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Worse-than-usual visual fields measured in retinitis pigmentosa related to episodically decreased general health

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Abstract

Background/aims—We examined whether retinitis pigmentosa (RP) subjects' worse-than-usual vision measures were related to episodic changes in psychosocial factors and/or general health.

Methods—In a prospective, cohort study, 37 RP subjects self-administered personal computer (PC)-based visual acuity (VA), contrast sensitivity (CS) and visual field (VF) tests at home twice a week, for 16 sessions in 2–3 months. Subjects rated their general health prior to each vision test session, and completed the Perceived Stress Scale, Positive and Negative Affect Schedules, and Epworth and Stanford Sleepiness Scales immediately after each session.

Results—Nine subjects with reduced mean VA >0.5 log minimal angle of resolution (logMAR) on average had statistically significant 26% more sessions with measured deviations ≥ 0.1 logMAR from their mean (95% CI 20% to 32%; $p < 0.001$), which were not significantly related to changes in psychosocial factors or general health. Measured deviations ≥ 0.1 logCS from mean CS were not statistically significantly related to any measured factors. We found a statistically significant increased frequency of sessions with $\geq 20\%$ VF reduction from the mean ($p < 0.001$) as mean log VF area was reduced. Subjects reporting reduced general health during a session had a statistically significant over twofold greater odds of having a VF reduction from the mean beyond 1 SD (95% CI 1.26 to 5.00; $p = 0.009$).

Conclusions—Measured episodic VF reductions were more common in advanced RP and related to decreased general health at a session, which should be considered during clinical

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examinations and trials when determining true changes in vision. We did not find evidence that fluctuations in psychosocial factors were significantly correlated with vision reductions across subjects.

INTRODUCTION

Patients with vision loss due to photoreceptor degenerations, in particular retinitis pigmentosa (RP), are among those who report that their vision is either better or worse on some days than others.¹ Short-term day-to-day fluctuations in vision may be problematic for patients since they create uncertainty in their ability to perform activities in daily living, and are also an issue for eye care providers and researchers monitoring vision. Variability during visual acuity (VA), contrast sensitivity (CS) and visual field (VF) testing is 2–3 times greater in RP subjects than normally-sighted individuals.²³ Therefore, it becomes more challenging for clinicians and researchers to determine whether a true, permanent change in vision has occurred at a visit, or if the fluctuation is merely temporary or due to measurement noise.

Prior to our study, factors potentially related to short-term vision fluctuations in RP had not been formally measured and elucidated. RP patients have previously indicated that they believe their vision fluctuations may be related to stress.¹⁴ At the present time, it is not well understood if RP patients are referring to aspects of central vision (VA and/or CS), peripheral vision (VF) or both, when they note that their vision is worse-than-usual on a given day and possibly influenced by stress. personal computer (PC)-based tests self-administered by subjects at home provide a convenient means to obtain frequent measures without requiring several visits to our centre for testing.⁵ We found that some of the mean variability (SD) of PC-based log VF area in RP can be explained by greater than minimal depressive symptoms or reduced physical functioning.⁶ The aim of the current study was to determine if episodic reductions in PC-based VA, CS and VF tests were related to subjects' mean level of vision, or day-to-day changes in general health or psychosocial states, such as stress, mood or sleepiness.

METHODS

The protocol for the study was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study.

Subjects

We report data from a total of 37 study participants who completed PC-based vision testing. Thirty-three of the 37 subjects enrolled at our centre to confirm their RP diagnosis and rule out other ophthalmological disorders with clinical testing and optical coherence tomography described elsewhere.⁶ Four subjects not residing locally were enrolled over the phone via oral consent, and their diagnosis and vision was verified by their local eye care providers' records. The majority of the subjects (n=25; 68%) were recruited from low vision optometrists or retinal specialists at the Johns Hopkins Wilmer Eye Institute. The remaining

subjects self-referred after learning of the study through online listings. Eligibility criteria were confirmed diagnosis of RP, over age 18 years, any level of vision, provided they could read reverse contrast, large sized font on the PC to complete the questionnaires and vision tests in the study. Participants possessed basic computer skills at minimum, and the study provided a loaner PC if they did not have regular access to one. Two subjects initially enrolled in the study were ineligible since they were determined not to have RP upon screening at our centre. In addition to the 37 subjects reported here, 15 other eligible subjects signed a consent form but never initiated the PC-based vision tests for reasons that were unknown or related to other comorbidities.

