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Fixation Location and Stability in Best Vitelliform Macular Dystrophy

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Purpose: To analyze fixation location and stability in best vitelliform macular dystrophy (BVMD) and test their association with best-corrected visual acuity (BCVA).

Design: Observational, cross-sectional study.

Participants: Thirty patients (55 eyes) affected by genetically confirmed BVMD were followed up at the Retinal Heredodystrophies Unit of IRCCS San Raffaele Scientific Institute, Milan.

Methods: Patients underwent testing with macular integrity assessment (MAIA) microperimeter. Fixation location was measured as distance in degrees (°) between preferred retinal locus (PRL) and estimated fovea location (EFL); fixation was defined as eccentric when the distance between PRL and EFL exceeded 2°. Fixation stability was graded as stable, relatively unstable, or unstable and expressed as bivariate contour ellipse area (BCEA, $^{\circ 2}$).

Main Outcome Measures: Fixation location and stability.

Results: The median distance of the PRL from the anatomic fovea was 0.7°, and fixation location was eccentric in 27% of eyes. Fixation was graded as stable in 64% of eyes, relatively unstable in 13%, and unstable in 24%, with a median 95% BCEA of 6.2$^{\circ 2}$. The atrophic/fibrotic stage was associated with worse fixation parameters (all $P < 0.01$). Both PRL eccentricity and fixation stability were linearly associated with BCVA: every 1° increase in PRL eccentricity was associated with a 0.07 logarithm of the minimum angle of resolution (logMAR) worse BCVA ($P < 0.0001$) while every 1$^{\circ 2}$ increase in 95% BCEA was associated with a 0.01 logMAR worse BCVA ($P < 0.001$). No significant intereye correlation was found for PRL eccentricity and fixation stability, as well as no association between the patient's age and fixation parameters.

Conclusions: We demonstrated that most eyes affected by BVMD retain a central stable fixation and provided evidence that both fixation eccentricity and stability are strongly associated with visual acuity in BVMD. These parameters may serve as secondary end points for future clinical trials.

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Best vitelliform macular dystrophy (BVMD, (Online Mendelian Inheritance in Man [OMIM] #153700) is an inherited retinal disease caused by dominant variants in the *BEST1* gene (OMIM #607854).[1,2] It is generally considered a rare disease but represents the second most common macular dystrophy and the most frequent among autosomal dominant ones, with an estimated prevalence between 1 in 10 000 and 1 in 100 000 in the population of European descent.[3,4] The degree of visual impairment in BVMD is highly variable, with visual acuity often staying stable until the macula experiences vitelliruptive or atrophic changes.[5] Therefore, best-corrected visual acuity (BCVA) provides a limited representation of the visual impairment associated with BVMD, and the identification of alternative outcome measures will be of primary importance for the design of clinical trials as well as for effective disease monitoring over the follow-up.

In this regard, microperimetry (MAIA) is based on simultaneous visualization of the fundus and perimetric testing to provide an exact correlation between retinal structure and function.[6] Retinal sensitivity in BVMD is influenced by lesion composition and outer nuclear layer thickness, and scotomata have also been detected beyond the borders of the macular lesion.[2,7–9] Additionally, MAIA allows a quantitative assessment of fixation eccentricity and stability, which have already been shown to correlate with BCVA loss in other macular dystrophies (most notably Stargardt disease)[10,11] but not in the rod-dominated retinitis pigmentosa.[12,13] However, scant data are available on fixation in BVMD. In this cross-sectional study, we report data on fixation stability, eccentricity, and their association with BCVA in a cohort of patients with molecularly confirmed BVMD.

Methods

Research Design, Population, and Observational Procedures

This study presents a cross-sectional analysis of baseline data obtained from a prospective natural history study on BVMD. The research was conducted at a single referral center for inherited

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retinal diseases (Retinal Heredodystrophies Unit, Department of Ophthalmology, IRCCS San Raffaele Hospital, Milan, Italy). The research followed the Declaration of Helsinki and was approved by the ethics committee of San Raffaele Hospital (MIRD2020). Signed informed consent for the genetic testing and permission to use medical data for research purposes were obtained from all participants. Clinical examinations and imaging procedures were performed from November 2020 to December 2022. The diagnosis of BVMD was based on the biomicroscopic fundus picture and the molecular confirmation of a likely (pathogenic) variant in the *BEST1* gene according to the criteria of the American College of Medical Genetics.[14] The baseline genetic characteristics of this cohort of patients have been previously described.[9] Eyes with subclinical disease were excluded from this analysis,[15] as well as those with any other retinal or optic nerve disorders, optical media opacities, previous ophthalmic surgery, and systemic diseases or therapies potentially able to alter retinal anatomy or function.

