Clinical characteristics and management of retinitis pigmentosa

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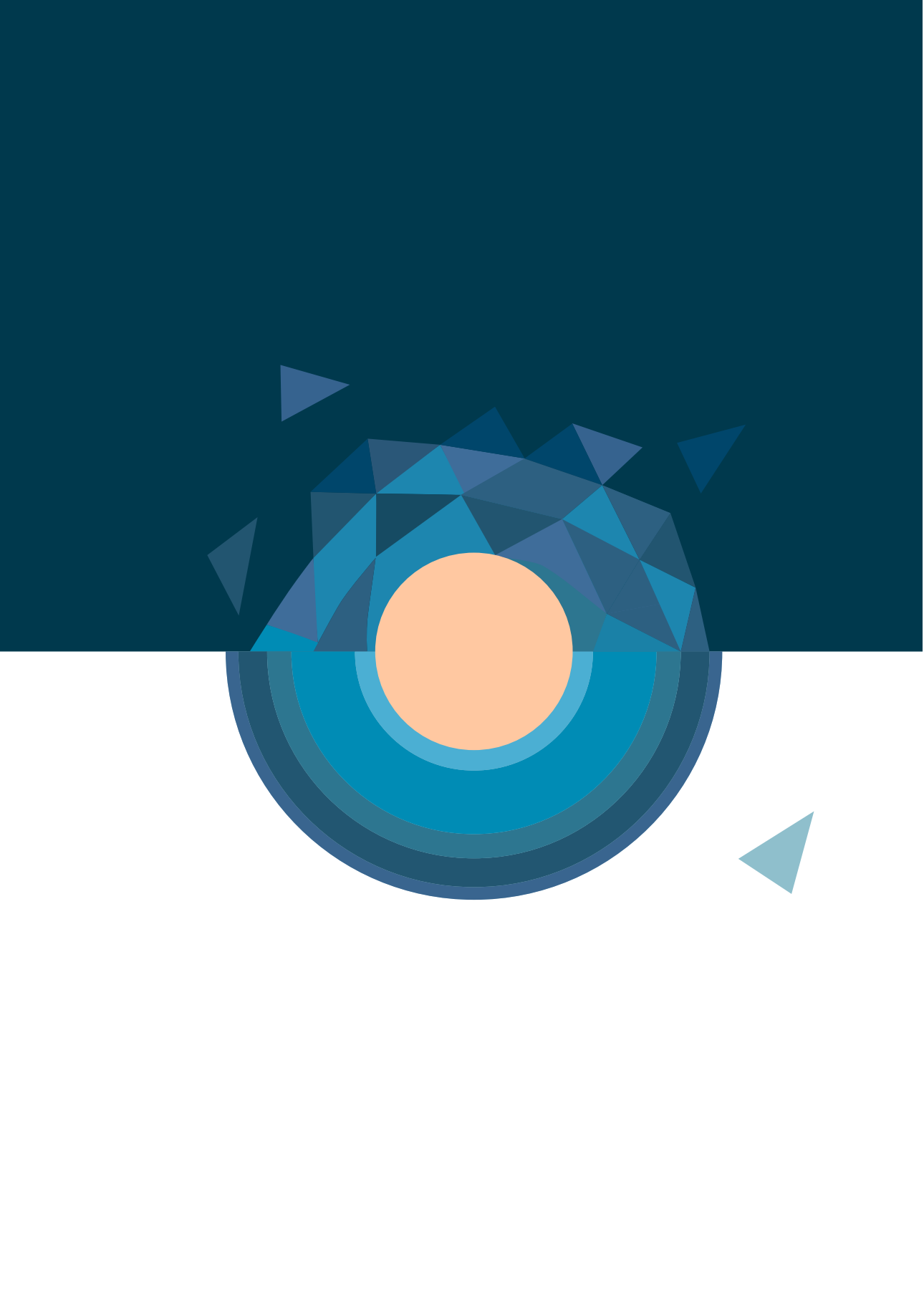

CHAPTER 3.3

QUALITY OF LIFE IN PATIENTS WITH *CRB1*-ASSOCIATED RETINAL DYSTROPHIES: A LONGITUDINAL STUDY

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ABSTRACT

Purpose

To assess the longitudinal vision-related quality of life among patients with *CRB1*-associated inherited retinal dystrophies.

Methods

A longitudinal questionnaire study included 22 patients with pathogenic *CRB1* variants. The National Eye Institute Visual Function Questionnaire (39 items, NEI VFQ-39) was applied at baseline, two-year follow-up, and 4-year follow-up. Classical test theory was performed to obtain subdomain scores and in particular 'near activities' and 'total composite' scores. The Rasch analysis based on previous calibrations of the NEI VFQ-25 was applied to create visual functioning and socio-emotional subscales.

