Morpho-functional analysis of Stargardt Disease for reading

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ABSTRACT ●

Objective: To analyze Stargardt disease (STGD) by morpho-functional examination and investigate the relationship between morpho-functional measures and reading performance.

Design: Observational case series study.

Participants: Fifteen patients with STGD.

Methods: Twenty-six eyes of 15 patients underwent complete ophthalmic evaluation. Spectral domain optical coherence tomography, fundus autofluorescence (FAF), best corrected visual acuity (BCVA), and microperimetric examinations were performed. FAF and optical coherence tomography (OCT) overlap on microperimetric images was obtained in order to evaluate both tomographic and FAF features passing through the eccentric fixation area. Both morphologic features and functional data were correlated with magnification of prescribed device and reading rate.

Results: Univariable analysis showed a significant correlation between magnification power and greatest linear dimension of both OCT and FAF ($r = 0.69$ and $r = 0.67$; $p < 0.05$). Magnification power was related to best corrected visual acuity ($r = 0.56$; $p < 0.05$). Retinal sensitivity map ($r = 0.57$; $p < 0.05$) was considered an indicator of reading rate. Magnification levels showed a positive correlation with eccentric preferred retinal location ($p = 0.03$) and the degree of FAF alteration (normal, dishomogeneous, ipoautofluorescence; $p < 0.0001$).

Conclusions: As a result of the overlapping of OCT/FAF imaging on microperimetric exam, residual activity of outer retinal layers passing through the eccentric fixation area seems to be related with required magnification and reading rate. Identification of morpho-functional parameters is helpful for designing a customized rehabilitative program.

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Stargardt disease (STGD) is the leading cause of juvenile macular dystrophy with a prevalence of at least 1 in 10 000.[1] The disease is caused by mutations in *ABCA4* gene, located on the short arm of chromosome 1, resulting in accumulation of A2E (*N*-retinylidene-*N*-retinylethanolamine), the major component of lipofuscin, which is responsible for toxic effects on retinal pigment epithelium (RPE) and photoreceptors, thus leading to progressive macular atrophy. In affected patients, a gradual reduction in visual occurs, with the potential development of an absolute central scotoma over time, limiting the ability to perform many activities of daily living, such as reading and writing, with an important impact on patients' quality of life.[2–5]

Due to the loss of foveal fixation, patients develop 1 or multiple preferred retinal loci (PRL) localized near the central scotoma in healthy or less-altered retinal areas.[6–9] Although several attractive options are being explored for future therapeutic applications for STGD, such as embryonic stem cells and gene therapy,[10,11] to our knowledge there is no effective treatment for this inherited maculopathy. Visual rehabilitation currently represents the only useful intervention to compensate for visual acuity (VA) impairment and restore reading functioning.[12]

The purpose of this study was to analyze morphologic and functional data in patients with STGD as evaluated through VA measurement, fundus autofluorescence (FAF), optical coherence tomography (OCT), and microperimetric values in order to verify the existence of a correlation with visual rehabilitation outcomes, such as reading performance, and magnification power of prescribed low-vision devices based on their own demands and identify the best morpho-functional parameters for visual rehabilitation.

Methods

Twenty-six eyes of 15 consecutive patients (10 females, 5 males; median age 42.6 years, range: 16–53) with STGD were analyzed at the Retina Service of the Catholic University of Rome and the National Centre of Services and Research for the Prevention of Blindness and Rehabilitation of Low Vision Patients, IAPB Italia Onlus, in a prospective observational study. Patients with a genetic *ABCA4* mutation were referred to the centre between March 2012 and April 2013 for a specific retinal examination and a prescription for low-vision devices. Patients were included based on diagnosis of STGD and

http://dx.doi.org/10.1016/j.jcjo.2016.10.015
ISSN 0008-4182/16

Canadian Ophthalmological Society | Société canadienne d'ophtalmologie
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established clinical criteria: RPE changes and macular atrophy, yellow-white fundus flecks, a best corrected visual acuity (BCVA) 1 logMAR or better, bilateral central vision impairment. All patients had a disease duration of ≥ 5 years and showed extensive macular atrophic-appearing RPE changes at the posterior pole, classified as phenotype III according to Fishman classification.[13] All patients spoke Italian as first language. Participants were excluded if they had any other concomitant eye or neuro-ophthalmologic disease, were cognitively impaired, had significant media opacities, or had ocular surgery performed in the previous 3 months. All patients were trained binocularly, but in 4 patients only the best eye was considered for rehabilitative purpose due to the poor VA of the fellow eye and the wide morpho-functional differences between the 2 eyes.