Subjects' duration of night vision loss ranged from 1 to 71 years (mean 27; SD 18 years). Fifty-one per cent of the subjects were women, and subjects' ages ranged from 20 to 77 years, with a mean of 51 years. Eight per cent of the subjects were African-American (n=3), 11% were Hispanic (n=4) and 81% were Caucasian (n=30). Eleven of the subjects (30%) had macular oedema at enrolment; however, a progressive or sudden, sustained increase or decrease in central vision was not measured in any of these subjects during the study period.

Data collection

Data collection occurred from December 2008 through June 2010. Immediately following the enrolment visit, subjects self-administered PC-based vision tests and questionnaires at home during 16 test sessions twice a week over a period of ~2–3 months. The vision tests included binocular letter VA, CS, and static VF, which took about 15–20 min total to complete, and were previously developed at our centre and validated in RP subjects on placebo during a clinical trial⁵ and described in more detail elsewhere.⁶ The suprathreshold VF test was completed at a 25 cm test distance, and the VF radius was measured along meridians at 15° intervals as the test algorithm flashed a static dot along one of these 24 axes. The VF test determines remaining central areas of vision, and subjects with log<2.2 cm² had Goldmann kinetic VF diameters <30° with the V4e stimulus. All tests used a Bayesian adaptive algorithm to find the threshold in a minimum number of trials: 16 for VA, and 11 for CS and VF (outer limit of vision along each axis). When the PC-test software was installed, each subject calibrated their monitor's pixel size using a dollar bill placed in the upper left corner of the monitor and their mouse to move horizontal and vertical lines to frame the bill. The gamma function of the monitor was calibrated by comparing an even grey field with a field of fine black and white lines, using the mouse to adjust the greyscale level of the field so it matched the average of the fine lines.

Thirty (81%) of subjects completed all of the 16 test sessions, while three completed 15, two completed 14, one completed 13, and one completed 10 sessions. In order to attempt to capture a wide range of vision variability during various times of the day and week, the test times were equally randomised such that tests were taken in the morning before noon on weekends (n=4) and weekdays (either Wednesday or Thursday) (n=4), and in the evenings after 18:00 on weekends (n=4) and the same weekdays (n=4). There were a total of 576 sessions completed across 37 subjects.

Using the PC-based programme, prior to each vision test session, subjects rated their general health status on the day of the test as either worse, better or the same as usual. Examples of

possible causes of worse-than-usual general health were bodily pain or having a cold/flu. Four standardised questionnaires to assess psychosocial factors were administered after each PC-based vision test session: the Stanford Sleepiness Scale (SSS),⁷⁸ Epworth Sleepiness Scale (ESS),⁹ Perceived Stress Scale (PSS)¹⁰ and the Positive and Negative Affect Schedules (PANAS).¹¹ The SSS uses a single item 7-point scale to determine sleepiness at time of test administration, and the ESS contains eight items to inquire about tendency to doze during various activities on the test day. We used the 14-item version of the PSS, and the PANAS consisted of 10 items to assess positive mood and 10 items to assess negative mood, scored individually. The PSS and PANAS were based on experiences in the last 24 h, using a 5-point scale for each item.

Data analysis

For each subject, we determined the mean PC-based VA, CS and VF across sessions and determined the deviation from their mean at each session in log units for VA and CS, as well as per cent deviation in log VF area. To determine the occurrence or frequency of significant reductions in vision, we dichotomised the vision test results according to sessions with a reduction of 0.10 log units for VA and CS, or 20% for VF area, relative to the mean values for each subject. These values for the dichotomisation reflect episodic changes outside the typical mean variability in RP previously reported for VA and CS,²⁵ and VF.¹² For each subject, we also identified the sessions during which the log VF area differed from the mean by at least 1 SD, as an indicator of VFs that were outliers, as measured by their individual variability.

Multi-level, mixed effects models with logistic regressions, using clustering by subject for the repeated measures, explored the relationships between reductions in vision and psychosocial factors or general health status at a session. Models assuming random intercepts were used for the final analyses, although models assuming both random slopes and random intercepts were explored. Log likelihoods for these models were approximated by adaptive Gaussian quadrature. Simple linear regressions explored the frequency of vision reductions across sessions according to each subject's mean level of vision. Data were analysed using Stata/IC V.10.0 (Stata Corp., College Station, Texas, USA).