Results

In total, 22 patients with pathogenic *CRB1* variants were included, with a median age of 25.0 years (IQR: 13–31 years) at baseline and mean follow-up of 4.0 ± 0.3 years. A significant decline at 4 years was observed for 'near activities' (51.0 ± 23.8 vs 35.4 ± 14.7, p = 0.004) and 'total composite' (63.0 ± 13.1 vs 52.0 ± 12.1, p = 0.001) subdomain scores. For the Rasch-scaled scores, the 'visual functioning' scale significantly decreased after 2 years (−0.89 logits; p = 0.012), but not at 4-year follow-up (+0.01 logits; p = 0.975). The 'socio-emotional' scale also showed a significant decline after 2 years (−0.78 logits, p = 0.033) and 4 years (−0.83 logits, p = 0.021).

Conclusion

In the absence of an intervention, a decline in vision-related quality of life is present in patients with pathogenic *CRB1* variants at 4-year follow-up. Patient-reported outcome measures should be included in future clinical trials, as they can be a potential indicator of disease progression and treatment efficacy.

INTRODUCTION

Inherited retinal dystrophies (IRDs) are a spectrum of hereditary degenerations of the retina which can result in photoreceptor loss. Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP) are among the more severe phenotypes within IRDs. LCA usually presents within the first year of life with nystagmus, severe visual impairment, and (nearly) non-detectable responses on electroretinography. RP is caused by a degeneration of photoreceptors, initially rod photoreceptors followed by cone photoreceptors. Accordingly, patients suffer from reduced night vision and progressive loss of the peripheral visual field. As cone photoreceptors deteriorate and macular function is lost in later stages, patients notice a loss of visual acuity, limited contrast sensitivity, and loss of colour discrimination. Both LCA and RP patients are significantly affected by their IRD in daily life and substantially limited in their everyday activities.

LCA and RP can both be caused by relatively common pathogenic variants in the crumbs cell polarity complex component 1 (*CRB1*) gene. Studies have shown that patients with *CRB1*-associated IRD are likely to be classified as having low-vision by the median age of 18 years, and being blind by the median age of 40 years.[1, 2] With the current advances in gene augmentation research and the advent of gene therapy for LCA caused by mutations in *RPE65*,[3] treatment for *CRB1*-associated IRDs seems feasible. Experiments in mice and retinal organoids using adeno-associated viral vectors for *CRB1*-*CRB2* have shown encouraging results to facilitate upcoming gene therapy trials for *CRB1*-associated IRDs. Such trials require sensitive and clinically-relevant outcomes which have been identified using retrospective studies and a prospective natural history study. The latter has described the progression and course of *CRB1*-associated IRDs based on ophthalmological examinations including visual acuity, perimetry, microperimetry, full-field stimulus threshold (FST) testing, and multimodal imaging.[4, 5]

These clinical measurements are useful for detecting possible treatment effects, but do not reflect patient experiences in their daily life and activities. For instance, patients may have an improved visual acuity on psychophysical measurements without a meaningful treatment effect from a patient's perspective. Additionally, clinical measurements are often variable and fail to address daily obstacles associated with the retinal dystrophy.

Assessing patient context and quality of life is a critical part of treatment evaluation, but has been relatively scarcely addressed in therapeutic trials for IRDs to date. Without proper measurements for patient experiences, clinical trials may fail in capturing the most meaningful outcome. Patient-reported outcome measures (PROMs) are recognised and encouraged by the US Food and Drug Administration (FDA) as clinical trial outcome measures.[6, 7] An IRD PROM should ideally be based on patient input, and should be reliable, validated, and able to detect changes, before it can be used

for clinical trials. The National Eye Institute developed a 25-item questionnaire called the National Eye Institute Visual Function Questionnaire (NEI VFQ-25), which assesses difficulties with visual activities and condition-specific symptoms for a wide range of chronic eye diseases.[8] Fourteen additional items were added in an appendix to enhance the reliability of the various domains and resulted in the NEI VFQ-39.[9]

The NEI VFQ-25 and NEI VFQ-39 are well-established questionnaires that focus on different domains specific to a patient's day-to-day functioning and well-being.[8] Thus far, several clinical gene therapy trials have used the NEI VFQ-25 as PROM.[10-12] However, these questionnaires do not meet the requirements of the FDA for a PROM as they are not specifically developed for IRD patients. Moreover, the analysis of the NEI VFQs is flawed according to current methodology standards, as it is based on classical test theory which assumes equal difficulty per question.[13-15] Instead, expert consensus suggests using questionnaires based on item response theory, such as the Rasch analysis, which is based on the notion that some questions are more difficult than other questions and which enables estimates from ordinal responses on an invariant scale.[16] One method to maintain the use of the NEI VFQ is to apply the Rasch analysis to calibrate item measures to an invariant scale as was done by Goldstein *et al.* (2022).