Approval for this study was obtained from the Ethical Committee of the Catholic University of Rome. Informed consent was obtained from all participants, and the study conformed to the Declaration of Helsinki. All patients underwent complete ophthalmic evaluation, including BCVA, using the Early Treatment of Diabetic Treatment Study charts at 4 m (Precision Vision, Bloomington, Ill.) in logMAR, slit-lamp examination, binocular ophthalmoscopy, colour fundus photography, OCT, FAF, and microperimetry (MP-1). Afterward, based on ophthalmic evaluation and patient demands, a low-vision intervention was performed as described here.

Procedures

FAF images were taken with a confocal scanning laser ophthalmoscope (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany). After pupil dilatation, a series of 30 × 30 degree FAF images encompassing the macular area and including the optic nerve were obtained. Standard procedure was used for the acquisition of FAF images.[14] The optic disk was considered the reference for the lowest amount of FAF. We measured the greatest linear dimension of the area of absent FAF corresponding to the central scotoma using the calipers provided by the Spectralis HRA-OCT software.

Spectral domain (SD)-OCT images were obtained with the same scanning laser ophthalmoscope system (Spectralis 3.1 HRA-OCT; Heidelberg Engineering) using the blue peak laser autofluorescence beam: 19 horizontal scans covering a 20 to 15 degree macular area were obtained (10 A-scans/B-scans averaging). Additionally, we obtained the overlap of both FAF and OCT on MP-1 images and analyzed autofluorescence and OCT findings in the eccentric fixation area (Fig. 1); based on qualitative assessment, we divided FAF findings (Eccentric FAF) into 3 groups: normal, dishomogeneous, and hypoautofluorescent. The scan passing through the greatest linear dimension (GLD) of

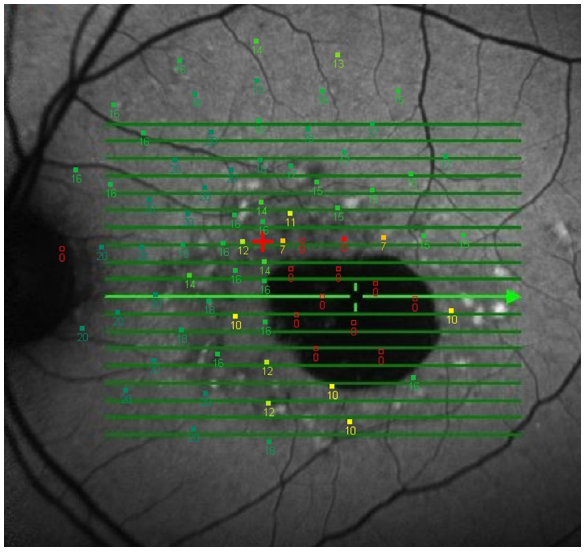

Fig. 1—Overlapped image showing FAF and microperimetric sensitivity. FAF, fundus autofluorescence.

FAF absence was used to measure the OCT GLD of inner-outer photoreceptor (IS/OS) junction loss. Moreover, we analyzed IS/OS junction layer (Eccentric IS/OS) and outer-limiting membrane layer (Eccentric OLM) passing through the eccentric fixation area and classified both tomographic features into 3 groups: present, loss, and disorganized. (Fig. 2A, 2B) Two independent examiners carried out the measurements. In case of disagreement, a third retinal specialist was involved for final classification.

Fixation stability and retinal sensitivity were evaluated using an MP-1 microperimeter (Nidek Instruments, Padova, Italy) with dilated pupil. During fixation task, patients were asked to fixate for 30 seconds on a red cross

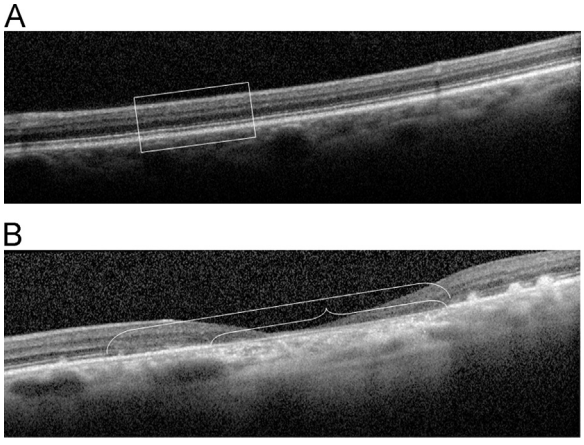

Fig. 2—Overlapped image showing FAF-OCT and eccentric fixation. (A) Scan passing through eccentric fixation area. (B) Scan passing through the greatest linear dimension of the area of absent FAF. Angle bracket showing EPR loss. Square bracket showing IS/OS junction loss. RPE, retinal pigment epithelium; FAF, fundus autofluorescence; IS/OS, inner/outer segment; OCT, optical coherence tomography.