All patients underwent a comprehensive ophthalmic examination, including measurement of BCVA using an ETDRS chart, color fundus photography, OCT, radial and raster scans centered on the fovea (Spectralis HRA + OCT), and MAIA. Specifically, the MAIA was performed after pupil dilation with 1% tropicamide and 15 minutes of dark adaptation. Each eye was tested separately by patching the fellow eye. Patients were asked to gaze as steadily as possible at the center of a 1° red circle fixation target. Upon completion of the test, MAIA determines a final preferred retinal locus (PRL) as the barycenter of the total fixation points recorded during the examination. According to manufacturer instructions, if fixation losses were > 30%, the test was considered unreliable, discarded, and repeated following further explanation of the procedure.

Data Collection and Outcome Variables

After the examination, an estimated fovea location (EFL) marker was manually placed over the MAIA fundus image. The location of the fovea was determined by 2 graders (L.B. and A.P.) on Spectralis infrared images, using structural OCT B-scans as a reference. To establish the EFL, the marked infrared image was then compared with the fundus image recorded by MAIA. For cases of foveal atrophy, the EFL was approximated as the point of maximal inner layer convergence and outer nuclear layer thickness.

The fixational task can be summarized as the eccentricity of the PRL from the anatomical fovea and its stability. Thus, the following continuous variables were automatically calculated by the integrated software and extracted as raw data: PRL eccentricity (°); 63% bivariate contour ellipse area (BCEA) and 95% BCEA, corresponding to the area enclosing 65% or 95% of all fixation points (°^{2}), as a measure of fixation stability[16–18]; and P1 and P2, which represent the percentage of fixation points located within the 2° and 4° circles centered in the gravitational center of all fixation points, as an alternative measure of fixation stability.[19] In addition, we assessed fixation eccentricity and stability using categorical variables. An eye was defined as having an eccentric fixation when the distance between PRL and EFL was > 2°; otherwise, the fixation was defined as "noneccentric."[10] We also recorded whether the eccentric PRL was shifted toward the superior, temporal, inferior, or nasal sector. According to Fujii, an eye's fixation was defined as stable when P1 was > 75%, relatively unstable when P1 was < 75% but P2 was > 75%, and unstable when both P1 and P2 were < 75%.[19]

Statistical Analysis

All descriptive data are expressed as mean, median, standard deviation (SD), and interquartile range for continuous variables and as frequencies and percentages for categorical ones. Pearson's chi-square test was used to compare distribution differences among categorical variables, while Pearson's coefficient was used to express linear correlations between continuous variables as well as intereye correlations. Generalized estimating equations were used to perform regression analysis between PRL eccentricity, fixation stability, age, and Gass' stage while accounting for intereye correlations. Effect on the outcome of one unit change in the predictor variable was reported as beta coefficient (β), standard error, 95% confidence interval (CI), and *P* value. All tests were two-sided, and the level of statistical significance was set at $\alpha < 0.05$. Analyses were performed using SPSS Statistics 25.

Results

Overall, 55 eyes of 30 patients (22 [73.3%] males and 8 [26.7%] females) with a mean (SD) age of 39.8 (21) years were included in the analyses. The vitelliruptive stage was the one most frequently encountered in our cohort (28 [50.9%] eyes). The mean (SD) BCVA was 0.3 (0.3) logarithm of the minimum angle of resolution (logMAR), approximately corresponding to 20/40 Snellen. The median (interquartile range) distance of the PRL from the anatomic fovea was 0.7° (0.3°−2.6°). Fixation location was eccentric (that is, > 2° from the EFL) in 15 (27.3%) eyes, and the PRL has shifted toward the nasal sector in more than half of those cases (9 [60%] eyes). Fixation was graded as stable in 35 (63.6%) eyes, relatively unstable in 7 (12.7%), and unstable in 13 (23.6%), whereas the median (interquartile range) 63% and 95% BCEA were, respectively, 2.1°^{2} (0.4°^{2}−7.2°^{2}) and 6.2°^{2} (1.2°^{2}−21.7°^{2}). Table 1 shows the demographic characteristics and fixation metric in the overall cohort and across Gass' stages, while Table 2 reports the results of univariable regression analyses for PRL eccentricity, fixation stability, and BCVA.