RESULTS

The mean (and range) of measured vision across subjects' was 0.46 (0.1–2.1) logMAR for VA, 1.47 (0.15–2.26) logCS for CS and 1.98 (0.5–2.87) log cm² for VF. Fluctuations in vision test results were not significantly related to increasing session number across subjects for VA ($p=0.68$), CS ($p=0.36$), or VF ($p=0.63$); that is, we did not find evidence of a learning effect over time. Episodic reductions in VA or CS (0.1 log units from each subject's mean) occurred during 7% or 10% of the test sessions, respectively, but reductions of 0.1 log units in both VA and CS at a session only occurred 1% of the time. Thirteen (35%) and 26 (70%) subjects had a reduction in VA or CS, respectively, of 0.1 log units from the mean during at least one of their test sessions. Reductions in VF area from each subject's mean that were >20% or beyond 1 SD occurred during 11% or 13% of the test

sessions, respectively. All except one subject had a reduction in VF area from the mean that was >20% or outside their SD during at least one of their test sessions.

On average, nine subjects with mean VA worse than 0.5 logMAR had statistically significant 26% more sessions with 0.10 logMAR reductions in VA from their mean than subjects with better mean VA (95% CI 20%, 32%; $p<0.001$; $R^2=0.71$), depicted in the scatter plot in the top panel of figure 1. On average, the frequency of sessions with 0.10 logCS reduction from the mean was not statistically significantly related to mean CS (3%; 95% CI -4%, 10%; $p=0.40$; $R^2=0.02$), shown in the middle panel of figure 1, with a linear regression slope not significantly different from zero. On average, for every one unit decrease in mean log central VF area, there was a statistically significant 10.5% increase in the frequency of sessions with 20% VF reductions (95% CI 5.4%, 15.5%; $p<0.001$; $R^2=0.36$), as depicted in the scatter plot in the bottom panel of figure 1.

The table 1 displays the ORs for reductions in VA or CS greater than 0.1 log units or VF reductions from the mean according to 10% changes in the questionnaire scores from the mean. The odds of subjects experiencing a reduction from their mean VF area outside of their SD was over twice as high at times when subjects reported that their general health was worse-than-usual. Subjects reported worse-than-usual general health at 10% of test sessions ($n=57$). Reductions in VF area were not statistically significantly related to changes in perceived stress, mood or sleepiness with the Epworth or Stanford scales. Psychosocial questionnaires or general health were not statistically significantly related to enlargements from the mean VF outside of each subject's SD for their VF tests. Episodic reductions or improvements in VA or CS from the mean (>0.1 log units) were not statistically significantly related to changes in sleepiness, mood, stress or general health.

To illustrate the scales of these questionnaires, there was about a +3% change in overall score across subjects for each positive 1-point item score change from the mean, reflecting increased stress/negative mood; similarly, the effect of a 1-point negative shift in item score (decreased stress/negative mood) was a -8-9% change in mean overall score. Thus, a 10% increase or decrease in perceived stress/negative mood from the mean would roughly correspond to a 3 or 1-point score change, respectively. The perceived stress scale has a possible score range of 0-56 points, and our subjects' ranged from 8-44, with a positive change of about 4 points or 14% on average across sessions, while the mean negative change was roughly 3 points or 22%. The negative mood scale has a possible score range of 10-50 points, and our subjects' ranged from 10-39, with a positive change of about 4 points or 17% on average across sessions, while the mean negative change was roughly 2 points or 21%.

DISCUSSION

These results provide some insight into whether psychosocial factors or perceived health may underlie subjects' day-to-day changes in visual function measurements in RP. Episodic reductions in VF among RP subjects were more common in advanced RP subjects with reduced mean VF. We also found that the subjects' reports of day-to-day reductions in general health were significantly related to measured reductions in VF. Therefore, if a

possible decrease in VF is detected at a visit when the patient is not feeling as well as usual, we recommend repeating the VF on a different day when they are feeling better, or to simply avoid VF testing on days when patients report that their general health is worse-than-usual. It appears that reliable central vision outcome measures (VA and CS) may be obtainable even when RP patients are not feeling as well as usual.

