ORIGINAL ARTICLE

Diffuse Colour Discrimination as Marker of Afferent Visual System Dysfunction in Amyotrophic Lateral Sclerosis

Lindsay Boven^a, Qin Li Jiang^b, and Heather E. Moss^c

^aDepartment of Ophthalmology and Visual Sciences, University of Illinois College of Medicine, Chicago, Illinois, USA; ^bDepartment of Neurology and Rehabilitation, University of Illinois at Chicago, Chicago, Illinois, USA; ^cDepartments of Ophthalmology and Visual Sciences and Neurology and Rehabilitation, University of Illinois at Chicago, Chicago, Illinois, USA

ABSTRACT

Abnormalities of the inner and intermediate retinal structures in patients with amyotrophic lateral sclerosis (ALS) have been described using optical coherence tomography and histopathology. Colour vision is a potential marker of these structural changes. The purpose of this study is to test the hypothesis that colour vision impairment is associated with ALS. Monocular (right eye) colour vision was assessed in subjects with definite or probable ALS ($n = 25$, aged 50–80 years) and control ($n = 21$, aged 46–89 years) subjects with corrected near visual acuity of at least 20/40 using the L'Anthony D15 color test (desaturated), scored by c-index, a measure of diffuse colour discrimination. Of ALS subjects, 16/25 (64%) had impaired colour vision (c-index >1.8). Comparing with our normal subjects and accounting for age, 72% ($n = 18$) of ALS subjects had colour vision below the 50th percentile, 52% ($n = 13$) had colour vision below the 25th percentile, 24% ($n = 6$) had colour vision below the 10th percentile, and 8% ($n = 2$) had colour vision below the 2nd percentile. In multivariate models of $\ln(\text{c-index})$ and age, the intercept was higher and the slope was flatter in ALS subjects, suggesting that colour vision deficits are more prominent in younger ALS patients. Diffuse colour discrimination deficits are detected in ALS subjects at younger ages than in control subjects. Further study is needed to confirm these findings and to determine if the ALS colour discrimination abnormalities correlate with structural markers of retinal involvement and ALS disease severity.

ARTICLE HISTORY

Received 12 April 2017
Revised 24 April 2017
Accepted 29 April 2017

KEYWORDS

Amyotrophic lateral sclerosis;
colour vision; desaturated
L'Anthony D-15;
retinal disease

Introduction

Retinal abnormalities described in association with amyotrophic lateral sclerosis (ALS) include histopathological inclusions in the human¹ and transgenic mouse² intermediate retina and loss of retinal ganglion cells in vivo and on histopathology in humans.² In vivo changes, specifically macular retinal nerve fibre layer, measured using optical coherence tomography, correlate inversely with disease duration² and pulmonary function tests.³ With regards to visual function correlates of these structural abnormalities, one study found impaired high contrast (black on white) and low contrast (grey on white; LCVA) visual acuities in ALS versus control subjects.⁴ A follow-up study did not confirm this finding but reported an inverse association between LCVA and disease duration.⁵ A concern with LCVA is that it may not be the best candidate to capture dysfunction

related to both the intermediate and inner retinal pathology that has been described in ALS. Colour discrimination is of interest, as it is likely to be affected by damage to the intermediate retina and ganglion cells. A small study reported abnormal colour discrimination in 4/12 ALS subjects.² However, there was no comparison with age-specific norms, which is important because colour vision declines with increasing age. We hypothesise that colour vision is impaired in ALS patients relative to control subjects and investigate this in a study of ALS and control subjects of similar ages.

Materials and methods

Adults with a diagnosis of definite or probable ALS by El Escorial criteria were recruited from University of Illinois at Chicago multidisciplinary ALS clinic. Adults without a diagnosis of ALS were

recruited as controls subjects from companions of ALS subjects and from the University of Illinois at Chicago Ophthalmology Clinics. Subjects were excluded from the study if they were less than 18 years of age, had neurological disease other than ALS, or had ophthalmological disease other than corrective lenses or cataracts. Inclusion and exclusion criteria were assessed by interview and chart review and subject interview. Recruitment and data collection occurred during an 11-month period from June 2014 to April 2015. This study was approved by the institutional research board at the University of Illinois at Chicago and has been performed in accordance with the ethical standard laid down in the Declaration of Helsinki and its later amendments. Informed written consent was obtained from all participants.

