ORIGINAL ARTICLE

Validation of Simplified Visual Acuity Testing Protocols in Amyotrophic Lateral Sclerosis

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ABSTRACT

High- and low-contrast visual acuity (HCVA, LCVA) are potential quantitative markers of neurological dysfunction in amyotrophic lateral sclerosis (ALS). The complex nature and duration of gold standard (GS) protocols precludes widespread use in neurology settings. This study compares simplified to GS visual acuity (VA) protocols. Monocular HCVA and LCVA were measured in ALS ($n = 10$) and control ($n = 4$) subjects using six protocols, varying by two chart and three refraction methods. Intraclass correlation coefficients between simplified and GS protocols ranged from 0.83 to 0.98 (HCVA, excellent agreement) and 0.56 to 0.75 (LCVA, moderate agreement). Differences between LCVA and GS protocols exceeded test-retest reliability. Simplified HCVA protocols using LCD (liquid crystal display) tablet charts and/or pinhole correction produced valid measurements. None of the modified LCVA testing protocols produced valid measurements.

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KEYWORDS

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Introduction

Dysfunction of the afferent visual system, characterised by impairments in high-contrast visual acuity (HCVA) and low-contrast visual acuity (LCVA), has been demonstrated in patients with multiple sclerosis (MS) and Parkinson's disease, among others.^{1,2} In addition to capturing both overt and occult visual pathway disease, HCVA and LCVA test integrated neurological function beyond the primary visual system and may correlate with other markers of neurological impairment.³ Owing to their quantitative nature, HCVA and LCVA have potential for use as clinical trial outcome measures.

Although data have been conflicting, afferent visual system involvement in amyotrophic lateral sclerosis (ALS) is supported by studies showing decreased binocular LCVA and HCVA⁴ and retinal changes on optical coherence tomography⁵ and histopathology.⁶ An association between afferent visual system deterioration and other markers of ALS has been demonstrated both with regards to function (LCVA and disease duration)⁷ and structure (macular retinal nerve fibre layer and

pulmonary function tests).⁸ Larger clinical studies are needed to understand the extent of afferent visual pathway involvement in ALS, how it correlates with other markers of disease, and the functional implications of this. However, there are practical barriers to implementing widespread studies of visual function in the neurology clinic, where patients with neurological disease are primarily seen. The measurement equipment (e.g., Early Treatment Diabetic Retinopathy Study [ETDRS] charts or Sloan charts mounted on an illuminator cabinet) and environmental requirements (light-controlled environments) required for gold standard VA measurement protocols are readily available in ophthalmology clinics, but mobility limitations and fatigue of potential ALS subjects limits recruitment when the study site is distant from their site of care. In our experience, there is more enthusiasm among potential ALS subjects to participate in studies that are coordinated in both time and location with their clinical care. An additional barrier to implementation of VA testing in ALS patients is the time and expertise required for refraction that is part of gold

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standard vision testing. This is often fatiguing for subjects.

Modifications to time-intensive gold standard vision testing techniques, including LCD (liquid crystal display) tablet-presented charts and use of subjects' own glasses or pinhole in place of best refraction may overcome some of these barriers to facilitate widespread measurement of HCVA and LCVA in ALS patients attending a neurology clinic. The modified protocols shorten the duration of LCVA and HCVA testing and require less specialised equipment and less examiner expertise. The goal of this study is to assess and validate modified HCVA and LCVA testing protocols in a sample of the ALS patient population.

Methods

Ten adults greater than 18 years old with a diagnosis of definite or probable ALS by El Escorial criteria were recruited from the University of Illinois at Chicago multidisciplinary ALS clinic, and four adults without diagnosed neurological or ophthalmic disease were recruited from the University of Illinois at Chicago ophthalmology clinic. Patients were excluded from the study if they had neurological disease other than ALS, had ophthalmologic disease other than corrective lenses or cataracts, and/or were using medications known to influence visual function. Inclusion and exclusion criteria were assessed by interview and chart review. Recruitment and data collection occurred during a 6-month period from June 2014 to December 2014. The research followed the tenets of the Declaration of Helsinki, informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study, and the research was approved by the University of Illinois at Chicago Institutional Review Board.

Demographic information of age, gender, race, and habitual corrective lens use were obtained by patient interview. Medication list, ALS diagnosis, ALS duration, and ALS Functional Rating Scale—Revised⁹ scores were obtained from the medical record for ALS subjects.