The present study reports on the physical and social functioning and well-being of patients with a *CRB1*-associated IRD based on the NEI VFQ-39 over the course of 4 years in order to provide an insight into the quality of life using the pre-calibrated item measures of the NEI VFQ to meet current psychometric standards.

METHODS

Subjects

Participants were recruited from the RD5000 database, a Dutch registry of patients with IRDs,[17] and from the Delleman archive for inherited ophthalmic disorders at Amsterdam University Medical Centers. This study is part of a larger cohort study, which investigated the natural history of *CRB1*-associated IRDs.[4, 5] As such, inclusion criteria have been described earlier, but shortly include the following: (1) biallelic pathogenic variants in the *CRB1* gene, and (2) a Snellen best-corrected visual acuity (BCVA) of 1.3 logMAR (equivalent to 20/400) in the better-seeing eye.[4] Initially, 22 patients were included of which 10 patients originated from a Dutch genetic isolate that has been previously described.[18] This study adhered to the tenets of the Declaration of Helsinki and has obtained approval from the Erasmus Medical Center Medical Ethics Committee and from the Leiden University Medical Center Ethics Review Board. Informed consent was given by all patients, and obtained from their caretakers if applicable.

Clinical assessment

For this study we focused on BCVA, microperimetry, and the NEI VFQ-39.[4, 5] Refraction and BCVA were determined using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter charts. BCVA was initially noted in decimal as is common in the Netherlands, and later converted to logMAR values. Microperimetry was used to determine mesopic macular sensitivity with the Macular Integrity Assessment System (MAIA, CenterVue) and a standard 37-stimuli grid. The follow-up function was used at every follow-up visit. Some patients were not able to complete all measurements due to young age. All patients were asked to complete the NEI VFQ-39 before each visit at baseline, at the two-year follow-up, and at the 4-year follow-up. During the second follow-up the questionnaire was not completed by two patients due to their young age and during the final follow-up, one questionnaire was not completed by one elderly patient due to the COVID-19 pandemic.

NEI VFQ-39 questionnaire

The NEI VFQ-39 is a 25-item questionnaire with 14 supplemental items and consists of the following subdomains: general health', 'general vision', 'ocular pain', 'near activities', 'distance activities', 'social functioning', 'mental health', 'role differentiation', 'dependency', 'colour vision', and 'peripheral vision'. Per classical test theory, composite scores for each domain of the NEI VFQ-39 were calculated as the sum of all items for each patient at each time point, resulting in separate scores per subdomain, and a total composite score which was calculated as an average of all subdomain scores (excluding 'general health'). A higher score reflects a better quality of life relating to that specific subdomain. The subdomain scores range from 0 to 100 units. Of specific interest were the subdomain 'near activities' and total composite score for the other analyses.

Modification and calibration of item measures of the NEI VFQ-25

The NEI VFQ-25 is a well-known and often-used questionnaire; however it also has inherent problems with multidimensionality, item fit validity, and differential item functioning.[13-15] To resolve these problems and to bypass Rasch analysis on this small test sample, Goldstein *et al.* suggested using modified versions and calibrated item measures.[19] In brief, the NEI VFQ-25 was modified to two separate questionnaires: NEI VFQ-VF and NEI VFQ-SE, focusing on visual function and on socio-emotional functioning respectively. A third modification led to the NEI VFQ-25C, which excludes general health and eyesight quality, and serves as an overall measure. Goldstein *et al.* combined the data of 3342 patients with retinal diseases (mostly age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion) into a single dataset which was used for Rasch analysis and the method of successive dichotomisation to estimate person and item measures. For this study, the calibrated item measures based on the NEI VFQ-25 provided by Goldstein *et al.* were used to estimate person measures. ranging from −3 to +3, which translate to low and high perceived visual function, respectively. [19] There are currently no calibrated item measures for the NEI VFQ-39 available.

Statistical analysis

Data were analysed in SPSS (version 25.0.0; IBM Corp) and in R software using the R package 'msd'. Normal-distributed data are presented as mean ± standard deviation (SD), and non-normal distributed data are presented as median and interquartile range (IQR). Changes in scores were assessed using a linear mixed model. *p*-Values of ≤0.05 were considered statistically significant, unless *p*-values were corrected for multiple testing.