Eccentric fixation was most frequently observed in the advanced stages of the disease. Almost 90% of eyes with eccentric fixation were in the vitelliruptive or atrophic/fibrotic stage, whereas only 2 were in the vitelliform and pseudohypopyon stages ($P = 0.089$) (Table 1). In more detail, the atrophic/fibrotic stage was associated with a 1.7° more eccentric PRL compared to the vitelliform stage (95% CI, 0.5°−2.9°; $P = 0.0065$). No significant association between PRL eccentricity and patient age was observed ($P = 0.95$) (Table 2). Similarly, 11 of 13 eyes with unstable fixation (84.6%) were in the vitelliruptive or atrophic/fibrotic stage, whereas only 2 were in the vitelliform and pseudohypopyon stages ($P = 0.21$) (Table 1). Fixation stability metrics (65% BCEA, 95% BCEA, P1, and P2) were all strongly correlated with each other (all r > 0.9; all $P < 0.0001$); thus, only 95% BCEA was used for further analyses. The atrophic/fibrotic stage was associated with 18.7°^{2} larger 95% BCEA compared to the vitelliform stage (95% CI, 5.6°^{2}−31.7°^{2};

Table 1. Demographic and Clinical Characteristics of Patients with Best Vitelliform Macular Dystrophy, According to Gass Stage

	Overall Cohort	Gass' Stage			
		Vitelliform	*Pseudohypopion*	*Vitelliruptive*	*Atrophic/Fibrotic*
Total number (eyes)	55	14 (25.5%)	4 (7.3%)	28 (50.9%)	9 (16.4%)
BCVA (logMAR)					
Mean (SD)	0.25 (0.25)		0.23 (0.21)	0.25 (0.25)	0.44 (0.31)
Median (IQR)	0.15 (0.05–0.40)	0.10 (0.00–0.19)	0.20 (0.05–0.43)	0.18 (0.06–0.40)	0.40 (0.20–0.65)
Eccentric fixation	15 (27.3%)	1 (7.1%)	1 (25%)	8 (28.6%)	5 (55.6%)
Location of eccentric locus					
Superior	4 (26.7%)	0 (0%)	0 (0%)	3 (37.5%)	1 (20%)
Nasal	9 (60%)	1 (100%)	1 (100%)	4 (50%)	3 (60%)
Inferior	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Temporal	2 (13.3%)	0 (0%)	0 (0%)	1 (12.5%)	1 (20%)
PRL eccentricity (°)					
Mean (SD)	1.7 (2)	0.9 (1.2)	1 (1.7)	1.8 (2.3)	2.8 (1.8)
Median (IQR)	0.7 (0.3–2.6)	0.5 (0.3–1.1)	0.2 (0.1–2.7)	0.6 (0.2–3.3)	2.6 (1.1–4.4)
Fixation stability					
Stable	35 (63.6%)	11 (78.6%)	2 (50%)	18 (64.3%)	4 (44.4%)
Relatively unstable	7 (12.7%)	2 (14.3%)	1 (25%)	4 (14.3%)	0 (0%)
Unstable	13 (23.6%)	1 (7.1%)	1 (25%)	6 (21.4%)	5 (55.6%)
63% BCEA ($°^2$)					
Mean (SD)	4.8 (5.8)	2.9 (2.8)	2.9 (3.8)	4.3 (5)	10 (9.3)
Median (IQR)	2.1 (0.4–7.2)	1.6 (1–3.9)	1.4 (0.3–6.9)	2.1 (0.3–6.3)	7.2 (1.7–20.4)
95% BCEA ($°^2$)					
Mean (SD)	14.2 (17.4)	8.7 (8.5)	7.8 (9.9)	12.8 (14.9)	29.9 (27.9)
Median (IQR)	6.2 (1.2–21.7)	4.8 (2.8–11.7)	4.2 (1–18.1)	6.3 (0.9–18.6)	21.7 (4.9–61)
P1 (%)					
Mean (SD)	70.1 (31.4)	79.2 (23.6)	75.8 (30.7)	71.5 (31.5)	48.8 (36.7)
Median (IQR)	82 (33–98)	84 (74.8–94.8)	85 (43.3–99)	86.5 (33–98.8)	33 (15–84)
P2 (%)					
Mean (SD)	86.6 (16.8)	91.9 (12.2)	91.3 (14.3)	87.1 (15.6)	74.6 (23.6)
Median (IQR)	95 (71–99)	97.5 (91.3–98.3)	97.5 (76.5–99.8)	94 (72.3–100)	70 (49–99.5)