In previous research, RP patients had significantly increased daytime sleepiness, reduced alertness and more disturbed night time sleep than normally-sighted individuals.¹³ Symptoms of sleepiness and tendency to doze measured by the ESS did not appear to correlate with vision fluctuations in our study. The construct measured by the ESS is uncertain, and it may represent something other than daytime sleepiness or sleep propensity.^{14,15} Another limitation of the ESS is that it asks subjects to imagine themselves in situations which they may rarely or never experience. Fatigue and sleepiness may be two distinct constructs.¹⁶ Sleepiness refers to the propensity for spontaneous sleep onset, while fatigue indicates that it is difficult to maintain motor or mental energy levels, and may recover with rest, not necessarily sleep. We, therefore, would recommend future studies to evaluate the relationship between vision fluctuations and fatigue measured by the Fatigue Severity Scales¹⁷ rather than sleepiness.

Our study design randomised the test times during the week rather than asking participants to complete the tests at times when they thought that their vision was much better or worse-than-usual, and therefore we likely did not capture many of the largest magnitude fluctuations that RP patients experience. We would expect that the association between reduced VF and general health status revealed in the present study would still hold for larger changes in these variables. There may have been a selection bias for those who were more likely to experience fluctuations in their vision to be motivated to participate in this study, and therefore there may be limitations to the generalisability of the findings.

We did not find evidence that vision measures were more likely to be reduced at times of increased perceived stress, which had been previously reported by RP patients.¹⁴ The perceived narrowing of VF, attention or decreased reaction time during stressful situations may be explained by the fact that anxious individuals tend to be more distracted, since attentional resources are devoted to task-irrelevant cues.¹⁸ Attending to, selecting and processing the most critical environmental cues are important skills needed when attempting to function with minimal, constricted and/or scotomatous VFs in RP. It is possible that increased stress has a potential impact on the daily functioning of RP patients during mobility and other activities involving peripheral vision, as they may be more likely to miss things visually when distracted.¹

Reducing or accounting for patient-related general health factors that may affect episodic deviations in VF measures may enhance clinicians and researchers' ability to make judgments regarding whether true changes in vision have occurred. The hypothesis that RP patients with more advanced vision loss are prone to experience more frequent variability in VA and VF was supported by the present study, and determination of individual subjects' variability should be considered when designing and evaluating clinical trials involving legally blind RP patients.

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Figure 1.

Scatter plots for the frequency of worse-than-usual vision across PC-test sessions for each subject in relation to their mean visual acuity (VA) (top panel), contrast sensitivity (CS) (middle panel) and visual field (VF) (bottom panel).

Table 1

Crude odds of worse than usual VA, CS and VF according to changes in questionnaire scores

Questionnaires	VA (0.1 logMAR)		CS (0.1 logCS)		VF (beyond 1 SD)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Worse general health	0.62 (0.15 to 2.65)	0.52	1.84 (0.80 to 4.25)	0.38	2.51 (1.26 to 5.00)	0.009*
Perceived Stress Scale [†]	1.01 (0.87 to 1.17)	0.93	0.97 (0.87 to 1.08)	0.55	0.97 (0.89 to 1.07)	0.59
Negative mood (PANAS) [†]	1.12 (0.96 to 1.30)	0.15	1.06 (0.94 to 1.19)	0.33	1.03 (0.92 to 1.14)	0.63
Positive mood (PANAS) [‡]	0.94 (0.84 to 1.05)	0.24	1.02 (0.92 to 1.13)	0.77	0.97 (0.89 to 1.04)	0.37
Epworth Sleepiness Scale [†]	0.93 (0.78 to 1.11)	0.42	0.96 (0.84 to 1.09)	0.51	1.06 (0.93 to 1.20)	0.39
Stanford Sleepiness Scale [†]	0.99 (0.93 to 1.06)	0.82	0.99 (0.94 to 1.03)	0.53	1.01 (0.96 to 1.06)	0.63

CS, contrast sensitivity; PANAS, Positive and Negative Affect Schedules; VA, visual acuity; VF, visual field.

* Statistically significant (p<0.05).

[†] Per every 10% score increase from the mean.[‡] Per every 10% score decrease from the mean.