

RESEARCH

Low-contrast visual acuity versus low-luminance visual acuity
in choroideremia

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Clinical relevance: Choroideremia is a progressive X-linked inherited rod-cone dystrophy. Patients present with nyctalopia and progressive visual field loss, but visual acuity remains well preserved early on. This study showed that low-luminance visual acuity may be a useful clinical outcome measure during earlier disease stages.

Background: Choroideremia is a progressive X-linked inherited rod-cone dystrophy. Patients present with nyctalopia and progressive visual field loss. However, visual acuity remains well preserved until late in the disease process, limiting its usefulness as a clinical trial endpoint across the disease spectrum. Visual acuity measurements under low-luminance and low-contrast conditions may be affected sooner and have been suggested as early markers in other ocular diseases. This study assesses whether low-luminance visual acuity and low-contrast visual acuity provide useful endpoints in choroideremia clinical trials.

Method: Standard high-contrast and low-luminance visual acuity was obtained on 29 choroideremia subjects and 16 healthy controls, using a logMAR chart, set at four metres. Low-luminance visual acuity was tested using a 2.0-log unit neutral density filter, with the same chart set-up, without formal dark adaptation. This was followed by low-contrast visual acuity measured using 1.25 per cent and 2.5 per cent low-contrast logMAR charts placed also at four metres. Data from the right eyes only were analysed using non-parametric statistics. High-contrast visual acuity minus low-luminance and low-contrast visual acuity provided the low-luminance and low-contrast difference scores.

Results: A higher number of choroideremia subjects were able to complete the low-luminance test than the low-contrast visual acuity tests. Choroideremia subjects had significantly higher low luminance, 2.5 per cent low-contrast and 1.25 per cent low-contrast difference scores compared with controls ($p < 0.01$, Mann-Whitney U-test); 1.25 per cent low-contrast visual acuity revealed the poorest performance. A strong positive correlation was found between low-luminance and high-contrast visual acuities ($\rho = 0.818$, $p < 0.001$) and 2.5 per cent low-contrast and high-contrast visual acuities ($\rho = 0.671$, $p < 0.001$).

Conclusion: The low-luminance visual acuity test may be a useful additional clinical trial outcome measure for early-to-moderate disease, when high-contrast visual acuity is preserved.

Key words: choroideremia, low-contrast visual acuity, low-luminance visual acuity, visual acuity outcome measures

Choroideremia is a progressive X-linked inherited rod-cone dystrophy affecting primarily the retinal pigment epithelium (RPE), with secondary degeneration in the photoreceptors and choroid. All males with the *CHM* gene mutation will show clinical disease signs, although there is some variation in severity and progression rate. Female carriers present with a more varied phenotype, some being mildly affected while others are severely affected with a similar phenotype to male patients.¹ Patients

present typically during the second decade of life with nyctalopia and progressive visual field loss. Mid-peripheral retinal degeneration gradually encroaches into the centre affecting visual acuity, while at the same time progressing peripherally. Ultimately this leads to legal blindness, sometimes as soon as the fourth decade. However, the degree of the disease progression is variable.² Good visual acuity is maintained until very late into the disease process.³ It is therefore necessary to

explore alternative visual outcome measures to aid earlier detection of reduced visual function and reliably monitor disease progression. Sensitivity markers play a role in the monitoring of the response to promising gene therapy treatments in patients with milder disease.^{4,5}

Low-luminance visual acuity involves the simple addition of a neutral density filter placed in front of the tested eye, while undertaking the standard visual acuity assessment procedure developed for the

Early Treatment Diabetic Retinopathy Study (ETDRS) – the room lights are switched off and only the retro-illuminated ETDRS letter chart is on.⁶ This test has been shown to be a useful outcome measure and predictor of subsequent high-contrast visual acuity loss in geographic atrophy of the RPE, a specific subtype of age-related macular degeneration.⁷

Low-contrast visual acuity involves specialised ETDRS charts incorporating fainter letters, typically at 1.25 per cent and 2.5 per cent contrast levels (Hilcovision, Plainville, MA, USA). They are long-established commercially available tests, which have been shown to detect visual dysfunction in early diabetic retinopathy, glaucoma and neurological conditions such as Parkinson's disease and multiple sclerosis, where conventional high-contrast visual acuity remains well preserved.^{8,9}

Both the low-contrast and low-luminance visual acuity tests appear easy to perform, requiring only minimal execution time and cost in comparison to alternative electrophysiological and psychophysical assessments. Therefore, this study aimed to assess the usefulness of low-luminance and low-contrast visual acuity testing in patients with choroideremia; in order to establish whether they could be suitable clinical trial endpoints. The ideal visual acuity test would be one that many subjects can perform and provides a wide variance in results across the disease spectrum. This is particularly required in early disease when high-contrast visual acuity is relatively well preserved.