BCEA = bivariate contour ellipse area; BCVA = best-corrected visual acuity; IQR = interquartile range; logMAR = logarithm of the minimum angle of resolution; PRL = preferred retinal locus; SD = standard deviation.
Values are presented as number (%) unless otherwise indicated.

$P = 0.0053$). No significant association between fixation stability and patient age was observed ($P = 0.22$) (Table 2).

When testing relationships between visual acuity and fixation, we found that an increase of 1° in PRL eccentricity from the EFL was associated with a 0.07 logMAR worse BCVA (95% CI, 0.04–0.10 logMAR; $P < 0.0001$), while eccentric fixation was associated with a 0.3 logMAR worse BCVA (95% CI, 0.14–0.45 logMAR; $P < 0.0001$), corresponding to a loss of 15 ETDRS letters (Fig 1A). Moreover, a less stable fixation also corresponded to a worse visual acuity: each $1°^2$ increase in 95% BCEA was associated with a 0.01 logMAR decrease in BCVA (95% CI, 0.004–0.013 logMAR; $P = 0.00011$), corresponding to a 5 ETDRS letters loss for a $10°^2$ increase in 95% BCEA (Table 2 and Fig 1B).

Among eyes showing noneccentric fixation, 34 (85%) had a stable fixation, while 6 (12.5%) had a relatively unstable fixation ($P < 0.0001$). Indeed, PRL eccentricity from the fovea and fixation stability are linked by a robust linear relationship, as shown in Figure 1C: 1° more eccentric PRL was associated with a $5.4°^2$ larger 95% BCEA (95% CI, $3.16°^2$–$7.71°^2$; $P < 0.0001$) (Table 2). Conversely, we have not found significant intereye correlations for both PRL eccentricity and 95% BCEA (r = 0.16, $P = 0.26$, and r = 0.26, $P = 0.060$, respectively).

Discussion

This cross-sectional study has described data on fixation parameters and has investigated their association with BCVA in a cohort of patients with molecularly confirmed BVMD.

Our results show that the vast majority (62%) of eyes affected by BVMD exhibit both a central and stable fixation, while only 10% of patients show bilateral eccentric and unstable fixation in a cohort with a mean age of 40 years. These results significantly differ from what has been observed in Stargardt disease, the most common macular dystrophy, in which fixation is eccentric in 76% of eyes and 85% of patients have bilateral eccentric fixation at a mean age of 34 years (Fig 2).[10] This further underscores the

Table 2. Univariate Regression Analyses for PRL Eccentricity, Fixation Stability, and Visual Acuity in Best Vitelliform Macular Dystrophy