Age, gender, race, and ethnicity were evaluated by interview. Monocular vision testing was performed using the right eye in standard clinic examination rooms without windows, with overhead lights on and habitual glasses on. Testing was performed using the right eye. The left eye was patched. Near Snellen visual acuity was assessed using pinhole and converted to logMAR units. Colour vision was assessed using the L'Anthony D-15 color test (desaturated) (D-15ds) (Richmond Products, Albuquerque, New Mexico, USA), which requires the subject to arrange 15 coloured discs in order of hue starting with a reference disc. The result is the numeric order in which the subject arranges the discs. These were qualitatively mapped on two-dimensional colour space specific to the D-15ds and evaluated for evidence of protan, deutan, and tritan colour deficit patterns.^{6,7} C-index, a measure of diffuse colour discrimination, was calculated using the method described by Vingrys and King-Smith,⁸ as implemented by

Török.⁹ Normal c-index values range from 1 to 1.8, with perfect arrangement of the discs receiving a score of 1. A score greater than 1.8 is diagnostic of diffuse colour discrimination.

Multivariate linear regression models with ln(c-index) as the outcome, group (ALS, control), age, gender, and ALS $\times$ age interaction term were used to evaluate for age-independent and age-dependent differences between colour discrimination between ALS and normal subjects. To evaluate the suitability of colour discrimination as a screening test in ALS, linear regression was performed of age against ln(c-index) for control subjects and used to calculate the percentiles and predicted 95% confidence intervals (CIs) for normal individuals. C-index scores for ALS subjects were compared against these age-dependent norms in order to classify their percentile and identify subjects whose colour discrimination fell outside the 95% CI for control subjects. Analysis was performed using SPSS version 23 (IBM, Armonk, New York, USA).

Results

Testing was completed in 25 ALS subjects and 21 control subjects (Table 1). Ages were similar between ALS and control subjects ($p = 0.26$, t test), and there were more females in the control group ($p = 0.03$, Fisher exact test). Visual acuity was similar between groups ($p = 0.18$, t test), with no subject having near pinhole visual acuity worse than 20/40.

No subject had qualitative colour defects fitting a protan, deutan, or tritan pattern. C-index of >1.8 , diagnostic of impaired colour vision, was found in 64% ($n = 16$) of ALS subjects compared with 43% (9/21) control subjects. The youngest control subject with abnormal c-index was 69

Table 1. Subject demographics and visual function measurements.

Variable	ALS ($n = 25$)	Control ($n = 21$)	Comparison
Age in years (mean, range)	63.4 (50–80)	67.1 (46–89)	$p = 0.26$ (t test)
Female gender, n (%)	8 (29%)	13 (62%)	$p = 0.03$ (Fisher exact test)
Race, n (%)	14 (56%) White 4 (16%) Black 1 (4%) Asian 5 (20%) Missing	18 (87%) White 3 (13%) Black 0 Asian	$p = 0.44$ (Fisher exact test; white vs. other)
Hispanic ethnicity	4 (16%)	4 (19%)	$p = 0.29$ (Fisher exact test)
Visual acuity (logMAR)	0.12 (0–0.3)	0.09 (0–0.3)	$p = 0.18$ (t test)
c-index, mean (range)	2.1 (1–3.5)	1.6 (1–3.5)	$p = 0.01$ (t test)
Abnormal c-index, n (%)	16 (64%)	9 (43%)	$p = 0.24$ (Fisher exact test)

years old. The youngest ALS subject with abnormal c-index was 50 years old.

In a multivariate linear regression model with $\ln(\text{c-index})$ as the outcome variable, age (0.024/year, 95% CI: 0.012–0.036, $p < 0.0005$), ALS (1.36, 95% CI: 0.14–2.59, $p = 0.03$), and ALS $\times$ age interaction ($-0.019/\text{year}$ in ALS, 95% CI: -0.037 – 0.000 , $p = 0.047$) were independently associated with $\ln(\text{c-index})$. Female gender (-0.085 , 95% CI: -0.29 – 0.121 , $p = 0.41$) was not independently associated with $\ln(\text{c-index})$ and was not included in the final model. The resulting models for control and ALS subjects as a function of age are illustrated in Figure 1. For both groups, $\ln(\text{c-index})$ linearly increases with age. Compared with the control model, the ALS model has a higher intercept and a shallower slope, indicating colour discrimination deficits compared with controls at younger ages only.