All testing was performed in standard windowless examination rooms with the overhead lights

extinguished. One hundred percent high-contrast visual acuity (black on white) and 2.5% low-contrast visual acuity (grey on white) were assessed using each subject's right eye at 2 m using each of two chart conditions: illuminator cabinet (Precision Vision, LaSalle, IL, USA)–mounted partially transparent charts (EDTRS 1 for HCVA, Sloan 2.5% for LCVA; Precision Vision) (gold standard) or LCD tablet (iPad Air 2 with antiglare screen) displaying electronic charts (Variable Contrast Sensitivity Chart version 1.4 provided by King-Devick Test Inc., Oakbrook Terrace, IL, USA), with each of three refractive correction conditions: spherical refraction performed using ETDRS protocol on top of habitual lenses (gold standard), the subject's own glasses, and pinhole held over their own glasses. Thus, six HCVA and six LCVA measurements were made for each subject. Tests were performed in random order to minimise subject-learning and fatigue bias.

Visual acuity for each protocol was recorded as the total number of letters correctly identified on the chart. Correctly identifying 55 letters on high-contrast ETDRS charts is equivalent to 20/20 Snellen VA. HCVA and LCVA were compared between the gold standard protocol and each modified protocol (i.e., in pairs) using two-way mixed intraclass correlation coefficients (ICCs), with the raters being the protocols and the ratees being the subjects. HCVA and LCVA Bland-Altman plots were constructed for each modified protocol compared with the gold standard protocol by plotting the mean VA measure on the *x*-axis against the difference between VA measures for each subject.¹⁰ The degree and homogeneity of the differences was assessed by comparing each difference to ± 2 times the standard deviation of the differences. Analysis was performed using SPSS version 23 (IBM Inc., Armonk, NY, USA).

Results

Table 1 summarises the demographic, ALS disease characteristics, and gold standard visual acuity measurements of the enrolled subjects. All subjects had gold standard HCVA and LCVA within the range of that reported in a larger study of VA in ALS and control subjects.⁷ Median HCVA and

Table 1. Subject demographics.

Characteristic	ALS (n = 10)	Control (n = 4)
Median age (range)	61 years (50–80)	25 years (23–38)
Female gender	3 (30%)	4 (100%)
Race/ethnicity	5 (50%) NH white 2 (20%) Black 2 (20%) Hispanic 1 (10%) Other	3 (75%) NH white 1 (25%) Other
Median ALS-FRS-R (range)	25 (5–45)	—
El Escorial ALS diagnosis category	4 (40%) Probable 6 (60%) Definite	
Median ALS duration (range)	2.8 years (2–4)	
Habitual correction	5 (50%) Myopic 3 (30%) Hyperopic 2 (20%) None	3 (75%) Myopic 1 (25%) Hyperopic
Median additional spherical correction (range)	+0.25 (–1.00 to +1.00)	+0.125 (0.00 to +0.50)
Median HCVA (range)	48.5 letters (29–59)	59.5 letters (55–63)
Median 2.5% LCVA (range)	27 letters (4–38)	42.5 letters (24–45)

Note. NH = non-Hispanic; ALS FRS-R = revised ALS functional rating score; HCVA = high-contrast best-corrected visual acuity at 2 m using gold standard protocol; LCVA = low-contrast best-corrected visual acuity at 2 m using gold standard protocol.

LCVA in ALS subjects in this study are similar to those reported in the larger study (HCVA: 49, LCVA: 28).

Modified high-contrast visual acuity protocols had ICCs ranging from 0.83 to 0.98, with the two modifications using own glasses to correct

refractive error having the lowest (worst), although still excellent, ICCs (Figure 1). Bland-Altman plots show variation (± 2 SD of difference between protocols) to be largest for protocols using subjects' own glasses, with these also showing heterogeneous variation that decreases with increasing HCVA. There was underestimation of HCVA using habitual lenses compared with gold standard refraction. Modified protocols using LCD tablet charts and/or pinhole correction had narrow variation that was homogeneous across VA values.

Modified low-contrast visual acuity protocols had ICCs ranging from 0.56 to 0.75, with all modified protocols showing wide variability and many with bias compared with the gold standard protocol (Figure 2). In many cases, this variability exceeded test-retest reliability of 13 letters reported in the literature.¹¹ Pinhole correction was associated with consistent underestimation of LCVA.

