Fundus Autofluorescence Findings in Eyes With Birdshot Chorioretinitis

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PURPOSE. The purpose of this study was to describe fundus autofluorescence (FAF) findings in eyes with birdshot chorioretinitis (BSCR) and to compare findings to demographic, medical, and clinical characteristics.

METHODS. In this multicenter, prospective, cross-sectional study, 172 eyes (86 patients) with BSCR were investigated. Participants underwent a standardized evaluation including collection of demographic data, ophthalmic and treatment history, and ophthalmologic examination. Using a standardized protocol, hypo- and hyperautofluorescence in macular and extramacular regions and specific patterns of abnormal FAF could be scored for 167 eyes. Images were scored by two independent, masked graders. Measures of visual function included best-corrected visual acuity (BCVA), contrast sensitivity (CS), color vision, and Humphrey visual field mean deviation (HVF-MD).

RESULTS. Any abnormal FAF finding was observed in 132 eyes (79.0%); macular abnormalities were observed in 84 eyes (49.1%). The most common findings were peripapillary confluent hypoautofluorescence (122 eyes [73.1%]); extramacular granular hypoautofluorescence (100 eyes [59.9%]); and macular granular hypoautofluorescence (67 eyes [40.1%]). Confluent hypoautofluorescence was related to longer median disease duration (8.7 years) than granular hypoautofluorescence (7.9 years) or hyperautofluorescence (5.6 years). Macular confluent hypoautofluorescence was associated with BCVA ≤20/25 (odds ratio [OR] = 7.83, P = 0.007), BCVA ≤20/50 (OR = 4.94, P = 0.002), and abnormal CS (OR = 4.56, P = 0.009). Presence of macular or extramacular hypoautofluorescence was related to HVF-MD ≤−3 dB (OR = 2.43, P = 0.01 and OR = 2.89, P = 0.003, respectively).

CONCLUSIONS. In this large cohort, various FAF abnormalities were found, indicating that disorders of the retinal pigment epithelium are features of BSCR. Abnormal FAF is a marker of visual dysfunction in the disease.

Keywords: birdshot chorioretinitis, fundus autofluorescence, retinal pigment epithelium

Birdshot chorioretinitis (BSCR), an autoimmune disease, affects the choroid, RPE, and retina. Imaging studies can identify ocular abnormalities in eyes with BSCR that are not apparent on clinical examination alone. In a study of 86 individuals with BSCR, we showed that enhanced depth imaging optical coherence tomography (EDI-OCT) could identify choroidal lesions that do not correspond to "birdshot lesions" and are not apparent on examination of the fundus.[1] In other studies, fundus autofluorescence (FAF) imaging was also able to show abnormalities not identified by clinical examination or other modalities.[2–4]

FAF identifies lipofuscin accumulation in the RPE and provides information about RPE structure and health. Unmasking of underlying RPE autofluorescence because of photoreceptor loss is an additional mechanism of hyperautofluorescence.[5,6] In eyes with BSCR, FAF imaging may demonstrate RPE atrophy not corresponding to hypopigmented birdshot lesions.[2,3]

Previous studies of FAF imaging and BSCR involved small numbers of individuals, and they were primarily descriptive, without extensive comparison to other disease features or visual function.[2–4] To expand our understanding of FAF in eyes with BSCR, we performed a prospective study of FAF findings in

4015

the same cohort of 86 individuals whose choroids were studied by EDI-OCT.[1] As in that study, we compared imaging findings to demographic and medical factors, clinical examination findings, and multiple measures of visual function. Findings may provide a better understanding of the spectrum of abnormalities associated with BSCR, suggest disease mechanisms, and identify features of the disease that should be monitored in future clinical studies.

METHODS

Study Population

We recruited patients with BSCR at the following five institutions for this prospective, cross-sectional study: University of California, Los Angeles (UCLA), Los Angeles, CA, USA; Johns Hopkins University, Baltimore, MD, USA; Northwestern University, Chicago, IL, USA; University of Utah, Salt Lake City, UT, USA; and Duke University, Durham, NC, USA. All study participants met criteria for the diagnosis of BSCR that were established by an international group of investigators.[7] Excluded were individuals with media opacities that precluded imaging. Also excluded from the original cohort were individuals with high myopia or hyperopia (spherical equivalent >6 diopters [D]), AMD, or diabetic retinopathy, as these conditions have been associated with choroidal abnormalities on EDI-OCT (the subject of our initial study[1]).[8–10] The study was approved by the institutional review boards at each clinical site, and written informed consent was obtained from each study participant. The study adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

A detailed description of the cohort, data collection, and study methods has been published.[1] Briefly, all study participants underwent a standardized clinical examination, including a series of visual function tests and imaging studies on a single day. In addition, a questionnaire was administered at the study visit to determine the presence or absence of eight prospectively defined visual symptoms in each eye (blurry vision, floaters, nyctalopia, poor contrast, abnormal color vision, vibrating vision, metamorphopsia, and decreased peripheral vision).[11]