RESULTS

Baseline measurements

We identified 22 patients with a *CRB1*-associated IRD. Most patients (n = 20; 90%) had (early-onset) RP, followed by cone-rod dystrophy (n = 1; 5%) and macular dystrophy (n = 1; 5%). Study participants ranged in age at first visit from 6 to 74 years, with a median age of 25.0 years (IQR: 13.0–31.0 years) (Table 1). At the time of the first visit, the estimated mean disease duration was 19.0 ± 10.6 years based on the age of the first symptoms. Median BCVA was relatively low with 1.0 logMAR (0.6–1.2 logMAR), equivalent to 20/200 Snellen. Retinal sensitivity on mesopic microperimetry was performed on 13 patients at baseline with median sensitivity of 6.9 dB (2.7–12.8 dB). At baseline measurement, the NEI VFQ-39 was not completed by six patients, due to a variety of reasons including young age (n = 3), incomplete questionnaire (n = 2), and the development of acute glaucoma after topical use of mydriatics (n = 1).

Table 1. Baseline characteristics of patients with *CRB1*-associated retinal dystrophies included in this study

Baseline characteristics	Number (%) or median (IQR)
Gender	
Male	13 (41%)
Female	9 (59%)
Age at first visit	25.0 (13.0 – 31.0 years)
Follow-up time	4.0 ± 0.3 years
IRD diagnosis	20 (90%)
(Early-onset) RP	1 (5%)
Cone-rod dystrophy	1 (5%)
Macular dystrophy	
Estimated duration of disease at time of first visit	19.0 ± 10.6 years
Part of genetic isolate	
Yes	10 (45%)
No	12 (55%)
logBCVA ODS	1.0 logMAR (0.6 – 1.2 logMAR)
Retinal sensitivity on microperimetry* (n= 13, 3 missing at baseline)	6.9 dB (2.7 – 12.8 dB)
IRD = inherited retinal dystrophy; RP = retinitis pigmentosa; logMAR = logarithm of the minimum angle of resolution. *n=13, 3 missing at baseline	

*IRD = inherited retinal dystrophy; RP = retinitis pigmentosa; logMAR = logarithm of the minimum angle of resolution. *n=13, 3 missing at baseline*

Follow-up after 2 and 4 years

Disease progression in patients was evaluated on a biennial basis up to 4 years (4.0 ± 0.3 years) with mean follow-up times of 2.0 ± 0.1 years and 2.0 ± 0.3 years between the first two and the last two visits, respectively. At 2 years, the median BCVA of both eyes at 0.9 logMAR (0.6–1.1 logMAR; i.e. 20/160 Snellen) did not significantly differ from baseline (p = 0.069), whereas at 4 years; median BCVA (1.1 logMAR; IQR: 0.8–1.3; i.e. 20/240 Snellen) significantly decreased compared to baseline (p = 0.003). Microperimetry was performed on 20 patients during the 2-year follow-up with two patients being too young to perform reliably. During the 4-year follow-up, microperimetry was performed on 19 patients with one patient being too young and two patients being unable to visit the hospital due to the COVID-19 pandemic. Median retinal sensitivity changed significantly from baseline over 2 and 4 years, from 6.9 dB (2.7–12.8 dB) to 4.3 dB (1.4–9.9 dB, p = 0.001) and 3.7 dB (0.0–7.9 dB, p = 0.004), respectively.

Composite scores NEI VFQ

Individual questions on the NEI VFQ were clustered into the following generally accepted domains: 'general health', 'general vision', 'ocular pain', 'near activities', 'distance activities', 'social functioning', 'mental health', 'role differentiation', 'dependency', 'colour vision', and 'peripheral vision'. Finally, a final score was produced by compressing all domain scores into one score 'total composite score' (Table S1). Overall, there was a downward trend in most domains from baseline until final visit, especially those that relate best to IRD symptoms, such as 'general vision', 'near and distance activities', and 'peripheral vision' (Figure 1). However, after correction for multiple testing, none of these downward trends was statistically significant. The other domains remained stable over 4 years.