	β Coefficient	SE	95% CI	P Value
PRL eccentricity (°)				
Age (years)	0.01	0.02	−0.03 to 0.03	0.95^{ns}
Gass' stage				
Vitelliform			Reference	
Pseudohypopyon	−0.17	0.33	−0.81 to 0.48	0.61^{ns}
Vitelliruptive	1.03	0.53	0.00−2.06	0.051^{ns}
Atrophic/fibrotic	1.68	0.62	0.47−2.89	0.0065**
95% BCEA ($°^2$)	0.07	0.01	0.05−0.1	< 0.0001****
95% BCEA ($°^2$)				
Age (years)	0.15	0.12	−0.09 to 0.40	0.22
Gass' stage				
Vitelliform			Reference	
Pseudohypopyon	2.30	2.72	−3.03 to 7.6	0.40^{ns}
Vitelliruptive	3.63	3.01	−2.28 to 9.54	0.23^{ns}
Atrophic/fibrotic	18.64	6.68	5.55−31.73	0.0053**
PRL eccentricity (°)	5.43	1.16	3.16−7.71	< 0.0001****
BCVA (logMAR)				
Age (years)	0.03	0.002	0.00−0.01	0.076
Gass' stage				
Vitelliform			Reference	
Pseudohypopyon	0.10	0.01	−0.09 to 0.29	0.30^{ns}
Vitelliruptive	0.14	0.06	0.02−0.26	0.020*
Atrophic/fibrotic	0.36	0.11	0.15−0.57	0.00071***
PRL eccentricity (°)	0.07	0.02	0.04−0.10	< 0.0001****
Eccentric fixation	0.29	0.08	0.14−0.45	0.00027***
95% BCEA ($°^2$)	0.01	0.002	0.004−0.013	0.00011***

BCEA = bivariate contour ellipse area; BCVA = best-corrected visual acuity; CI = confidence interval; logMAR = logarithm of the minimum angle of resolution; PRL = preferred retinal locus; SE = standard error.
Dependent outcome variables are shown in bold. Independent predictor variables are shown in italics.
Fixation is defined as eccentric when the PRL is > 2° far from the estimated fovea location.
ns = $P > 0.05$; * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$; **** = $P < 0.0001$.

inherent differences between macular dystrophies, which must be considered for the design of clinical trials and prognostication of individual patients. Moreover, we found a strong linear relationship between fixation eccentricity and stability with BCVA: an increase of 1° in the eccentricity of the fixation point (PRL) from the anatomic fovea was associated with a loss of approximately 4 letters on the ETDRS visual acuity chart, while a $10°^2$ larger 95% BCEA was associated with a loss of approximately 5 letters on the ETDRS chart. Even though there is no effective treatment for BVMD at present, several options are under investigation.[20–23] The potential efficacy of these therapies will need to be measured in clinical trials using surrogate structural and functional end points in addition to standard visual acuity. For example, in their phase I/II clinical trial of gene therapy in choroideremia, MacLaren et al reported about a patient who had complete loss of foveal fixation and showed a shift of his PRL toward the region exposed to the vector 6 months after injection.[24] However, any surrogate end point must show a strong correlation with visual function in order to prove a clinical benefit for patients.[25] Thus, PRL eccentricity and 95% BCEA may be helpful as secondary end points for future clinical trials, allowing a more granular assessment of central visual function in BVMD than in BCVA. Indeed, even though only eyes in the atrophic/fibrotic stage show a significant decrease in both fixation parameters and BCVA with respect to those in earlier stages, almost all patients in our cohort had 95% BCEA values well below 2 SDs from the mean of healthy individuals ($2.40°^2 \pm 2.04°^2$), while visual acuity could also be normal or slightly reduced.[26]

We also observed that a more eccentric fixation is associated with a less stable fixation (1° more eccentric PRL was associated with a $5.4°^2$ larger 95% BCEA). However, we could not determine the directionality of this relationship, that is, whether the development of an eccentric fixation point implies a loss of stability owing to its dependence on cone spacing[27] or if the progressive deterioration of foveal function and subsequent fixation instability leads to the development of an alternative eccentric fixation point. Only longitudinal prospective data will clarify how fixation parameters modify over time, also in relation to the structural changes of the macular lesion.

Lastly, we found no intereye correlation concerning fixation location and stability. Indeed, Jarc-Vidmar et al[7] already demonstrated that the stability of fixation in BVMD is never symmetric between the eyes of the same patient, except for those patients with stable bilateral