Four measures of visual function were determined for each eye. Best-corrected visual acuity (BCVA) was assessed using Early Treatment of Diabetic Retinopathy Study (ETDRS) charts, with manifest refraction. Color vision was assessed with the Lanthony desaturated 15-hue color test[12] and the confusion index (C-index), as described by Vingrys and King-Smith,[13] was determined for each eye by entering study participant responses into a web-based application available at http://www.torok.info/colorvision/d15.htm (provided in the public domain). The minimum possible score for C-index is 0.96, with higher C-index values indicating poorer color vision; C-index values of 1.78 or higher were considered abnormal. Contrast sensitivity (CS) was measured using Pelli-Robson charts.[14,15] The log of the CS measurement (logCS) was calculated and used for analyses; logCS values <1.5 were considered abnormal, as previously described.[16] Automated perimetry was performed using the 24-2 threshold program of the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA). Mean deviation (HVF-MD) scores were used in analyses; values of −3.0 dB or less were considered abnormal.[17,18]

The following ophthalmologic variables were recorded: intraocular pressure (IOP) determined by applanation tonometry; anterior chamber cells by slit-lamp biomicroscopy (categorized according to Standardization of Uveitis Nomenclature [SUN] Working Group recommendations[19]); vitreous inflammatory reactions (cells and haze, as described by
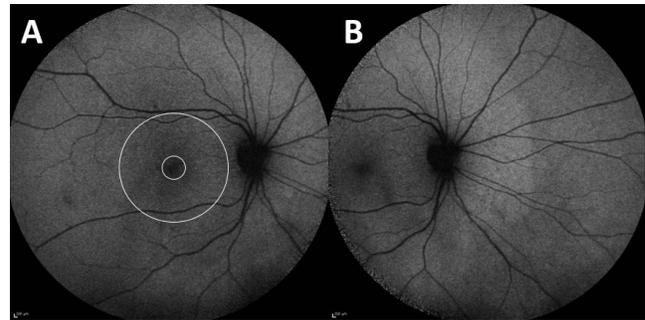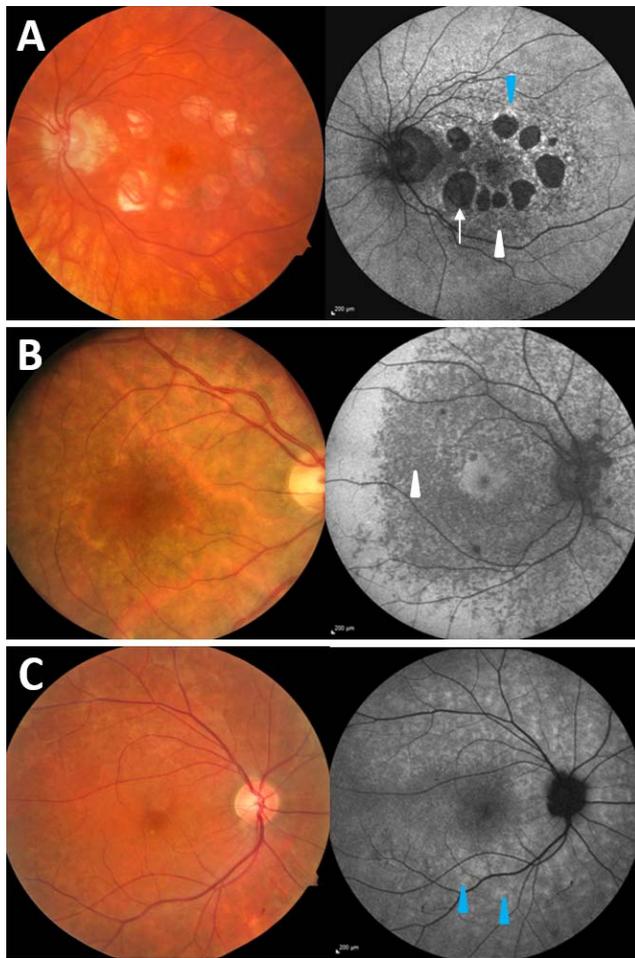

FIGURE 1. Normal fundus autofluorescence images showing protocol settings. A fovea-centered image (A) shows areas of analysis, including foveal region (inside the central [inner] circle); pericentral-macular ring (between the inner and outer circles); and extramacular area (outside the outer circle); for purposes of analyses, the macular region included the combined areas of the pericentral-macular ring and the central circle. A optic disc–centered image (B) allowed analysis of the peripapillary region of the fundus. Findings on the optic disc–centered image were included in all analyses of the extramacular region.

Nussenblatt et al.[20]); and fundus findings, including the presence or absence of cystoid macular edema (CME) and the presence or absence of retinal vasculitis. Information about treatment with corticosteroids and immunomodulatory agents (methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, infliximab, and adalimumab) was recorded, as described previously.[1] For study purposes, active disease was defined as a vitreous haze score of ≥0.5+. Presence of CME was confirmed with OCT.

Image Acquisition Protocol and Image Evaluation

Autofluorescence was acquired with a standardized protocol using the Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) system, set at 55° with a minimal automatic real time (ART) setting of 30. Included were a fovea-centered FAF image and an optic disc-centered FAF image (Fig. 1). Two authors (CB and RFS), masked to clinical data, graded the presence of autofluorescence abnormalities. Areas of hypoautofluorescence were classified as being either confluent or granular (Fig. 2). Confluent hypoautofluorescence was defined as a round or oval area of absent autofluorescence larger than 0.5 mm in largest linear diameter; granular hypoautofluorescence was defined as a round or oval area of decreased, nonhomogeneous autofluorescence, compared with normal surrounding areas, that was greater than 0.5 mm in largest linear diameter. All areas of hyperautofluorescence greater than 0.5 mm in greatest diameter had a granular appearance. Isolated FAF abnormalities smaller than 0.5 mm in diameter were considered to be not clinically relevant and were not recorded. For the purposes of these analyses, global hypo- and hyperautofluorescence were defined as the presence of any hypo- and hyperautofluorescence, respectively, located in macular or extramacular locations. For each eye, disagreement between the two readers were adjudicated before recording of data.