1 degree in height on a black background. The cross was enlarged to 2 degrees for patients with poor VA. Fixation stability was classified according to the Fujii criteria as "stable" when >75% of fixation points fell within a circle 2 degree in diameter centred on the mean fixation position; "relatively unstable" if <75% fell within 2 degrees but >75% laid within a 4-degree–diameter circle fixation; and "unstable" if <75% of the points were within 4 degree fixation.[14,15]

Test–retest variability was analyzed for fixation assessment. To better quantify fixation stability, an automated registration of a bivariate contour ellipse area (BCEA) encompassing 1 SD (68.2%) was performed, according to other authors' findings[16,17] (Fig. 3). The area of the ellipse was calculated in degrees^2 using Steinman's technique.[18] Retinal sensitivity was assessed by an automatic pattern of examination: macula 20 degree 0 dB including 76 stimuli extending to 10 degrees of eccentricity; the mean sensitivity was calculated. Goldmann III standard size was used as stimulus, and its duration was of 200 millseconds. A 4-2 threshold strategy was used. Microperimeter MP-1 software allows importation of retinal images and creation of a new examination of the retinal fundus. The overlapped images were created through the "Import Image" command. The FAF and OCT images were identified and imported on the microperimetric patient's chart. For every patient, both the fixation and microperimetric exams were recorded with the relative FAF/OCT images using the offline recording. Registration "Extended Manual" procedure consisted of the following steps: Both images (fixation or microperimetric exam and FAF/OCT image) were displayed with the same size. The examiner was prompted to select, as accurately as possible, 2 reference points in each image. After selection, the correct position of the reference points on the 2 retinal images was verified. If the correspondence was considered valid, the operator confirmed the results.

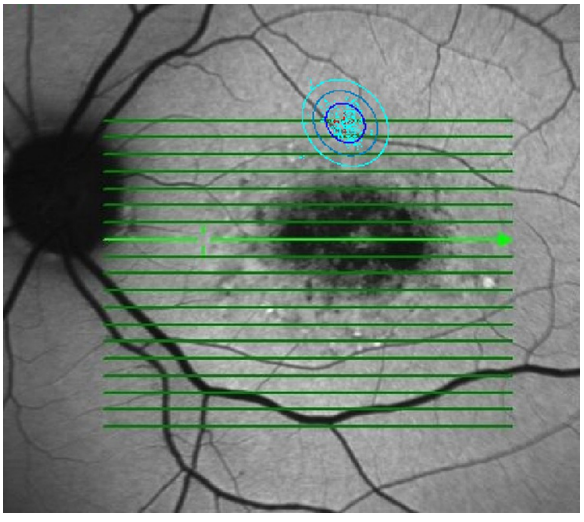

Fig. 3—Overlapped image showing fixation with BCEA on fundus autofluorescence and OCT scans. BCEA, bivariate contour ellipse area; OCT, optical coherence tomography.

Rehabilitation pathway

During clinical assessment, all patients were asked about the main difficulties they experienced in performing activities of daily living, such as reading. The visual rehabilitation program focused on identifying the most suitable device for reading, managing the device, identifying the magnifier-eye distance used during reading, and teaching page navigation strategies (e.g., forward and retrace navigation). The visual rehabilitation program was set according to patients' requirements, in order to achieve a fluent reading performance of 0.3 logMAR on Mnread charts through the use of the lowest required magnification.

The most suitable low-vision aid was determined on the basis of best reading speed while comparing different visual aids, including high plus reading glasses, prismatic magnifying spectacles, monocular magnifying spectacles, and aplanatic system. Reading rate, calculated as number of words per minute by the formula (words / reading time[s]) × 60 using the same Italian newspaper article of 9 character print in Times New Roman, was evaluated monocularly and binocularly: If reading speed was similar in both eyes, magnification was provided binocularly. The training was performed during the study period.