Methods

Subjects were seen as part of the screening process for a phase two choroideremia gene therapy trial (ClinicalTrials.gov identifier NCT02407678, approved by the UK Research Ethics Committee [ref:15/LO/1379]) conducted in accordance with the Declaration of Helsinki (seventh revision 2013) at the Oxford Eye Hospital, UK. Subjects required visual acuity of 1.0 logMAR or better to be included in the study; those with additional ocular disease were excluded from the study. Only male choroideremia subjects were eligible for the study – female carriers were excluded due to the extremely variable phenotype.

All tests were completed according to the standardised ETDRS visual acuity assessment

protocol.⁶ The room lights were switched off and only the retro-illuminated ETDRS chart (Precision Vision, Woodstock, IL, USA), placed at four metres was switched on. The retro-illuminated chart contained two fluorescent lamps with fenestrated sleeves (diffuser) to control the light level and ensure uniform chart illumination (Precision Vision), to a background luminance of 160 cd/m². All subjects completed the low-luminance visual acuity test first, followed by the standard high-contrast visual acuity test, then the 1.25 per cent and 2.5 per cent low-contrast visual acuity tests. The low-luminance visual acuity test was performed first to prevent any bias from subjects memorising the ETDRS letters. A 2.0 log unit neutral density filter (Hilcovision) was placed in front of the testing eye to achieve the low-luminance conditions (1.0 cd/m²). There was no formal dark adaptation time provided. The standard high-contrast visual acuity test followed as it limited the number of ETDRS chart changes required, optimising test duration. For the 1.25 per cent and 2.5 per cent low-contrast visual acuity tests, the corresponding charts were displayed in the same retro-illuminated cabinet set-up detailed above.

Only right eye data were analysed to reduce statistical errors from using highly correlated data from both eyes.¹⁰ Non-parametric comparative statistical analyses were applied due to non-normal data distribution, using SPSS Statistics Version 25.0.0.1 (IBM, Armonk, NY, USA). The low-luminance and low-contrast difference was calculated by subtracting the low-luminance/low-contrast visual acuity from the high-contrast visual acuity.

Results

Twenty-nine male subjects with a confirmed mutation in the *CHM* gene (median age 31 years, range 17–71 years) and 21 age-matched controls (median age 35 years, range 20–46 years, $p = 0.469$ Mann-Whitney U-test) were recruited. Table 1 details subject demographics. The control subjects, both male and female, were recruited from accompanying persons in the eye clinics. All control subjects were able to read letters on all four of the visual acuity tests. In the choroideremia group, all subjects successfully read some letters on the standard high-contrast visual acuity test and so were eligible for the study. Only 62 per cent (18/29) of subjects managed to read letters on the

1.25 per cent low-contrast chart. In comparison, 79 per cent (23/29) were able to read letters on the 2.5 per cent low-contrast chart and 97 per cent (28/29) could read letters on the low-luminance test.

Choroideremia subjects had significantly higher low-luminance difference scores ($p = 0.013$), 2.5 per cent low-contrast difference scores ($p = 0.001$) and 1.25 per cent low-contrast difference scores ($p < 0.001$) compared with controls (Mann-Whitney U-test) (Table 1). Both groups showed the poorest performance with the 1.25 per cent low-contrast test causing higher difference values. Better performance and smaller difference values were seen with the low-luminance test (Table 1). The floor effect seen with the 1.25 per cent low-contrast measurement in choroideremia reflected the higher percentage of subjects who were unable to complete the test. Both the low-luminance and 2.5 per cent low-contrast results show a moderate spread of results, the 2.5 per cent low-contrast groups having a lower range compared with the low-luminance visual acuity results (Figure 1). The standard high-contrast visual acuity was also significantly different between the control and choroideremia groups ($p < 0.001$). However, as many of the subjects maintained reasonably good levels of standard high-contrast visual acuity the range of results was small compared to the other tests (Figure 1).