During evaluation of the fovea-centered image, the ETDRS macular grid was used to identify three areas: within the central 1-mm circle (termed central circle), between the 1- and 6-mm circle (termed pericentral-macular ring), and extramacular (outside the 6-mm circle, including both the macular and disc-centered scans). Hypo- and hyperautofluorescence were graded separately for each area. For purposes of analysis, the macula was the combined areas of the pericentral-macular ring and the central circle.
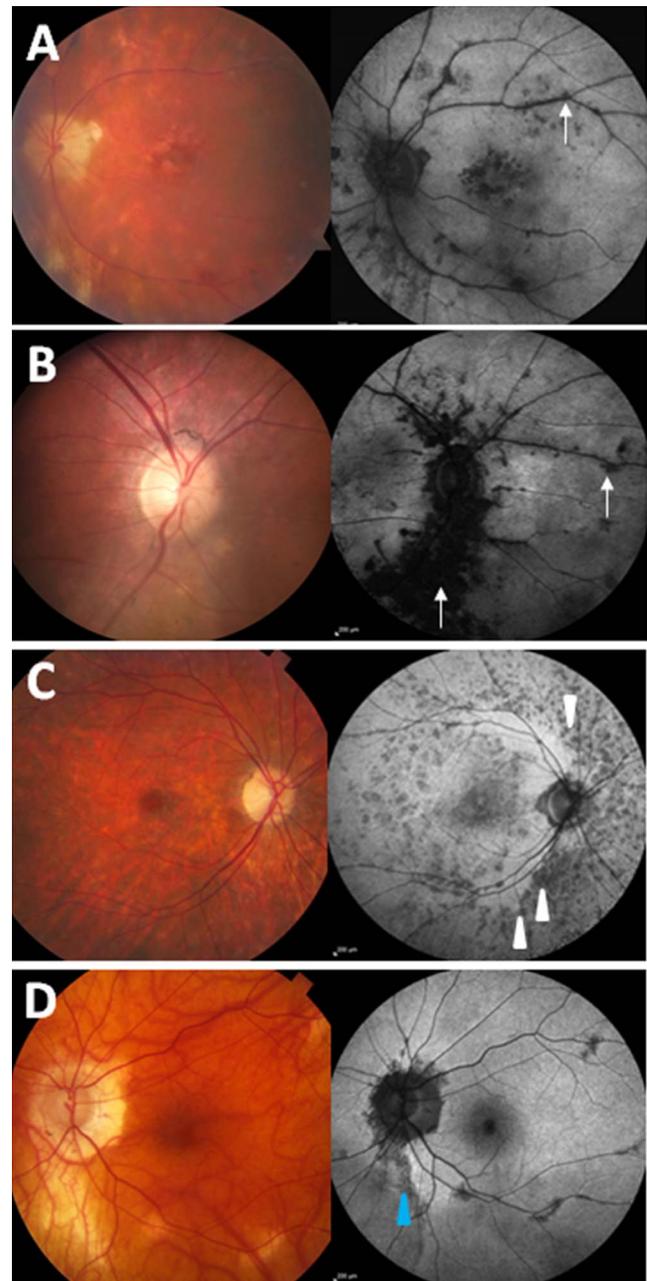
FIGURE 2. Fundus photographs and autofluorescence images of eyes with BSCR. (**A**) Example of combined confluent (*arrow*) and granular hypoautofluorescence (*white arrowhead*); note that there is also subtle granular hyperautofluorescence (*blue arrowhead*). (**B**) Example of extensive granular hypoautofluorescence (*white arrowhead*) with foveal sparing; the fundus photograph of the same eye shows only subtle pigmentary changes in the posterior pole. (**C**) Example of granular hyperautofluorescence (*blue arrowheads*); the fundus photograph of the same eye does not show obvious abnormalities.

The graders also identified the presence or absence of multiple patterns of FAF that have been described previously.[2,3,21] When confluent hypoautofluorescence existed in the area within 1 disc diameter from the optic disc, it was categorized as the pattern of peripapillary confluent hypoautofluorescence. The perivascular pattern (Fig. 3) was a distribution of hypo- or hyperautofluorescence that followed the retinal vessels. A descending tract (Fig. 3) was a downward leading swathe of hypoautofluorescence originating from the posterior pole to extend below the level of the inferior arcade, as described previously.[21] We also identified an additional distinct pattern, not described previously, but present in many participant eyes with BSCR that we termed the arcuate pattern (Fig. 3); it was characterized by a curved distribution of hypoautofluorescence that was present superior and inferior to the disc and that was typically sharply delineated.