Statistical analysis

A descriptive analysis of the sample of 13 eyes was performed by means of absolute and relative frequencies with respect to qualitative variables and by means and SD or median and interquartile range for quantitative variables. Pearson's and Spearman's correlation coefficients were used to assess the relationship between magnification/reading speed and parametric and nonparametric variables, respectively. Due to the significant correlation of functional and morphological parameters between the right and left eye, only data from the right eye were included in the analysis. Patients with central fixation also were excluded. Statistical significance was set at $P \leq 0.05$. Statistical analysis were performed with Prism 6.0e (GraphPad Software, Inc. La Jolla, CA, USA).

Results

The patients' clinical features are reported in Table 1.

We analyzed 26 eyes of 15 patients. For the whole sample, the mean BCVA of the study eye was 0.7 (SD 0.3) using logMAR notation. Mean magnification required for reading task was 8.2 spherical diopters (SD 6.3). None of the patients needed a desktop video magnifier to regain reading performance. Using a newspaper text, mean reading speed was 69.8 words per minute (SD 29.5).

Table 1—Summary of morpho-functional findings

				MP-1				OCT			FAF				
Eye	Age	Sex	BCVA (logMAR)	Mean (dB)	BCEA 68.2	Fixation	PRL/ Scotoma	GLD (μm)	E IS/ OS	E OLM	GLD (μm)	Area	E FAF	Magnification (sph dpt)	Reading speed (wpm)
1	47	M	1	9.6	1.4	S	S	2825	/	/	2780	5.41	/	20	92
2	26	F	0.5	16.5	0.8	S	S	2162	D	D	2072	3.01	D	6	153
3	26	F	0.6	16.9	1	S	S	2090	D	D	2089	2.19	N	6	153
4	16	F	0.7	7.1	0.9	S	S	2163	D	D	1971	2.95	N	5	59
5	16	F	0.8	6.8	1.6	S	S	2861	D	D	2773	3.21	N	5	59
6	48	M	1	13	2.3	S	S	1913	P	P	1936	2.34	D	8	87
7	48	M	0.9	13.5	10.8	U	S	2380	P	P	2341	3.5	D	8	87
8	44	F	1	2.6	1	S	S	3989	P	P	3933	10	D	20	73
9	44	F	1	4.2	0.6	S	S	3155	D	D	2990	5.1	I	20	73
10	52	F	0.8	13.3	2.7	S	S	2560	D	D	2597	4.77	D	8	70
11	52	F	0.7	14.6	2.1	S	S	2300	P	P	2463	7.68	D	8	70
12	42	F	0.9	9.8	5.8	RU	S	2020	D	D	1760	2.92	D	6	42
13	42	F	0.8	10.8	7.3	RU	S	3850	D	D	3830	20.34	D	6	42
14	61	F	0.9	12.1	3.1	RU	S	2458	P	P	2388	2.2	D	6	56
15	43	F	1	3.7	1.3	S	S	4100	L	L	4055	9.72	I	6	47
16	43	F	0.9	1.4	0.7	S	S	3387	D	D	3575	11.07	D	6	47
17	53	F	0.8	12.8	1.8	S	S	2565	P	P	1907	1.99	D	6	65
18	53	F	0.8	12.1	1.8	S	S	2224	P	P	1865	2.07	D	6	65
19	45	F	0.6	16.8	0.3	S	C	370	P	P	370	0.14	N	4	105
20	50	F	1	0.9	3.3	RU	S	4373	L	L	4363	13.2	I	28	64
21	38	M	0.2	0.3	0.7	S	S	1357	D	D	2212	3.71	N	4	60
22	38	M	0.3	0.4	0.2	S	S	1200	D	D	2085	1.91	N	4	60
23	37	M	0.8	1.9	8.6	S	S	2509	P	P	2281	0.77	D	7	40
24	37	M	0.9	1.9	8.3	RU	S	2263	P	P	2258	0.92	D	7	40
25	53	M	0	3.8	0.1	S	C	3660	D	D	3600	7.1	N	2	53
26	53	M	0	3.4	0.1	S	C	1934	P	P	2130	4.1	N	2	53

BCEA, bivariate contour ellipse area; BCVA, best corrected visual acuity; C, central; D, disorganized; E, Eccentric; IS/OS, inner/outer segment; FAF, fundus autofluorescence; GLD, greatest linear dimension; MP-1, microperimetry; N, normal; OCT, optical coherence tomography; OLM, outer membrane layer; P, present; PRL, preferred retinal location; RU, relatively unstable; S, stable; sph dpt, spherical diopters; U, unstable; wpm, words per minute.