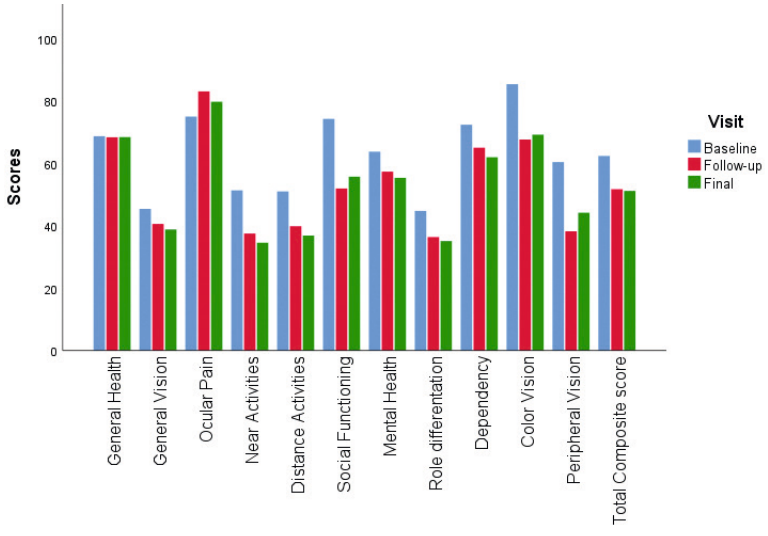

Figure 1. Bar chart demonstrating the different subdomains of the National Eye Institute Visual Function Questionnaire, and the mean scores given by patients with *CRB1*-associated retinal dystrophies at each visit.

Relationship between BCVA and microperimetry vs. scores for near activities (V_{NA}) and total score (V_{TOT})

We were interested in studying the relationship between the scores on the VFQ-39, for near activities (VNA) and total score (VTOT), and functional measurements of BCVA and macular sensitivity on microperimetry. Using a linear mixed model, we found significant positive relationships between BCVA and the composite score for 'near activities' (VNA), where every 0.002 increase in visual acuity ($p = 0.004$) and every 0.086 dB increase in microperimetry ($p = 0.002$) resulted in a unit increase in VNA (Figure 2a,b). In addition, with every 0.002 increase in visual acuity ($p = 0.008$) and every 0.095 dB on microperimetry ($p = 0.0003$), total composite score (VTOT) increases one unit (Figure 2c,d).

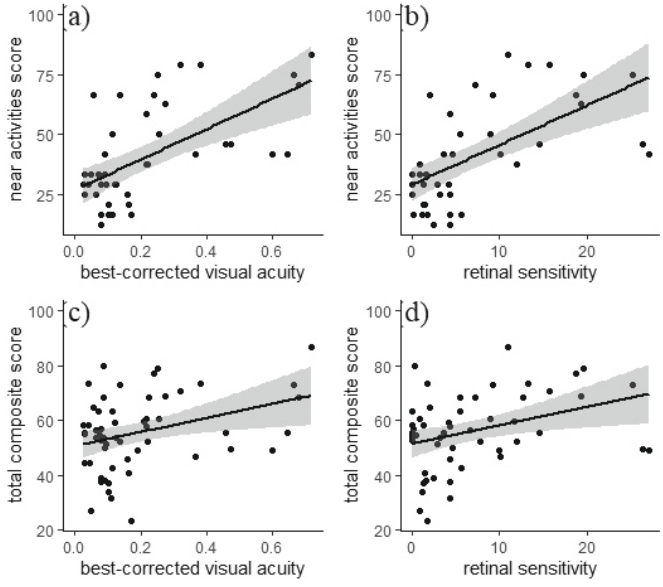

Figure 2. Significant positive relationships between BCVA, macular sensitivity and scores for 'Near Activities' and 'Total composite score' based on linear mixed model analysis. **A**) Significant relationship between BCVA and NEI VFQ-25 score for 'Near Activities' (V_{NA}). **B**) Significant relationship between retinal sensitivity as measured on microperimetry and V_{NA}. **C**) Significant relationship between BCVA and total composite score of NEI VFQ-25. **D**) Significant relationship between retinal sensitivity and total composite score of NEI VFQ-25. Significance is denoted as $p \leq 0.05$.

Inter-visit progression

Overall progression was determined by comparing baseline measurements with the measurements taken at the final visit, revealing a significant drop in score of 15 units in VNA ($p = 0.005$) and of 10 units in VTOT ($p = 0.001$). Interestingly, these declines appear to occur between the first and second visits, with VNA decreasing with 13 points after the first 2 years ($p = 0.008$) and VTOT with nine points ($p = 0.004$). There

was no significant decrease in VNA and VTOT between the 2-year follow-up and 4-year follow-up, p = 0.684 and p = 0.626, respectively.