Data Analyses and Statistical Techniques

Characteristics and patterns of FAF findings were quantified, and relationships between various characteristics were inves-

FIGURE 3. Fundus photographs and autofluorescence images showing fundus autofluorescence patterns in eyes with BSCR. (**A**, **B**) Examples of the perivascular pattern. Note in **A** that the hypoautofluorescent dots are distributed along the retinal vessels (*arrow*). Note in **B** that the hypoautofluorescent dots are distributed along both larger and smaller retinal vessels (*arrows*). (**C**) Example of the arcuate pattern; hypoautofluorescence is present in a curved distribution superior and inferior to the disc, whereas unaffected RPE is sharply delineated (*white arrowheads*). (**D**) Example of the descending tract pattern; the downward leading swathe of decreased autofluorescence originates from the posterior pole and extends below the level of the inferior arcade (*blue arrowhead*). All examples also exhibit confluent peripapillary hypoautofluorescence, a very frequent finding in eyes with BSCR.

tigated. FAF findings were compared with demographics, disease duration, treatment, signs of intraocular inflammation on clinical examination, and findings on EDI-OCT. Percentages were calculated for categorical variables. Means with SDs and

median values with interquartile range (IQR) were calculated for continuous variables. The associations between FAF findings and clinical data were evaluated using logistic regression, and odds ratios (ORs) were reported. Both crude and adjusted ORs were calculated using logistic regression models that incorporated generalizations of generalized estimating equations to account for any correlation between eyes of an individual patient.[22] *P* values for all analyses were nominal, with a value of <0.05 considered statistically significant. All statistical analyses were performed with Intercooled Stata SE 12.0 (Stata Corp LP, College Station, TX, USA).

Analyses involving choroidal findings for this cohort have been published previously.[1] Evaluation of retinal OCT image findings will be reported in a subsequent publication.

RESULTS

Included in the study were 172 affected eyes of 86 individuals with BSCR. Study design and demographic, medical, and clinical data for the cohort were described in a previous publication.[1] Briefly, median age of participants was 56 years (IQR, 51–64 years); 54 (63%) were female; and each of 83 participants tested were HLA-A29 positive. Median disease duration was 5 years. Disease was active (≥0.5+ vitreous haze) in 50 (29%) eyes, and CME was present in 38 (22%) eyes at the study visit. Median BCVA at the study visit was 20/25. Median logCS was 1.5 (IQR, 1.35–1.65); 51 eyes (35%) had abnormal CS. Median color index was 2.4; 70 eyes (69%) had abnormal color vision results. Median HVF-MD was −3.5 dB (IQR, −9.4 to −1.8 dB); 79 eyes (55%) had an abnormal visual field result. BCVA was 20/20 or better in 74 (42%) eyes; among these eyes, 40 (54%) had abnormal color vision, 17 (23%) had abnormal HVF-MD, and 7 (10%) had abnormal CS.[1]

FAF images were missing for 5 eyes (five study participants), leaving 167 eyes for analysis. An abnormal FAF finding was observed in 132 eyes (79.0%); macular abnormalities were observed in 82 eyes (49.1%). Table 1 summarizes FAF findings by pattern and region. Four patterns were identified: perivascular, arcuate, descending tract, and peripapillary confluent hypoautofluorescence. The most common findings were confluent peripapillary hypoautofluorescence (122 eyes [73.1%]), extramacular granular hypoautofluorescence (100 eyes [59.9%]), and macular granular hypoautofluorescence (67 eyes [40.1%]). In the central circle, 6 (3.6%) eyes of 4 study participants had confluent hypoautofluorescence and 22 (13.2%) eyes of 15 study participants had granular hypoautofluorescence, but no eyes had hyperautofluorescence in this region. The proportion of eyes having each type of FAF abnormality increased as regions became more peripheral (i.e., from central circle to pericentral-macular ring to extramacular regions); however, specifically with regard to confluent hypoautofluorescence, the effect was small, and the trend was not statistically significant.

Of 82 eyes with any FAF abnormality in the macula, 76 (92.5%) also had extramacular FAF abnormalities. There were 77 (46.1%) eyes with hyperautofluorescence in any anatomic location (global hyperautofluorescence) and 132 (79.0%) eyes with hypoautofluorescence in any anatomic location (global hypoautofluorescence). FAF findings were asymmetric between eyes of many study participants; 51 (30.5%) eyes of 34 patients (39.5%) had normal FAF images in at least one eye. FAF images were normal in both eyes of 20 (23.2%) study participants.

Table 2 summarizes relationships between demographic and treatment variables and FAF findings. Increasing age and duration of disease were significantly associated with the

TABLE 1. Fundus Autofluorescence Findings for 167 Eyes of 86 Individuals With BSCR

Autofluorescence Finding	Study Participants*, *n* = 86	Eyes, *n* = 167
Patterns, *n* (percentage)		
Perivascular pattern	30 (34.9%)	48 (28.4%)
Arcuate pattern	26 (30.2%)	44 (26.4%)
Descending tracts	16 (18.5%)	25 (14.8%)
Peripapillary confluent hypoautofluorescence	66 (76.7%)	122 (73.1%)
Areas, *n* (percentage)		
Central circle†		
Normal autofluorescence	80 (93.0%)	143 (85.6%)
Confluent hypoautofluorescence	4 (4.7%)	6 (3.6%)
Granular hypoautofluorescence	15 (17.4%)	22 (13.2%)
Granular hyperautofluorescence	0	0
Pericentral-macular ring‡		
Normal autofluorescence	56 (65.1%)	85 (50.9%)
Confluent hypoautofluorescence	14 (16.3%)	19 (11.4%)
Granular hypoautofluorescence	42 (48.8%)	67 (40.1%)
Granular hyperautofluorescence	16 (18.6%)	23 (13.8%)
Extramacular region§		
Normal autofluorescence	32 (37.2%)	55 (32.9%)
Confluent hypoautofluorescence	24 (27.9%)	33 (19.8%)
Granular hypoautofluorescence	56 (65.1%)	100 (59.9%)
Granular hyperautofluorescence	30 (34.9%)	46 (27.5%)

* Participants with findings in at least one eye.