Table 2—Median and interquartile values

Variables	Median (IQR)
BCVA (logMAR)	0.8 (0.33)
Mean dB	8.35 (10.7)
BCEA 68.2	1.5 (2.5)
OCT greatest linear dimension	2419 (1141)
FAF greatest linear dimension	2311 (1090)
FAF area	3.36 (5.09)

BCEA, bivariate contour ellipse area; BCVA, best corrected visual acuity; FAF, fundus autofluorescence; IQR, interquartile range; OCT, optical coherence tomography.

A summary of morpho-functional features is reported in Table 2.

Microperimetry

Of the 26 eyes, 23 had an eccentric PRL located in the superior retina, whereas the remaining 3 had a central foveal fixation. In accordance with Fuji classification, 20 eyes were identified as stable, 5 as relatively unstable, and 1 as unstable. Bivariate contour ellipse area mean value for 1 SD was 2.6 degrees^2 (SD 2.9). Microperimetric exam demonstrated the presence of an absolute scotoma in the atrophic retinal area and in the surrounding retinal area. Retinal sensitivity map, obtained from the automatic pattern examination, had a mean value of 8.0 dB (SD 5.7).

Fundus autofluorescence

Mean value of the GLD of the atrophic area was 2562.4 μm (SD 887.8). The average size of the atrophic area was 5.1 mm^2 (SD 4.6). Qualitative assessment of autofluorescence through the eccentric fixation area showed dishomogeneous autofluorescence surrounding hypoautofluorescence atrophic area in 14 of 25 eyes (56%), normal in 8 (25%), and hypoautofluorescent in 3 (12%).

OCT

The average extent of GLD of photoreceptor loss measured on OCT images was 2564.1 μm (SD 934.2). There was no significant difference between GLD based on OCT and GLD based on FAF ($P > 0.05$). Inner–outer photoreceptors junction and outer-limiting membrane layer concerning the eccentric fixation area were obtained in 25 eyes: Organized IS/OS and OLM layers were observed in 11 (44%) eyes, whereas disorganized layers were observed in 12 patients (48%) and lost layers in the remaining 2 (8%). The overlapping of both OCT and FAF imaging on microperimetric exams showed a superior PRL location at the edge of the atrophic area in 23 eyes (88%) and a central fixation in the remaining 3 eyes (12%), where a ring scotoma was identified.

Relationship between morpho-functional measures and magnification power/reading speed

Association with quantitative variables, correlation coefficients, and p values were assessed as reported in Table 3. BCVA (logMAR) was strongly correlated with required magnification ($r = 0.56$; $p = 0.04$; Fig. 4A) but not with

Table 3—Correlation between morphological and functional parameters with reading speed and magnification (Pearson correlation coefficient).

	Magnification		Reading speed	
Variables	*r*	*p* value	*r*	*p* value
BCVA	0.56	0.04	0.23	0.28
MP-1 Mean dB	0.26	0.28	0.57	0.04
BCEA	0.09	0.68	–0.44	0.16
FAF GLD	0.67	0.01	–0.24	0.27
OCT GLD	0.69	0.009	–0.22	0.32
FAF area	0.35	0.09	–0.22	0.30

BCVA, best corrected visual acuity; FAF, fundus autofluorescence; GLD, greatest linear dimension; MP-1, microperimetry; OCT, optical coherence tomography.

Table 4—Correlation between qualitative parameters and reading speed and magnification (Spearman's test): p = < 0.05.

Variables	Magnification	Reading speed
Fixation	$r = 0.10$; $p = 0.22$	$r = -0.29$; $p = 0.12$
PRL	$r = 0.35$; $p = 0.03$	$r = 0.03$; $p = 0.91$
OCT (E IS/OS OLM)	$r = 0.08$; $p = 0.57$	$r = -0.06$; $p = 0.84$
FAF (E)	$r = 0.81$; $p < 0.0001$	$r = 0.03$; $p = 0.87$

E IS/OS, inner/outer segment; FAF, fundus autofluorescence; OCT, optical coherence tomography; OLM, outer membrane layer; PRL, preferred retinal location.