Discussion

We find that substitution of an LCD tablet-displayed chart for illuminator box-mounted translucent charts and/or substitution of pinhole for refraction achieve valid high-contrast visual acuity measurements compared with a gold standard protocol consisting of illuminator box-mounted

Figure 1. Bland-Altman plots comparing monocular high-contrast visual acuity (HCVA) measurements made using modified testing protocols versus a gold standard protocol. Testing protocols vary by chart used (ETDRS on light box [gold standard, top row], LCD tablet-displayed chart [bottom row]) and refractive correction (manual refraction [left column], habitual correction [middle column], and pinhole [right column]). The x-axes are the number of letters identified (mean of two protocols being compared). The y-axes are the difference in number of letters identified between the two protocols being compared. Horizontal black lines indicate ± 2 standard deviations of the HCVA difference for the protocols being compared. Each marker represents a subject. Intraclass correlation coefficients (ICCs) are indicated for each protocol comparison.

Figure 2. Bland-Altman plots comparing 2.5% low-contrast visual acuity (LCVA) measurements made using modified testing protocols versus a gold standard protocol. Testing protocols vary by chart used (Sloan chart on light box [gold standard, top row], LCD tablet–displayed chart [bottom row]) and refractive correction (manual refraction [left column], habitual correction [middle column], and pinhole [right column]). The x-axes are the number of letters identified (mean of two protocols being compared). The y-axes are the difference in number of letters identified between the two protocols being compared. Horizontal black lines indicate ± 2 standard deviations of the LCVA difference for the protocols being compared. Each marker represents a subject. Intraclass correlation coefficients (ICCs) are indicated for each protocol comparison.

charts and best spherical refraction in a sample of ALS patients and control subjects. This conclusion is based on excellent ICCs greater than 0.8 and narrow differences between modified and gold standard measurements with magnitude less than that for reported test-retest reliability within subjects (7 letters).^{12,13} Our results build upon prior validation of HCVA testing using an LCD tablet in the visually normal population^{14,15} and reports validating pinhole for refractive correction for HCVA measurements at different distances.¹⁶ Both LCD tablet and pinhole are much simpler to implement than gold standard protocols. To our knowledge, this is the first published comparison of HCVA testing protocols in subjects with ALS.

None of the modified protocols for LCVA resulted in valid measurements compared with a gold standard protocol. This conclusion is based on moderate ICCs and large differences between modified and gold standard measurements that exceed reported test-retest reliability within subjects and biased measurements for both pinhole protocols. To our knowledge, this is the first published comparison of modified LCVA protocols. On the basis of other reports regarding LCD tablet–based testing,¹⁷ we speculate that glare from the LCD tablet may have contributed variability, even though we

attempted to minimise this by using an antiglare screen and extinguishing room lights. We also speculate that pinhole may have reduced the amount of light entering the eye and made contrast distinctions more difficult.¹⁸ Alternative strategies might include use of autorefraction, which is likely to be faster than manual refraction but requires specialised equipment not typically available in neurology clinics.¹⁹ Another strategy is measurement of contrast sensitivity (for example, using Pelli-Robson charts), which are less sensitive to refractive error.

Use of own glasses was not a suitable substitute for best refraction in HCVA or LCVA protocols, with underestimation compared with gold standard measurements. A possible reason for this is that subjects' own glasses may not have been up to date or optimised for testing distance of 2 m. Observations of protocols using own glasses having lower HCVA and LCVA measures than gold standard protocols at lower levels of vision support this notion that subjects' own glasses are not a suitable representation of necessary refractive correction at 2 m for some subjects. As an example, the two subjects with the largest errors for ETDRS/habitual (−15, −13) also had the largest errors for iPad/habitual (−13, −10) but much lower error for pinhole HCVA protocols (−5 to 5).

The design of our study, done to accommodate patients with neurological disease, has some limitations. These include not assessing reliability of each protocol and use of spherical only refraction to limit subject testing time. The former was obtained from the literature. Pilot data of our own as well as published studies suggest that lack of cylindrical refraction does not significantly influence VA measurements for low/moderate cylinder.^{17,20} The performance of spherical refraction on top of habitual lenses did accommodate astigmatic correction to the level in the subject's habitual glasses.

Although LCVA and HCVA have been shown to be potential quantitative clinical markers of afferent visual system dysfunction in ALS patients, the resource-intensive and time-consuming nature of gold standard testing protocols limit wide-scale study of this population. The results of this study support using LCD tablets to display charts and use of pinhole to correct refractive error for HCVA measurements only. None of the studied modifications achieved valid LCVA measures. Additional study is needed to validate the modified HCVA protocols in other diseases and to develop valid, simplified LCVA protocols.

Declaration of interest

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

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