 82.0 [76.0 – 87.0] | **0.0001** | **0.0033** |
| Language | 23.0 [20.0 – 26.0] | 25.0 [24.0 – 26.0] | **0.0238** | **0.0101** |
| Verbal fluency | 18.0 [14.0 – 20.0] | 20.0 [18.0 – 20.0] | **0.0130** | **0.0040** |
| Executive functions | 30.0 [24.0 – 35.0] | 39.0 [35.0 – 41.0] | **0.0003** | **0.0027** |
| ECAS ALS nonspecific | 26.0 [23.0 – 28.8] | 28.5 [27.0 – 31.0] | **0.0058** | **0.0090** |
| Memory | 14.0 [12.0 – 17.0] | 17.0 [15.0 – 19.0] | **0.0073** | **0.0049** |
| Visuospatial | 12.0 [11.0 – 12.0] | 12.0 [11.0 – 12.0] | 0.1079 | - |
| ECAS Total score | 95.0 [84.0 – 108.0] | 111.0 [103.0 – 117.0] | **0.0001** | **0.0017** |
| | **Abnormal Saccady Head Movement** | **Normal Saccady Head Movement** | ***p-value*** | ***p-value**** |
| ECAS ALS specific | 71.0 [61.0 – 77.0] | 82.0 [76.0 – 86.0] | **0.0013** | **0.0200** |
| Language | 23.0 [20.0 – 26.0] | 25.0 [24.0 – 27.0] | **0.0464** | 0.1046 |
| Verbal fluency | 18.0 [14.0 – 20.0] | 20.0 [16.0 – 20.0] | 0.0784 | - |
| Executive functions | 31.0 [26.0 – 36.0] | 39.0 [35.0 – 41.0] | **0.0057** | **0.0149** |
| ECAS ALS nonspecific | 26.0 [23.0 – 29.0] | 28.0 [26.0 – 31.0] | **0.0087** | **0.0250** |
| Memory | 14.0 [12.0 – 17.0] | 17.0 [15.0 – 19.0] | **0.0098** | **0.0126** |
| Visuospatial | 12.0 [11.0 – 12.0] | 12.0 [11.0 – 12.0] | 0.3045 | - |
| ECAS Total score | 96.0 [85.0 – 105.0] | 111.0 [102.0 – 116.0] | **0.0006** | **0.0136** |
| | **Abnormal Pursuit Accuracy** | **Normal Pursuit Accuracy** | ***p-value*** | ***p-value**** |
| ECAS ALS specific | 72.0 [64.0 – 82.0] | 82.0 [76.0 – 86.5] | **0.0067** | **0.0556** |
| Language | 24.0 [21.0 – 26.0] | 25.0 [24.0 – 27.0] | **0.0352** | 0.1047 |
| Verbal fluency | 18.0 [14.0 – 20.0] | 20.0 [16.0 – 20.0] | 0.2924 | - |
| Executive functions | 33.0 [25.0 – 39.0] | 38.5 [35.0 – 40.5] | **0.0058** | **0.0351** |
| ECAS ALS nonspecific | 27.0 [23.0 – 29.0] | 29.0 [27.0 – 31.0] | **0.0090** | **0.0210** |
| Memory | 16.0 [12.0 – 17.0] | 17.0 [15.0 – 19.5] | **0.0073** | **0.0123** |
| Visuospatial | 12.0 [11.0 – 12.0] | 12.0 [12.0 – 12.0] | 0.0531 | - |
| ECAS Total score | 98.0 [85.0 – 111.0] | 111.0 [103.5 – 116.5] | **0.0027** | **0.0305** |
| | **Abnormal Pursuit Head Movement** | **Normal Pursuit Head Movement** | ***p-value*** | ***p-value**** |
| ECAS ALS specific | 71.0 [61.0 – 82.0] | 82.0 [75.0 – 86.0] | **0.0033** | **0.0356** |
| Language | 23.0 [21.0 – 26.0] | 25.0 [23.0 – 27.0] | 0.0902 | - |
| Verbal fluency | 18.0 [14.0 – 20.0] | 20.0 [16.0 – 20.0] | 0.1357 | - |
| Executive functions | 30.0 [24.0 – 37.0] | 38.0 [34.0 – 41.0] | **0.0065** | **0.0197** |
| ECAS ALS nonspecific | 26.0 [23.0 – 29.0] | 28.0 [26.0 – 31.0] | **0.0202** | **0.0406** |
| Memory | 14.0 [12.0 – 17.0] | 17.0 [15.0 – 19.0] | **0.0234** | **0.0281** |
| Visuospatial | 12.0 [11.0 – 12.0] | 12.0 [11.0 – 12.0] | 0.1430 | - |
| ECAS Total score | 96.0 [84.0 – 108.0] | 111.0 [102.0 – 116.0] | **0.0019** | **0.0246** |