MSD person measures

The calibrated item measures were developed specifically for the VFQ-25, and using these, we found a mean ± SD person measure of 0.428 ± 0.360 logit. The calculated person measures were plotted against their standard errors of the person measure (Figure S1). Extreme person measures, that is greater visual function, generally demonstrate lower precision, that is higher standard errors. Like the authors of the original paper, we also found a slight increase in standard error for higher person measures when using the calibrated item measures (Goldstein et al., 2022). Figure 3 plots the estimated person measures against the NEI VFQ-25 composite scores, demonstrating a near-linear relationship with a correlation of $R^2 = 0.905$. This indicates that the visual ability of a patient, as estimated with the person measures, is well-described by the composite scores of the NEI VFQ-25.

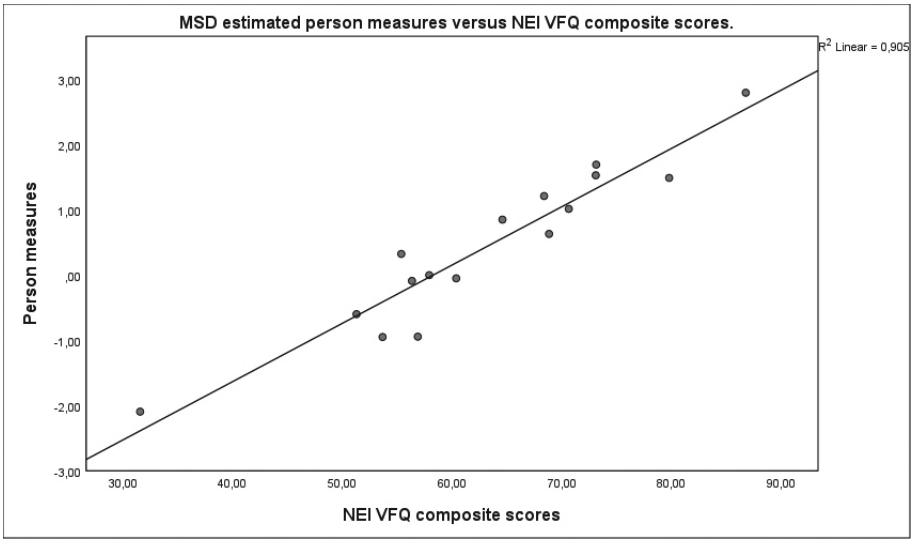

Figure 3. Near-linear relationship between estimated person measures and composite score of the NEI VFQ-25, R^2=0.905.

Quality of life based on visual function and socio-emotional impact

Goldstein et al. suggested domain-specific versions for the NEI VFQ-25 based on visual function, NEI VFQ-VF, and on socio-emotional impact, NEI VFQ-SE. We investigated the quality of life based on three modified versions of the NEI VFQ-25. Overall quality of life based on the VFQ-25C score declined significantly after two (–0.756; p = 0.006) and 4 years (–0.839; p = 0.002) after baseline. Visual function as measured with VFQ-VF was significantly decreased after 2 years (–0.889; p = 0.012), although this decrease did

not reach statistical significance over 4 years (0.010; p = 0.975). Scores on the socio-emotional domain as determined by the NEI VFQ-SE were also significantly lower after two (−0.776; p = 0.033) and 4 years (−0.831; p = 0.021).

DISCUSSION

In this study, we investigated the quality of life in patients with *CRB1*-associated retinal dystrophies based on the NEI VFQ-25 questionnaire and its appendix, and compared it to the functional measures BCVA and retinal sensitivity on microperimetry. Currently, many research groups are developing therapies for retinal dystrophies, including RP.[20, 21] Many of the functional outcome measures assessed in these studies may not reflect a patient's experience. Thus, PROMs are becoming increasingly important outcome measures. Being able to reliably assess key quality of life aspects in RP patients and correlating this knowledge to the disease course, may help in the design of future clinical trials.

Similar to previous RP studies, our patient cohort showed a significant general decline in quality of life over the course of 4 years.[22-24] Furthermore, we found a strong correlation between the deterioration of BCVA and macular sensitivity, and a decreasing total quality of life-score (V_{TOT}). More specifically, BCVA and macular sensitivity were found to be closely related to quality of life score for 'near activities' (V_{NA}). Interestingly, some earlier reports did not find a correlation between NEI VFQ-25 scores and visual acuity in RP, and visual field loss has been proposed as a better estimate of quality of life.[23, 24] Instead of visual field loss, we investigated macular sensitivity on microperimetry as an even more sensitive outcome measure in the present *CRB1*-IRD cohort. Here, we found another strong relationship between the deterioration of macular sensitivity and a decreasing quality of life based on V_{NA} and V_{TOT}.[5] This finding is corroborated by another study with 30 RP patients with a relatively high visual acuity of >0.2 logMAR (equivalent to 20/32 Snellen) who performed microperimetry on the Nidek MP1 microperimeter.[25] The NEI VFQ-39 scores deteriorated over time, but we found that the greatest significant decline occurred between baseline and second visit. The reason for the disparity in decline between the first 2 years and the second 2 years remains uncertain.