† Central Circle was defined as the area within 1 mm of the geometric center of the fovea.

‡ The pericentral-macular ring was defined as the area extending from the outer border of the central circle to 3 mm from the geometric center of the fovea.

§ The extramacular region was defined as the area peripheral to the pericentral-macular ring (greater than 3 mm from the geometric center of the fovea) and captured on the fovea-centered fundus autofluorescence image and the area captured on the disc-centered fundus autofluorescence image.

presence of global hypoautofluorescence and with the presence of peripapillary confluent hypoautofluorescence. Study participants with confluent hypoautofluorescence had longer disease duration (median, 8.7 years) than patients with granular hypoautofluorescence (median, 7.9 years) or those with granular hyperautofluorescence (median, 5.6 years). Those with normal autofluorescence in both eyes had the shortest duration of disease (median, 2.3 years; *P* for trend < 0.001). Study participants using systemic corticosteroids at the study visit were more likely to have global hypoautofluorescence (OR = 2.37, *P* = 0.009); those receiving immunomodulatory therapy had lower odds of having FAF abnormalities in general, but none of the associations achieved statistical significance. Multivariable analyses controlling for demographic characteristics and signs of intraocular inflammation did not reveal statistically significant associations between immunomodulatory therapy and FAF abnormalities, with one exception: it was associated with a lower odds of having the descending tract pattern (OR = 0.30, *P* = 0.02).

Table 3 summarizes relationships between signs of intraocular inflammation and FAF findings. Presence of retinal vasculitis was associated with peripapillary confluent hypoautofluorescence (OR = 4.30, *P* < 0.001), and macular edema was associated with global hypoautofluorescence (OR = 5.26, *P* < 0.001). Although vitreous haze was not significantly

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TABLE 2. Relationships Between Demographic and Medical Factors and FAF Findings Categorized by Global Findings and Patterns of Autofluorescence for 86 Individuals (167 Evaluable Eyes) With BSCR

| | | | | | Patterns | | | | | | | |
| Demographic and Medical Factors | Global Hypoautofluorescence | | Global Hyperautofluorescence | | Perivascular | | Peripapillary Confluent Hypoautofluorescence | | Arcuate | | Descending Tract | |
	OR	P Value	OR	P Value	OR	P Value	OR	P Value	OR	P Value	OR	P Value
Age, per year	1.08	0.001	1.02	0.19	1.01	0.68	1.08	<0.001	1.03	0.13	1.01	0.78
Disease duration,* per year	1.46	<0.001	1.04	0.22	1.03	0.28	1.19	<0.001	1.03	0.42	1.03	0.43
Sex, male vs. female	0.61	0.21	0.65	0.18	0.35	0.009	0.72	0.35	0.57	0.14	2.04	0.10
Refractive error, per +1.0 D	0.91	0.44	1.29	0.02	1.29	0.03	0.87	0.23	1.39	0.01	1.00	0.97
Current treatment												
IMT	0.86	0.71	0.99	0.99	0.87	0.70	0.64	0.26	0.48	0.05	0.42	0.05
Systemic corticosteroids	2.37	0.009	1.56	0.09	1.28	0.38	1.44	0.21	1.51	0.16	2.02	0.06

* Based on the interval since onset of disease-associated symptoms. IMT, immunomodulatory therapy.

TABLE 3. Relationships Between Measures of Intraocular Inflammation and FAF Findings Categorized by Global Findings and Patterns of Autofluorescence for 167 Eyes of 86 Individuals With BSCR

| | | | | | Patterns | | | | | | | |
| Measure of Intraocular Inflamamtion | Global Hypoautofluorescence | | Global Hyperautofluorescence | | Perivascular | | Peripapillary Confluent Hypoautofluorescence | | Arcuate | | Descending Tract | |
	OR	P Value	OR	P Value	OR	P Value	OR	P Value	OR	P Value	OR	P Value
Retinal vasculitis, present vs. absent	1.03	0.95	1.36	0.32	1.50	0.24	4.30	<0.001	1.73	0.12	2.04	0.11
Macular edema, present vs. absent	5.26	<0.001	1.64	0.20	0.28	0.09	0.72	0.43	0.54	0.20	0.99	0.99
Vitreous reactions												
Haze, ≥0.5+ vs. none	1.09	0.84	1.11	0.75	1.09	0.81	1.45	0.35	1.50	0.28	0.72	0.51
Cells, ≥0.5+ vs. none	1.29	0.57	2.14	0.04	1.93	0.07	2.30	0.08	3.41	0.003	2.24	0.04

associated with any FAF abnormalities, the presence of vitreous cells (≥0.5+) was associated with global hyperautofluorescence (OR = 2.14, *P* = 0.04) and the arcuate (OR = 3.41, *P* = 0.003) and descending tract (OR = 2.24, *P* = 0.04) patterns. Associations between vitreous cells and perivascular (OR = 1.93, *P* = 0.07) and peripapillary confluent hypoautofluorescence (OR = 2.30, *P* = 0.08) patterns were of borderline significance. Multivariable analyses controlling for demographic and treatment variables yielded similar results (data not shown).