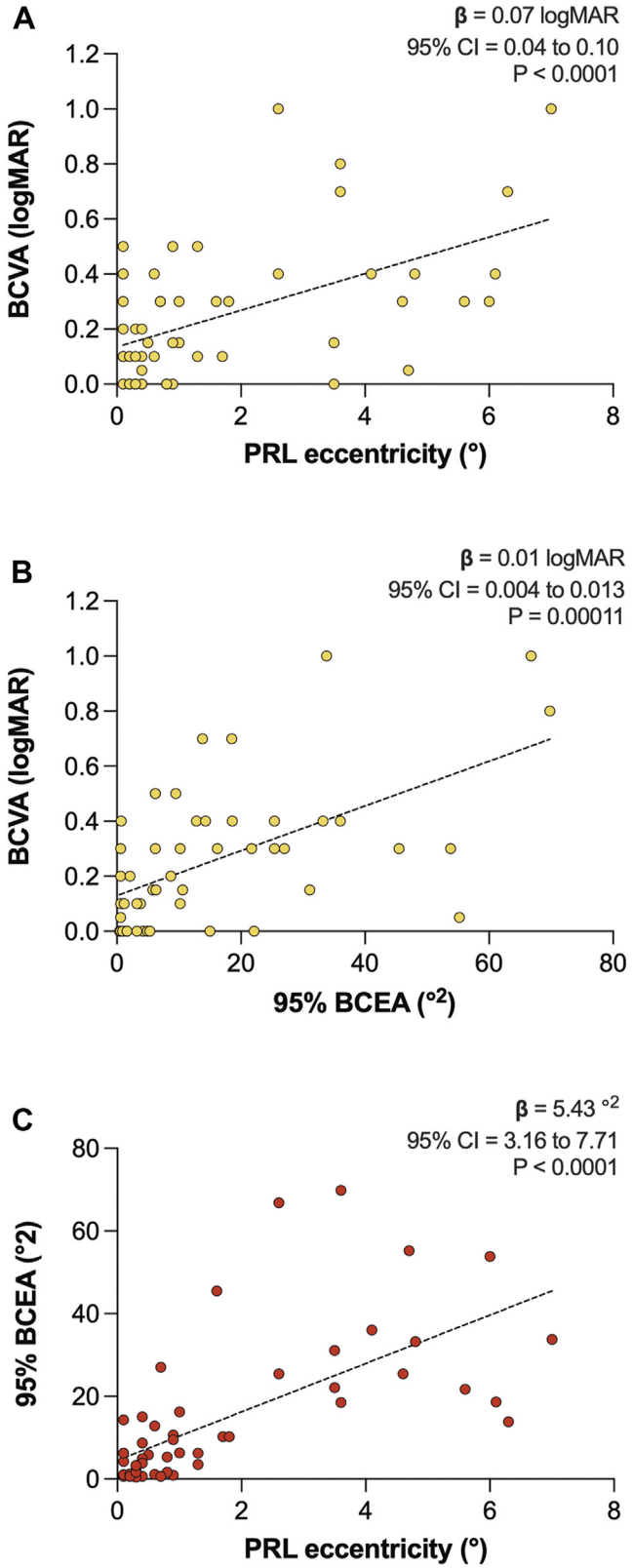

Figure 1. A, Scatterplot and regression line showing the relationship between preferred retinal locus (PRL) eccentricity and best-corrected visual acuity (BCVA). **B,** Scatterplot and regression line showing the relationship between 95% bivariate contour ellipse area (BCEA). **C,** Scatterplot and regression line showing the relationship between PRL eccentricity and 95% BCEA. CI = confidence interval; logMAR = logarithm of the minimum angle of resolution.