Fig. 2. – Associations between cognitive findings and NSUCO tests. *Adjusted for age at evaluation, sex, site of onset, disease duration and disease progression rate. Values are represented as median (interquartile range). The significant $p$-value is shown in bold. Abbreviations: NSUCO, Northeastern State University College of Optometry; ECAS, Edinburgh Cognitive and Behavioural ALS Screen.

## 3. – Results

Two-hundred ALS patients were enrolled for the study. Figure 1 includes a descriptive analysis of the cohort.

**3**˙1. *Optometric findings in ALS*. – Considering the overall cohort and the presence or not of ocular symptoms, sixty-six patients (33%) were asymptomatic, sixty-one patients (31%) were mildly symptomatic and seventy-three patients (36%) were severely symptomatic. Figure 1 showed the descriptive analysis of optometric tests.

**3**˙2. *Associations between ocular motility and cognitive data*. – The statistical relationship between ocular motility and cognitive data was assessed in a subgroup of 71 patients (analysis cohort) who underwent the ECAS test at the same time as the optometric tests. Demographic and clinical variables of this analysis cohort are reported in fig. 1. The binocular alignment, the refractive condition and the ocular symptoms revealed no significant relations with cognitive features (data not shown).

Looking at the ocular motility assessed by NSUCO tests (fig. 2), patients with abnormal saccade accuracy obtained a significantly lower ECAS score in all the domains except for the visuospatial function. Also, abnormal head movement in the saccade test was strongly associated to lower ECAS score in all the domains, except for verbal fluency and visuospatial areas. All these associations remained statistically significant also adjusting for the effect of sex, disease progression rate, disease duration and diagnostic delay. We observed similar results in the pursuit test, where lower executive functions, ALS nonspecific score, memory and ECAS total score were significantly related to abnormal pursuits accuracy and head movement, independently of sex, disease progression rate, disease duration and diagnostic delay. Moreover, ALS specific score resulted to be independently associated with the pursuit test for head movement only.

Considering the associations between cognitive data and both NPC and broad H test, the ECAS ALS specific domain is significantly lower in patients with abnormal eye movements in both tests. Moreover, a lower language domain score is significantly associated to abnormal NPC values, as well as the executive functions domain in patients with abnormal eye movements detected by broad H test. However, all these statistical relationships loss their significance when adjusting for the considered covariates.

## 4. – Conclusions

This study described the optometric findings collected in a large cohort of ALS patients and how they are related to cognitive data. A large number of patients complain of various ocular discomforts, emphasizing how this is a common feature in ALS. How these symptoms are related to functional impairment and to disease staging was described by Cozza *et al.* [13]: patients with severe functional impairment and in the more advanced stages of the disease are those more severely symptomatic. For this reason, it may be worth considering to routinely perform eye examinations to ALS people within the context of multidisciplinary care, attempting to take care of any ocular problem they may have in order to maintain the best quality of life for the patients and their families. Furthermore, our results suggest that ALS oculomotor functions and cognitive impairment may worsen in parallel; indeed, the total score and the majority subdomains' scores of ECAS were significantly lower in patients with the worst performance in ocular motility tests, independently of the stage of the disease and its aggressiveness. In our opinion, this is an interesting result, since it was obtained using feasible optometric tests that

could be easily performed in clinical practice. In conclusion, our data provide a baseline assessment performed in a large cohort of consecutive patients. How ocular involvement progresses over time and how it impacts on activities of daily living and patients' perceptions is currently being explored.

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