reading speed ($r = 0.23$; $p = 0.28$). Participants with better ETDRS (Early Treatment of Diabetic Retinopathy Study) VA needed lower magnification power. Retinal sensitivity analyzed by means of microperimeter MP-1 was unrelated to magnification ($r = 0.26$; $p = 0.28$); whereas it was associated with reading speed ($r = 0.57$; $p = 0.04$; Fig. 4B). Magnification was linearly correlated with both OCT and FAF GLD ($r = 0.69$; $p = 0.009$ and $r = 0.67$; $p = 0.01$, respectively; Fig. 4C, 4D), whereas reading speed did not show a relationship with these parameters. No significant correlations were noted between BCEA or FAF area with magnification and reading speed. Results of the Spearman's correlation test evaluating the association between qualitative variables and magnification as well as reading speed are described in Table 4. No significant correlations were found between any qualitative variable and reading speed ($p > 0.05$). On the other hand, magnification levels showed a positive correlation with eccentric PRL location ($p = 0.03$) and the degree of FAF alteration (normal, dishomogeneous, hypoautofluorescence; $p < 0.0001$).

Discussion

To our knowledge, this is the first study to demonstrate a new approach for evaluating both morphological data and functional measures through the overlap of the fixation and microperimetric examination and the FAF and OCT images. The use of a multimodal approach, including OCT, FAF, and microperimetric examinations, better defines the disease with its morpho-functional features and allows planning of a low-vision rehabilitation pathway tailored to each patient. The study's data reveal

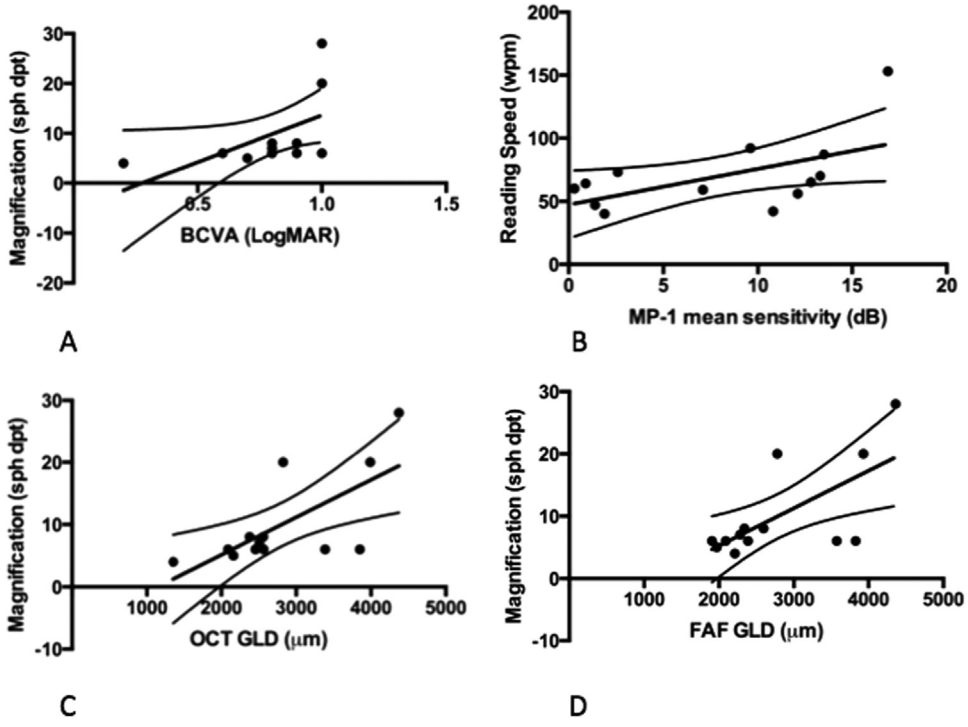

Fig. 4—(A) Linear regression analysis showing the correlation between logMAR visual acuity and the degree of magnification. (B) Linear regression analysis showing the positive correlation between microperimetry sensitivity and reading speed. (C) Linear regression analysis showing the correlation between OCT GLD and magnification. (D) Linear regression analysis showing the correlation between FAF GLD magnification. FAF, fundus autofluorescence; GLD, greatest linear dimension; OCT, optical coherence tomography.

that functional features such as BCVA, PRL location, and fixation stability are likely to be related to required magnification, whereas retinal sensitivity on MP1 is a better predictor of reading speed in patients with STGD. One of the most significant findings emerging from this study is the association, in the univariable analysis, between retinal sensitivity and reading speed. Patients involved in this study could benefit from the use of the area above the scotoma, characterized by higher sensitivity values, because of the higher spatial resolution.[19,20] The strong association between retinal sensitivity and reading performance indicates that the retinal sensitivity map may be a specific indicator of this activity. As previously reported by Ergun et al. in patients with subfoveal occult choroidal neovascularization in age-related macular degeneration, the size of absolute scotoma is significantly related to reading speed.[21] In the present study, patients with a larger scotoma and poor retinal sensitivity read more slowly than those with higher sensitivity.