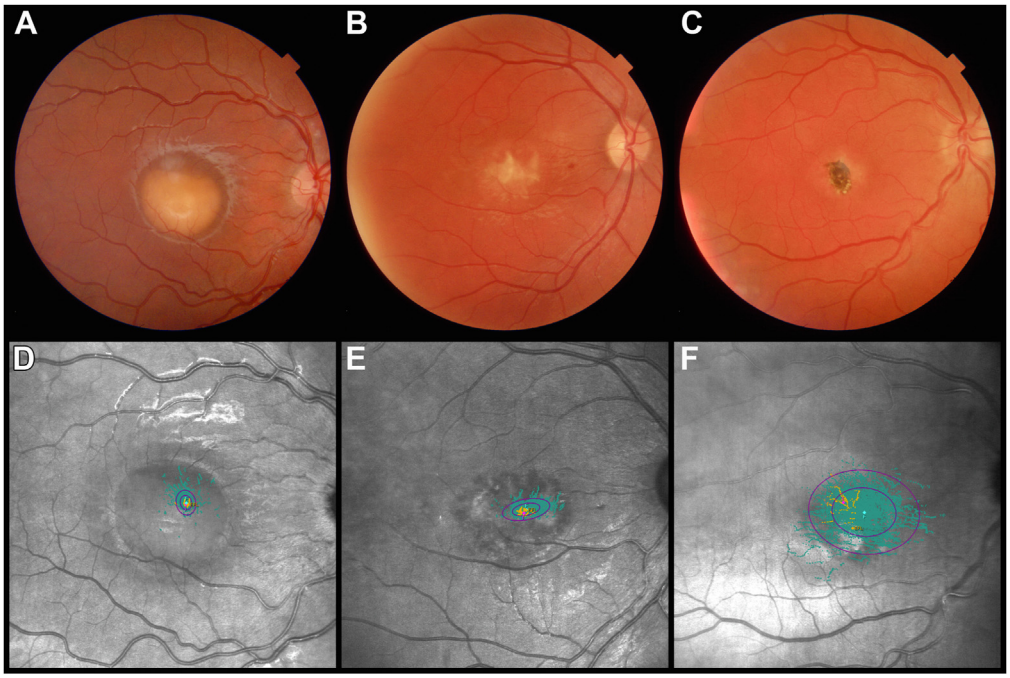

Figure 2. Examples of microperimetry fixation analysis in eyes with best vitelliform macular dystrophy at different stages of Gass' classification. **A, B,** Vitelliform stage, characterized by a central and stable fixation. **C, D,** Vitelliruptive stage, displaying a relative enlargement of the area containing 95% of fixation points albeit without a substantial eccentric shift of the preferred fixation locus. **E, F,** Atrophic/fibrotic stage, featuring pigmented central scarring on color fundus photograph, shows a further decrease in fixation stability and the development of an eccentric fixation locus approximately 3° superior nasally from the fovea. In (**B**, **D**, and **F**), the outer blue ellipse represents 95% bivariate contour ellipse area, the white rhombus corresponds to the preferred retinal locus determined by the microperimeter, while the orange one corresponds to the estimated fovea location set by the operator.

fixation. In addition, the patient's age was not associated with worse fixation parameters. These findings may be explained by the often sudden, rather than gradual, evolution of BVMD, with the abrupt collapse of vitelliform lesions or development of macular neovascularization,[28,29] resulting in a marked morphofunctional asymmetry between the 2 eyes of the same patient.

In conclusion, despite a limited number of patients and the lack of longitudinal data, we demonstrated that the majority of eyes affected by BVMD retain a central stable fixation and provided evidence that fixation eccentricity and stability are strongly associated with visual acuity in BVMD. Fixation parameters may serve as secondary end points for upcoming clinical trials.

Footnotes and Disclosures

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Disclosures:

All authors have completed and submitted the ICMJE disclosures form.

The authors made the following disclosures:

M.B.P.: Consultant – Novartis. F.B.: Consultant –Abbvie, Alimera, Bayer, Boehringer-Ingelheim, Fidia Sooft, Hofmann La Roche, Novartis, Ntc Pharma, Oxurion Nv, SIFI. The remaining authors have no proprietary or commercial interest in any materials discussed in this article.

HUMAN SUBJECTS:

Human Subjects were used in this study. The research followed the Declaration of Helsinki and was approved by the ethics committee of San Raffaele Hospital (MIRD2020). Signed informed consent for the genetic testing and permission to use medical data for research purposes were obtained from all participants. No animal subjects were used in this study.

Author Contributions:

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Data collection: Bianco, Antropoli, Franca, Mauro, Pina, Farah, Basile

Analysis and interpretation: Bianco, Arrigo, Marchese, Aragona, Bandello, Parodi

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Abbreviations and Acronyms:
BCEA = bivariate contour ellipse area; **BCVA** = best-corrected visual acuity; **BVMD** = best vitelliform macular dystrophy; **CI** = confidence interval; **EFL** = estimated fovea location; **logMAr** = logarithm of the minimum angle of resolution; **MAIA** = microperimetry; **PRL** = preferred retinal locus; **SD** = standard deviation.

Keywords:
Best vitelliform macular dystrophy, BEST1, Fixation eccentricity, Fixation stability, Mircoperimetry.

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