Comparisons between the choroidal findings described in our previous publication about this cohort,[1] and current FAF findings revealed only that thin choroids were associated with the presence of global hypoautofluorescence (*P* = 0.002) and peripapillary confluent hypoautofluorescence (*P* < 0.001). Macular choroidal lesions were not significantly related to macular FAF abnormalities (*P* > 0.05 for all comparisons).

Tables 4 and 5 summarize relationships between measures of visual function (including visual symptoms) and FAF findings (global FAF abnormalities and patterns in Table 4; FAF abnormalities by region in Table 5). BCVA worse than 20/20 was significantly associated with global hyperautofluorescence and the perivascular pattern, but these associations were not significant for the subpopulations of eyes with visual impairment (BCVA of 20/50 or worse) or blindness (BCVA of 20/200 or worse). Abnormal CS was associated with global hypoautofluorescence (OR = 3.20, *P* = 0.02), peripapillary confluent hypoautofluorescence (OR = 2.31, *P* = 0.04), and the descending tract pattern (OR = 4.08, *P* = 0.006). Abnormal visual field (HVF-MD <−3 dB) was associated with global hypoautofluorescence, global hyperautofluorescence, and the perivascular, the peripapillary confluent hypoautofluorescence, and the arcuate patterns (Table 4). The arcuate pattern was also associated with increased odds of abnormal color vision (C-index ≥ 1.78) and abnormal CS (logCS < 1.5), but each of its associations were of borderline significance (*P* values of 0.05–0.06). In general, visual symptoms were more tightly related to FAF abnormalities than other measures of visual function, particularly the symptoms of poor color vision, poor contrast, nyctalopia, and poor peripheral vision. Hypoautofluorescence was associated with a greater number of visual symptoms than were other FAF abnormalities.

As shown in Table 5, macular hypoautofluorescence, but not hyperautofluorescence, was associated with BCVA ≤20/25 and with visual impairment (20/50 or worse); extramacular hypoautofluorescence was not associated with BCVA. Abnormal CS and abnormal visual field were each associated with both macular and extramacular hypoautofluorescence. Abnormal color vision was associated only with macular hypoautofluorescence. The symptoms of abnormal color vision and poor contrast were each also associated with both macular and extramacular hypoautofluorescence, although some of the associations were weak. Controlling for demographic factors, treatment, and intraocular inflammation did not alter any of the statistically significant associations between vision and the FAF findings listed in Table 5 (data not shown).

In contrast to the relationships seen with other symptoms, there were significantly reduced odds of having vibrating vision in the presence of several FAF abnormalities (Tables 4 and 5). We also found a negative relationship between the symptom of vibrating vision and duration of disease; those with vibrating vision had a median duration of 2.6 years, whereas those without the symptom had a median duration of 6.5 years (*P* = 0.0001).

DISCUSSION

FAF imaging has been used to study a variety of inflammatory eye diseases, including multifocal choroiditis and panuveitis syndrome, punctate inner choroidopathy, serpiginous choroiditis, multiple evanescent white dot syndrome, and Vogt-Koyanagi-Harada disease.[23-37] In many conditions, FAF imaging reveals areas of disease activity that are more widespread than would be suspected by other imaging techniques or by clinical investigation, suggesting its potential value in the clinical assessment of patients with these disorders.

With our large cohort, we confirmed that FAF abnormalities are also widespread in eyes with BSCR. Peripapillary findings are most common, consistent with the fact that clinical birdshot lesions are most prevalent in the peripapillary area.[7] A variety of FAF characteristics and patterns of FAF abnormalities were seen in our cohort, and many were found to be statistically related to other disease-related factors, including intraocular inflammatory signs and measures of vision. No single FAF finding was dominant in these relationships, and further assessment, including longitudinal studies, will be required to determine the clinical relevance of specific FAF characteristics and patterns.

The most frequent FAF finding was peripapillary confluent hypoautofluorescence, present in 122 (73%) eyes. Approximately half of eyes had abnormal macular FAF. Overall, these observations are consistent with smaller and mostly retrospective studies of FAF in eyes with BSCR.[2-4,38,39] Peripapillary hypoautofluorescence was strongly related with age and disease duration. Global hypoautofluorescence (i.e., present in both the macula and extramacular region) was associated longer disease duration (OR = 1.46, *P* < 0.001) and presence of macular edema (OR = 5.26, *P* < 0.001), suggesting that hypoautofluorescence may be a marker for chronicity and severity of BSCR.

We also categorized hypoautofluorescence by type (granular versus confluent) and anatomic location (macula versus extramacular region) for additional, in-depth analyses. The granular form seems to reflect a preconfluent loss of RPE cells that can be observed before the development of confluent cell loss, as has been described in other retinal disease.[21,24] In support of this assumption was the observation that study participants with granular hypoautofluorescence had shorter disease duration than those with confluent hypoautofluorescence. In addition to progression from granular to confluent hypoautofluorescence, there was a suggestion of centripetal progression of confluence toward the central macula.