Although the NEI VFQ-39 has been shown as a marginally more informative questionnaire in IRD patients compared to the NEI VFQ-25, the latter has been a popular ophthalmic PROM since its first introduction in 2001 due to its simplicity and widespread use which facilitates international comparison.[8] However, to accommodate for its simplicity, the NEI VFQ-25 does not meet current psychometric standards as it lacks unidimensionality, has poor item fit validity, and has crude differential item functioning.[13-15] Rasch analysis has been proposed as a modern psychometric

technique to enable estimates on an invariant scale from ordinal responses. However, this form of item response theory can only be applied on sufficiently large patient cohorts. As IRDs are relatively rare and we have focused specifically on *CRB1*-associated IRDs, our cohort is too small for the Rasch analysis. So, we applied the Rasch-calibrated item measures provided by Goldstein *et al.* to analyse the quality of life in this cohort.

In addition to providing calibrated item measures, Goldstein *et al.* suggest adopting domain-specific versions to resolve the problem of multidimensionality of the NEI VFQ-25.[19] Two of these versions focus on visual function (VFQ-VF) and socio-emotional impact (VFQ-SE), and a third version excludes overall health and eyesight quality (VFQ-25C). Using these versions, we found that visual function as measured with the VFQ-VF decreased significantly after 2 years, but not after 4 years. Interestingly, these significant decreases did not follow the visual function parameters BCVA which decreased significantly after 4 years, but not after 2 years. This finding implies that patients are able to notice deterioration in experienced quality of life earlier, than BCVA as an objective visual function parameter can. Additionally, the socio-emotional impact of the *CRB1*-associated IRD was substantially higher after 2 years ($p = 0.033$) and after 4 years ($p = 0.021$) compared to the baseline visit. Likewise, macular sensitivity on microperimetry was significantly decreased after 2 and 4 years. Thus, macular sensitivity reflects visual function and socio-emotional impact as measured on the domain-specific VFQ-VF and VFQ-SE.

Our study has some limitations, mainly related to the content validity of the calibrated item measures and the NEI VFQ-25. The calibrated items and the resulting modified versions of the NEI VFQ-25 were estimated based on different patient populations with retinal disease diagnoses ranging from low-vision and age-related macular degeneration to retinal vein occlusion and diabetic retinopathy. As such, the calibrations may not be entirely applicable for inherited retinal dystrophies, and we suggest a calibration of item measures based on data sets of IRD patient cohorts. Moreover, the heterogeneity of our patient population, including adults and children, and IRD diagnoses of RP, cone-rod dystrophy, and macular dystrophy may hinder the generalisability of our findings, although the great majority of patients constituted of adult RP patients. As our patient cohort was too small for an individual Rasch analysis, the most suitable option for analysis was using the calibrated item measures. In doing so, we aim to provide some guidance in applying this method for future clinical IRD trials with relatively small patient cohorts. Regarding content validity of the questionnaire, the NEI VFQ-25 and the appendix focus on difficulties caused by general visual impairment, rather than consequences specifically caused by an IRD. Patients with a *CRB1*-associated IRD do not only experience progressive loss of visual acuity but also constriction of visual fields, nyctalopia, photophobia, and loss of colour and contrast discrimination.[2] These symptoms each result in a different set of obstacles which are currently not investigated in the NEI VFQ-25 or in the NEI VFQ-39. On the

other hand, ocular pain is a separate item on these questionnaires, but is not a regular symptom of an IRD and is thus not relevant to our study population.

At the time of assessment, the NEI VFQ-25 was widely used in ophthalmological clinical trials and accepted by the regulatory authorities as a means to evaluate vision-related quality of life. However, as the flaws of the NEI VFQ-25 questionnaire become more apparent and IRD research advances towards clinical applications, experts agree on the need for a specific IRD questionnaire that can evaluate meaningful changes for a patient.[26-28] A few PROMs have been developed for specific IRDs, such as Stargardt macular dystrophy and congenital stationary night blindness, but these tools have not been validated and are of limited use in larger IRD populations.[29, 30] IRD patients experience many similar symptoms; thus, a non-gene specific PROM may be useful for different IRD patient populations. Some questionnaires focus on a single domain, such as mobility for the Mobility Difficulties Questionnaire, Independent Mobility Questionnaire, or daily tasks for the Daily Task Performance Questionnaire and Everyday Task Questionnaire.[27] While informative, these single-domain questionnaires cannot be used to give an overall perspective of a patient's quality of life. Other IRD PRO instruments do not meet the current quality criteria or were not based on in-depth interviews with patients.[26, 27] A novel questionnaire, the Michigan Retinal Degeneration Questionnaire (MRDQ) has been developed and psychometrically validated by Lacy *et al.* that conforms to the FDA guidelines for the use in IRD clinical trials.[6] The MRDQ items were derived from both expert and patient interviews, and seven relevant domains were identified: central vision, colour vision, contrast sensitivity, scotopic function, photopic peripheral vision, mesopic peripheral vision, and photosensitivity. Item response theory techniques were applied for psychometric validation and test-retest variability was assessed. Since its introduction, the MRDQ has already been incorporated into several clinical trials for IRDs such as RP and LCA (NCT05203939, NCT05176717).