Univariable analysis identified BCVA as the first step to calculate required magnification in patients with low vision, according to other studies.[22–26] Results from the present study report that magnification is strongly related to PRL location, consistent with other findings.[27–29] In this study, PRL was found to be preferentially located above the central absolute scotoma, and thus below the lesion in visual space. Patients with eccentric fixation needed higher magnification compared with those who had central fixation for the presence of a ring scotoma.

As previously reported, in patients with a ring scotoma, enlarged character print is not the best rehabilitative solution because the retinal image cannot fit into the central spared area.[30,31] In reviewing the literature, no data were found concerning the association between fixation stability and required magnification. In the present study, patients with poor fixation stability needed a higher level of magnification than those with a more stable fixation.

The BCEA that encompasses 68.2% of fixation points by itself seems to be not related to magnification of prescribed low-vision aids. Among the factors that influence reading rate in individuals with visual impairment due to central scotoma, our results demonstrated, in accordance with other findings, that fixation stability may indeed influence reading rate.[17,31–33] A superior PRL location at the edge of the atrophic area was found in the majority of patients (23 eyes, 88%), whereas central fixation was found in the remaining 3 eyes (12%), where a ring scotoma was identified. Sunness et al. proposed that Stargardt's lesions are wider horizontally than vertically; therefore, these patients fixate superior to the central scotoma, gaining an advantage in terms of proximity to the fovea.[34] Morphologic features such as the extent of GLD of photoreceptor loss measured by OCT images, FAF/GLD of the atrophic area, and Eccentric FAF were significantly correlated with magnification power but not with reading speed. The extent of the GLD analysis for both OCT and FAF appears to be similar, probably because of the late stage of the disease in enrolled patients. In a previous study by Gomes et al., photoreceptor loss was considered a primary event preceding RPE degeneration, contrary to current view.[35] Therefore, it would be necessary to identify patients with STGD in the early stage of the disease through morpho-functional analysis and perform a follow-up to better understand the sequence of the disease process. Moreover, OCT analysis demonstrated the presence of the IS/OS photoreceptors junction and OLM in correspondence of the PRL in the majority of patients, although not perfectly preserved. FAF images revealed dishomogeneous autofluorescence of the region underlying PRL location, suggesting a residual function of outer retinal layers.

The patients in the present study had a good response to visual rehabilitation intervention as most of them did not need a high level of magnification to complete reading tasks with optical magnifying devices, demonstrating a good reading speed. Such a good response seems in accordance with Tingting Liu's findings, showing stronger evidence in favour of functional reorganization of the visual cortex after central field loss in patients with early-onset macular atrophy when compared with age-related macular degeneration forms.[36] An issue that was not addressed in this study was whether psychological status may contribute to the achievement of rehabilitation outcomes. Further studies focusing on this area are warranted.

In the present study, evaluation was based on morpho-functional analysis, and we identified several key factors needed to design the appropriate low-vision intervention to assist people for near activities such as reading: FAF/ELD of the atrophic area, distance VA, fixation behaviour, and retinal sensitivity map. In particular, the assessed residual activity of outer retinal layers passing through the eccentric fixation area demonstrated by the overlapping of both OCT and FAF imaging on microperimetric examination seems to be significantly related to vision rehabilitation outcomes, such as required magnification and reading rate. These findings have important implications for the development of a customized rehabilitative program for patients with Stargardt's maculopathy: A complete ophthalmologic assessment before low-vision intervention would improve the rehabilitation intervention as a whole. Further studies evaluating patients with early-stage STGD are needed to better define the natural history and progression of the disease and to design the best customized rehabilitative model.

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Footnotes and Disclosure:

The authors have no proprietary or commercial interest in any materials discussed in this article.

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Originally received Jul. 20, 2016. Accepted Oct. 24, 2016.

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