In contrast to hypoautofluorescence, the clinical relevance of hyperautofluorescence is less clear. In general, our data did not demonstrate strong associations with hyperautofluorescence, although we did find it to be significantly related to selected factors, including vitreous cells (OR = 2.14, *P* = 0.04) and some measures of vision, most notably abnormal visual field (both abnormal HVF-MD and the symptom of poor peripheral vision). Increased autofluorescence can be seen with RPE dysfunction. Lipofuscin has been shown to accumulate in experimental models of autoimmune uveitis, and oxidative damage to various ocular tissues seems to play a role in uveitic diseases.[23,40,41] Taken together, the visualization of lipofuscin accumulation in the RPE may reflect disease activity, especially in the early stages. Alternatively, hyperautofluorescence may indicate unmasking of underlying RPE autofluorescence by photoreceptor loss, and may indicate an earlier form of visual dysfunction.

With regard to specific patterns of abnormal FAF, Koizumi et al.[2] described linear hypoautofluorescent streaks along the retinal vessels in eyes with BSCR, and we observed a similar perivascular pattern in over one-third of study participants.

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TABLE 4. Relationships Between Measures of Vision and FAF Findings Categorized by Global Findings and Patterns of Autofluorescence for 167 Eyes of 86 Individuals With BSCR

| | Global Hypoautofluorescence | | Global Hyperautofluorescence | | Patterns | | | | | | | |
| | | | | | Perivascular | | Peripapillary Confluent Hypoautofluorescence | | Arcuate | | Descending Tract | |
Visual Function	OR	P Value	OR	P Value	OR	P Value	OR	P Value	OR	P Value	OR	P Value
BCVA												
Abnormal*	1.71	0.16	1.94	0.04	2.09	0.04	1.70	0.13	1.98	0.07	1.80	0.20
Visual impairment†	3.86	0.08	1.57	0.28	1.91	0.14	1.76	0.29	1.50	0.37	1.32	0.62
Blindness‡	1.06	0.96	1.78	0.53	0.61	0.66	1.49	0.72	0.69	0.74	1.16	0.90
Abnormal contrast sensitivity§	3.20	0.02	1.81	0.09	1.74	0.15	2.31	0.04	2.20	0.05	4.08	0.006
Abnormal color vision‖	1.43	0.48	2.18	0.09	1.20	0.70	1.53	0.37	3.42	0.06	1.77	0.41
Abnormal visual field¶	4.36	0.001	3.23	0.001	3.20	0.005	3.21	0.002	2.26	0.05	1.17	0.75
Symptoms												
Blurry vision	1.32	0.46	1.37	0.32	0.76	0.43	1.08	0.83	1.28	0.48	1.75	0.22
Poor color vision	2.66	0.02	2.69	0.002	1.93	0.06	1.45	0.29	1.97	0.06	1.93	0.14
Poor contrast	8.53	0.004	1.68	0.14	1.86	0.09	3.29	0.01	1.70	0.16	0.61	0.35
Floaters	0.92	0.84	0.90	0.75	0.80	0.54	0.69	0.35	0.58	0.14	1.13	0.80
Nyctalopia	3.16	0.007	2.20	0.01	1.35	0.38	2.44	0.02	1.35	0.39	0.90	0.82
Vibrating vision	0.50	0.08	0.72	0.36	1.07	0.85	0.54	0.10	1.27	0.53	0.43	0.14
Metamorphopsia	1.81	0.30	1.84	0.14	1.14	0.76	1.96	0.20	1.32	0.53	0.91	0.87
Poor peripheral vision	1.71	0.21	2.71	0.003	2.21	0.02	1.25	0.55	2.12	0.04	1.33	0.52

* Abnormal vision was defined as BCVA of 20/25 or worse.
† Visual impairment was defined as BCVA of 20/50 or worse.
‡ Blindness was defined as BCVA of 20/200 or worse.
§ Abnormal CS was defined as logCS values <1.5, as described by Shah et al.[16]
‖ Color vision was determined with the Lanthony desaturated 15-hue color test[12] and abnormal color vision was defined as a confusion index (C-index) of 1.78 or higher, as described by Vingrys and King-Smith.[13]
¶ Abnormal visual field was defined as a mean deviation score of −3.0 dB or less.

Investigative Ophthalmology & Visual Science

TABLE 5. Relationships Between Measures of Vision and FAF Findings Categorized by Region of the Fundus for 167 Eyes of 86 Individuals With BSCR

| | Macular* | | | | | | | | Extramacular† | |
| | Any Hypoautofluorescence | | Confluent Hypoautofluorescence | | Granular Hypoautofluorescence | | Hyperautofluorescence | | Hypoautofluorescence | |
Visual Function	OR	P Value	OR	P Value	OR	P Value	OR	P Value	OR	P Value
BCVA										
Abnormal‡	2.13	0.02	7.83	0.007	1.72	0.09	1.93	0.17	1.66	0.12
Visual impairment§	3.18	0.009	4.94	0.002	2.54	0.03	1.54	0.44	2.33	0.09
Blindness||	5.53	0.13	2.00	0.54	2.30	0.37	ND	ND	2.42	0.44
Abnormal contrast sensitivity¶	2.30	0.02	4.56	0.009	1.74	0.13	0.68	0.45	2.77	0.008
Abnormal color vision#	2.68	0.04	5.50	0.11	2.11	0.13	ND	ND	2.28	0.06
Abnormal visual field**	2.43	0.01	2.46	0.14	2.14	0.04	1.53	0.37	2.89	0.003
Symptoms										
Blurry vision	0.67	0.21	0.65	0.38	0.59	0.10	2.40	0.08	1.14	0.68
Poor color vision	1.70	0.09	1.66	0.30	1.60	0.14	3.02	0.02	2.32	0.01
Poor contrast	2.25	0.02	1.20	0.72	1.87	0.07	1.44	0.45	2.42	0.02
Floaters	0.53	0.06	0.70	0.49	0.63	0.18	1.64	0.36	0.93	0.84
Nyctalopia	1.26	0.46	2.77	0.05	1.19	0.59	6.84	0.001	1.36	0.34
Vibrating vision	0.34	0.005	0.27	0.09	0.35	0.007	0.21	0.04	0.44	0.02
Metamorphopsia	2.14	0.07	2.51	0.09	2.10	0.07	0.41	0.25	2.08	0.12
Poor peripheral vision	1.24	0.51	1.11	0.84	1.08	0.81	1.00	0.99	1.50	0.24

ND, not determined.