Investigating the vision-related quality of life in patients with gene-specific IRDs such as those caused by variants in the *CRB1* gene is important as it may form a key outcome measure for the upcoming gene therapy. This study is meaningful in that it investigated the use of calibrated item measures for the NEI VFQ-25 questionnaire in patients with IRDs and correlated these to visual function measures. The results from this study are useful for the design of future clinical trial designs for small IRD patient cohorts.

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SUPPLEMENTAL CONTENT

Table S1. NEI VFQ-39 mean total and subscale scores at baseline.

NEI VFQ-39 score	Baseline (mean ± SD, n=16)	2-year follow-up (mean ± SD, n=19)	4-year follow-up (mean ± SD, n=21)
General health	69.4 ± 10.0	70.1 ± 14.1	67.5 ± 15.8
General vision	46.3 ± 15.2	41.6 ± 21.2	38.1 ± 16.9
Ocular pain	80.5 ± 18.2	84.9 ± 18.9	83.3 ± 21.8
Near activities	51.0 ± 23.8	37.5 ± 20.3	35.4 ± 14.7
Distance activities	51.6 ± 20.7	40.3 ± 17.1	40.0 ± 16.9
Social functioning	72.2 ± 19.1	53.7 ± 23.1	53.9 ± 20.9
Mental health	66.6 ± 19.2	57.2 ± 17.0	56.2 ± 17.2
Role difficulties	48.4 ± 19.6	36.2 ± 17.6	37.5 ± 13.4
Dependency		65.1 ± 14.3	58.0 ± 19.2
74.2 ± 16.0			
Colour vision	84.4 ± 22.1	67.1 ± 25.1	70.2 ± 26.9
Peripheral vision	53.1 ± 30.1	38.2 ± 30.5	40.5 ± 31.1
Total composite score	63.0 ± 13.0	52.3 ± 14.0	52.0 ± 12.1

SD = standard deviation; NEI-VFQ = National Eye Institute Visual Function Questionnaire. A higher score reflects a higher visual function.

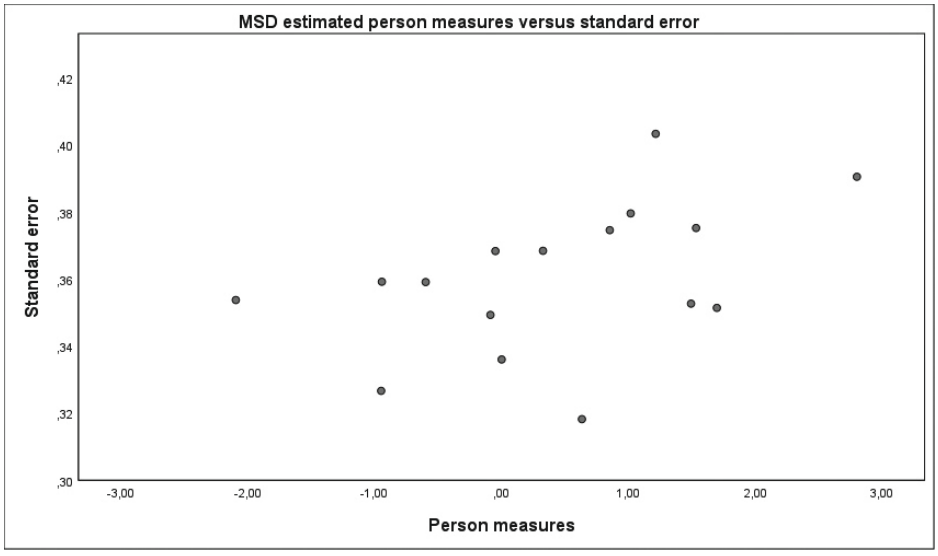

Figure S1. MSD estimated person measures vs standard error person measure at baseline.