ALS patient performance was compared with the predictive 95% confidence intervals for normal individual values, which were calculated based on linear regression of $\ln(\text{c-index})$ as a function of age for control subjects (Figure 2). Three ALS subjects had performance outside of the age-specific predictions for normal subjects. Of the ALS subjects, 72% ($n = 18$) had colour vision below the age-specific 50th percentile, 52% ($n = 13$) had colour vision below the age-specific 25th percentile, 24% ($n = 6$) had colour vision below the age-specific

Figure 1. Linear regression models of $\ln(\text{c-index})$ as a function of age in ALS and control subjects. Each marker represents either an ALS (open circle) or a control (filled circle) subject. Lines represent the regression model for ALS (dashed) or control (solid) subjects.

Figure 2. Colour vision in ALS subjects compared with age-specific predictive 95% confidence intervals for normal individuals. Each marker represents either an ALS (open circle) or a control (filled circle) subject. Lines represent the boundaries for the 95% confidence intervals for prediction of normal subjects, which was calculated from linear regression results for control subjects.

10th percentile, and 8% ($n = 2$) had colour vision below the age-specific 2nd percentile. Both of these were younger than 55 years old.

Discussion

In this study, younger age, ALS, and younger age in ALS are associated with colour discrimination impairment compared with control subjects. These results support a hypothesis of impaired colour vision compared with controls in younger individuals with ALS.

Although there is an association between ALS and colour vision, most ALS subjects did not have colour vision outside of 95% confidence intervals for control subjects. There were no ALS subjects over age 60 years with colour vision outside of the predictive 95% confidence intervals for control subjects. This suggests that exploration of colour vision as a disease marker in ALS may be best targeted to younger patients who are not yet experiencing age-associated colour vision deterioration. Colour vision testing with the L'Anthony D15 color test (desaturated) is attractive as a simple, quick test that can be easily performed in the neurology clinic setting where most ALS patients receive care.

The concept of ALS has grown beyond that of an isolated disease of motor neurons to a multi-system disorder with effects on cognition, supranuclear ocular motility, afferent vision, and other neurological systems in some patients.^{4,10} Our results contribute to evolving literature regarding afferent visual pathway involvement in ALS, including recent studies demonstrating structural changes in the intermediate retina,¹ inner retina (optic nerve),³ and functional changes such as colour vision impairment in 4/12 ALS subjects.² Our results provide evidence for colour vision deterioration at younger ages in ALS than in control subjects. Colour vision is attractive as a potential marker of the intermediate and inner retinal pathology that has been described in some ALS patients.^{1,2} Our study did not include structural imaging of the retina, so we cannot draw conclusions regarding the relationship between colour vision and retinal structure in individual patients. This is an important area for future investigation.

The results contribute more broadly to the literature of colour vision dysfunction in neurodegenerative diseases. Colour vision deficits measured using the L'Anthony D-15 (desaturated) in Alzheimer's disease subjects were consistent with age-related changes.¹¹ Studies in subjects with Parkinson's disease have demonstrated colour perception deficits compared with controls using the Farnsworth 100-hue test, but not the L'Anthony D-15 color test (desaturated),¹² and worse colour vision in patients with hallucinations versus no hallucinations using both tests.¹³ In multiple sclerosis (MS), colour vision deficits on the Farnsworth 100-hue test were detected in 70% ($n = 14$) of patients without history of optic neuritis in MS, with receiver operating curve area of 0.94 for separating MS from control subjects.¹⁴ However, a study comparing vision tests for use in characterising visual dysfunction in MS patients found the c-index calculated from L'Anthony D-15 color test (desaturated) to have receiver operating curve area of 0.71 for separating MS patients from controls, which was not better than high contrast visual acuity.¹⁵ Studies have reported an association between MS severity and colour vision deficits assessed using Hardy-Rand-Rittler (HRR) plates.¹⁶ However, these result must be interpreted in the context of a more recent study suggesting that

HRR plate testing does not correlate with colour vision as assessed using the Farnsworth D-15 test but is correlated with contrast sensitivity.¹⁷ The size of our data set along with lack of data regarding other markers of disease limits our ability to comment on possible relationships between colour discrimination and disease severity in ALS, although this is an important topic for future investigation.

Diffuse colour discrimination deficits occur in ALS at all ages and in normal subjects at older ages. This study supports the presence of afferent pathway visual dysfunction in association with ALS. Further study is needed to determine if colour perception abnormalities correlate with disease severity or retinal pathology in ALS patients.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Funding

This work was supported by National Institutes of Health grants K23 EY024345 and K12 EY02147; Research to Prevent Blindness Unrestricted Grant to the University of Illinois at Chicago Department of Ophthalmology; and Research to Prevent Blindness Unrestricted Grant to the Stanford Department of Ophthalmology.