With Spearman rank analysis, the 1.25 per cent low-contrast visual acuity showed a poor relationship that was not significantly correlated to high-contrast visual acuity in choroideremia ($\rho = 0.328$, $p = 0.082$). There was a strong positive correlation between low-luminance visual acuity and high-contrast visual acuity ($\rho = 0.818$, $p < 0.001$) and 2.5 per cent low-contrast visual acuity and high-contrast visual acuity ($\rho = 0.671$, $p < 0.001$) (Figure 2). The Steiger Z test was applied to look for similarity between these two correlations which could suggest the tests are reflective of the same retinal function. No significant difference was found between these correlation co-efficients (Steiger's Z test, $z = 1.22$, $p = 0.223$).

Discussion

Overall visual acuity results in choroideremia subjects in all the tests performed, including high-contrast visual

	Controls	Choroideremia	Mann-Whitney U-test
Subject demographics			
Subjects, n	16	29	
Age, median (range)	35 (17–71)	31 (20–46)	p = 0.469
Percentage of subjects completing tests (subject numbers)			
1.25% low-contrast VA	100 (16/16)	62 (18/29)	
2.5% low-contrast VA	100 (16/16)	79 (23/29)	
Low-luminance VA	100 (16/16)	97 (28/29)	
Standard high-contrast VA	100 (16/16)	100 (29/29)	
ETDRS letter score			
Standard high-contrast VA, ETDRS letters, median (IQR)	89 (88–95)	79 (72–84.5)	p < 0.001
ETDRS letter difference score			
Low-luminance difference, ETDRS letters, median (IQR)	11 (6.25–13)	14 (8.5–21)	p = 0.013
2.5% low-contrast difference, ETDRS letters, median (IQR)	22 (20.25–26)	33 (24–44)	p = 0.001
1.25% low-contrast difference, ETDRS letters, median (IQR)	29 (26.25–34.75)	42 (34–73)	p = < 0.001

ETDRS: Early Treatment Diabetic Retinopathy Study chart, IQR: interquartile range, SD: standard deviation, VA: visual acuity.

Table 1. Subject demographics, the number of subjects completing each test and the calculated low-luminance and low-contrast difference results

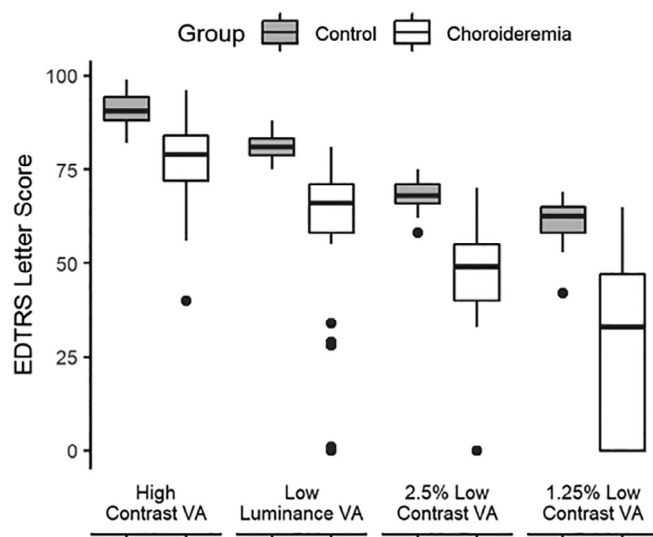


Figure 1. Box plot of four visual acuity tests comparing patients with choroideremia versus controls. ETDRS: Early Treatment Diabetic Retinopathy Study scores, VA: visual acuity.

acuity, low-luminance visual acuity and 1.25 per cent and 2.5 per cent low-contrast visual acuity were significantly worse than in controls. The low-luminance visual acuity and both low-contrast visual acuity results showed greater losses in the choroideremia group, which suggests these tests are more sensitive to early clinical

change and therefore could make viable clinical markers.

All three tests were easy to conduct and required standard ophthalmic equipment. The testing procedure was familiar to patients as letter reading is a classic element of all eye examinations in both primary and secondary care. The low-

luminance test was easier to set up in comparison to the low-contrast tests as the letter chart did not require changing. In comparison to central retinal sensitivity assessments, for example microperimetry, the low-luminance and low-contrast visual acuity tests are more straightforward, cheaper and clinically more practical to implement.

The 1.25 per cent low-contrast test had the poorest performance in both choroideremia subjects and controls, with only 62 per cent of choroideremia subjects able to read any letters to successfully perform the test. The poor correlation between the 1.25 per cent low-contrast visual acuity and high-contrast visual acuity suggests higher variability and difficulty. Overall in this cohort, this test appeared the least suitable. The better performance seen in the 2.5 per cent low-contrast test in both subject groups, as well as the moderate range of results and significant correlation with high-contrast visual acuity in choroideremia, suggests subjects found this test more manageable. However, low-luminance visual acuity had the best performance with 97 per cent of choroideremia subjects able to complete the test, producing a broad range of results and significant correlation to high-contrast visual acuity. Aside from the high-contrast visual acuity test, the low-luminance visual

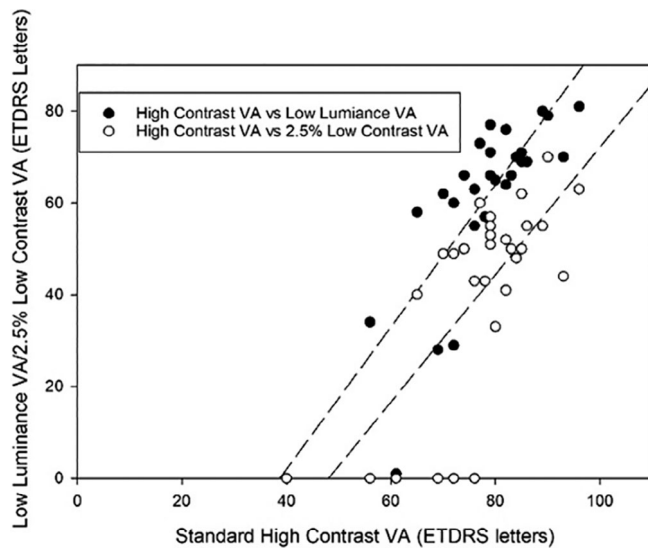


Figure 2. The positive Spearman rank correlations between high-contrast visual acuity with low luminance and 2.5 per cent low-contrast visual acuity

acuity test appeared to be the most manageable test for choroideremia subjects, with a wide range of results, suggesting greater sensitivity across the disease spectrum.

Two functions that describe different aspects of contrast are Weber contrast (C_W) and Michelson contrast (C_M). Weber contrast describes contrast as the luminance difference of the stimulus and background against the background alone. Stimulus luminance (L_s) and background luminance (L_b).

$$C_W = \frac{L_s - L_b}{L_b}$$

Michelson contrast describes contrast as a function of the difference between the highest luminance (L_{\max}) and lowest luminance (L_{\min}) of the background and stimulus.¹¹

$$C_M = \frac{L_{\max} - L_{\min}}{L_{\max} + L_{\min}}$$

Quantifying exact contrast levels of the different tests is difficult due to variable influencing factors such as object reflectance and other illuminating light sources. The topic of contrast and how our visual system sees contrast is complex. The low-contrast visual acuity tests used in this study obtain reduced contrast by making the stimulus fainter. This has a greater effect on the

Michelson contrast score but a lesser effect on the Weber contrast score, as the photopic background luminance remains constant. In comparison, with the low-luminance test, the applied assumption is that the letters are already at 100 per cent blackness. Adding the neutral density filter will only reduce the luminance of the background. For low-luminance visual acuity there will be a greater impact on Weber's contrast. Both conditions demonstrate reduced contrast; however, these contrast levels are manifested in different ways depending on whether it is the stimulus or background being modulated. It could be speculated that this could impact the neural adaptation and processing of the light information in the retina, reflecting different pathways in the visual system.¹¹ However, the statistically insignificant difference between the low-luminance visual acuity and 2.5 per cent low-contrast visual acuity correlation coefficient could suggest both tests are reflective of similar neuro-retinal functions. Low-contrast visual acuity is believed to be dependent on neural summation and reflective of axonal and neural function in the retina.¹² It could be hypothesised that low-luminance visual acuity may be representative of a similar physiological function.

The change in background luminance may be a significant factor. Low-luminance visual acuity appears to be a low-contrast test set in lower (mesopic) light conditions.

It could be hypothesised that low-luminance visual acuity is indicative of visual function in lower light levels and therefore may be helpful in conditions such as choroideremia where nyctalopia is a common early symptom.¹³ The low-luminance visual acuity test has also been shown to correlate with symptoms of poor night vision in patients with macular degeneration.¹⁴

In conclusion, the low-luminance visual acuity test is a useful additional clinical marker and clinical trial outcome measure for monitoring early-to-moderate disease, particularly when high-contrast visual acuity remains relatively well preserved. Further investigations are required to understand the structure and functional relationships of these measures and to determine whether these findings extrapolate to other rod-cone dystrophies.

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