References

- [1] Fawzi AA, Simonett JM, Purta P, Moss HE, Lowry JL, Deng HX, Siddique N, Sufit R, Bigio EH, Volpe NJ, Siddique T. Clinicopathologic report of ocular involvement in ALS patients with C9orf72 mutation. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15:569–580.
- [2] Volpe NJ, Simonett J, Fawzi AA, Siddique T. Ophthalmic manifestations of amyotrophic lateral sclerosis (an American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc* 2015;113:T12[1–15].
- [3] Simonett JM, Huang R, Siddique N, Farsiu S, Siddique T, Volpe NJ, Fawzi AA. Macular sub-layer thinning and association with pulmonary function tests in amyotrophic lateral sclerosis. *Sci Rep* 2016;6:29187.
- [4] Moss HE, McCluskey L, Elman L, Hoskins K, Talman L, Grossman M, Balcer LJ, Galetta SL, Liu GT. Cross-sectional evaluation of clinical neuro-ophthalmic abnormalities in an amyotrophic lateral sclerosis population. *J Neurol Sci* 2012;314:97–101.

- [5] Moss HE, Samelson M, Mohan G, Jiang QL. High and low contrast visual acuity are not affected in amyotrophic lateral sclerosis. *PLoS ONE* 2016;11:e0168714.
- [6] Geller AM, Hudnell HK. Critical issues in the use and analysis of the Lanthony Desaturate Color Vision test. *Neurotoxicol Teratol* 1997;19:455–465.
- [7] Farnsworth D-15 and Lanthony Test Instructions rev 1.7 http://www.richmondproducts.com/files/8113/1550/0538/FR_15_Farnsworth_and_LanthonyD15_Instructions_Rev_1.7_0506.pdf2006. Updated May 2006. Accessed April 11, 2017.
- [8] Vingrys AJ, King-Smith PE. A quantitative scoring technique for panel tests of color vision. *Invest Ophthalmol Vis Sci* 1988;29:50–63.
- [9] Török B. Farnsworth D-15 and Lanthony D-15 Color Vision Test Scoring <http://www.torok.info/colorvision/d15.htm>2013. Accessed April 11, 2017.
- [10] McCluskey L, Vandriel S, Elman L, Van Deerlin VM, Powers J, Boller A, Wood EM, Woo J, McMillan CT, Rascovsky K, Grossman M. ALS-Plus syndrome: non-pyramidal features in a large ALS cohort. *J Neurol Sci* 2014;345:118–124.
- [11] Bassi CJ, Solomon K, Young D. Vision in aging and dementia. *Optom Vis Sci* 1993;70:809–813.
- [12] Pieri V, Diederich NJ, Raman R, Goetz CG. Decreased color discrimination and contrast sensitivity in Parkinson's disease. *J Neurol Sci* 2000;172:7–11.
- [13] Diederich NJ, Goetz CG, Raman R, Pappert EJ, Leurgans S, Piery V. Poor visual discrimination and visual hallucinations in Parkinson's disease. *Clin Neuropharmacol* 1998;21:289–295.
- [14] Gundogan FC, Tas A, Altun S, Oz O, Erdem U, Sobaci G. Color vision versus pattern visual evoked potentials in the assessment of subclinical optic pathway involvement in multiple sclerosis. *Indian J Ophthalmol* 2013;61:100–103.
- [15] Baier ML, Cutter GR, Rudick RA, Miller D, Cohen JA, Weinstock-Guttman B, Mass M, Balcer LJ. Low-contrast letter acuity testing captures visual dysfunction in patients with multiple sclerosis. *Neurology* 2005;64:992–995.
- [16] Martinez-Lapiscina EH, Ortiz-Perez S, Fraga-Pumar E, Martinez-Heras E, Gabilondo I, Llufríu S, Bullich S, Figueras M, Saiz A, Sanchez-Dalmau B, Villoslada P. Colour vision impairment is associated with disease severity in multiple sclerosis. *Mult Scler* 2014;20:1207–1216.
- [17] Zhao J, Dave SB, Wang J, Subramanian PS. Clinical color vision testing and correlation with visual function. *Am J Ophthalmol* 2015;160:547–552.e1.