* The macular region included the area within 6 mm from the geometric center of the fovea (central circle and pericentral-macular ring on the fovea-centered FAF image).

† The extramacular region included the area captured peripheral to the pericentral macular ring (greater than 6mm from the geometric center of the fovea) on the fovea-centered FAF image and the area captured on the disc-centered FAF image.

‡ Abnormal vision was defined as BCVA of 20/25 or worse.

§ Visual impairment was defined as BCVA of 20/50 or worse.

|| Blindness was defined as BCVA of 20/200 or worse.

¶ Abnormal CS was defined as logCS values <1.5, as described by Shah et al.[16]

Color vision was determined with the Lanthony desaturated 15-hue color test[12] and abnormal color vision was defined as a confusion index (C-index) of 1.78 or higher, as described by Vingrys and King-Smith.[13]

** Abnormal visual field was defined as a mean deviation score of −3.0 dB or less.

Women had a significantly higher risk of having this pattern of FAF. As pointed out by Koizumi et al.,[2] the perivascular pattern is intriguing because major retinal vessels are located in the superficial retina, far above the RPE. RPE dysfunction below retinal vessels suggests a role for the retinal vasculature in disease pathogenesis. Sheathing of retinal vessels is a well-known, but not universal, finding in eyes with BSCR. Retinal vascular sheathing was not significantly associated with the perivascular pattern (Table 3); FAF imaging may be a more sensitive tool for monitoring vascular involvement in future studies of BSCR.

We also observed abnormal hypoautofluorescence in an arcuate pattern at the posterior pole. In contrast to the perivascular pattern, hypoautofluorescence in this pattern was not necessarily in proximity to retinal vessels. This presentation has not been described previously as a specific FAF pattern, but it was a frequent finding in our cohort (30% of study participants; 26% of affected eyes). This arcuate pattern was related to vitreous cells and to abnormalities in several measures of visual function. Also, study participants who were on immunomodulatory therapy had a lower risk for the arcuate pattern. These associations suggest the importance of this previous unreported pattern as a manifestation of BSCR.

Some eyes exhibited abnormal autofluorescence in a descending tract pattern, as has been observed in patients with central serous chorioretinopathy (CSC).[21,42,43] Study participants on immunomodulatory therapy had a lower risk of the descending tract pattern, whereas those on systemic corticosteroids had a higher risk. Corticosteroids have been identified as a risk factor for CSC, which raises the possibility of a common pathogenetic mechanism that could be investigated.

Although both choroidal findings, as reported in our previous publication about this cohort,[1] and FAF abnormalities were related to signs of intraocular inflammation, we did not find evidence of substantial, direct relationships between the choroid and RPE in eyes with BSCR. This observation suggests that the two sites may be affected independently during the course of disease by different mechanisms, and thus, it may be important to monitor each.

Unlike choroidal findings, various FAF abnormalities were related to vision, as mentioned above. The strongest relationships were found between hypoautofluorescence and abnormalities in BCVA, CS, and visual field. As shown in Table 5, although both granular and confluent hypoautofluorescence were associated with abnormal vision and visual symptoms, confluent hypoautofluorescence had overall the greatest risk of abnormal BCVA, visual impairment, and abnormal CS. As would be expected, BCVA, a central visual function, was associated only with macular FAF findings. The relationship between macular hypoautofluorescence and reduced BCVA is consistent with findings in eight individuals with BSCR reported by Koizumi et al.[2] Piffer et al.[38] studied 39 individuals with BSCR and also found that macular hypoautofluorescence was linked to worse visual acuity, but in contrast to our study, it was not affected by disease duration. The agreement between Goldmann visual field (GVF) and autofluorescence was analyzed in five individuals with BSCR by Jack et al.[4] they found a relatively small overlap, suggesting that GVF is insensitive to anatomic RPE loss. Our data in a larger cohort found several relationships between FAF findings and visual field, using the automated Humphrey Field Analyzer. We recognize that relationships between RPE and vision may be influenced by retinal abnormalities associated with BSCR. The relationships between RPE, retina, and vision will be explored together in a future publication about this cohort.

Many clinicians recognize "vibrating vision" (a sensation that the visual image is shaking) as a typical, albeit inconsistent, symptom of BSCR. In contrast to the positive associations between many other symptoms and FAF abnormalities, the odds of having vibrating vision were significantly lower in relation to FAF findings. It is possible that advanced disease, as reflected by FAF abnormalities, damages those tissues or processes responsible for vibrating vision, or masks the symptom by compromising other visual functions necessary to perceive it.

There are limitations to this study. As with any cross-sectional analysis, we could not establish causality or temporal relationships between autofluorescence findings and clinical characteristics. Data were collected from different sites, using different equipment, but images were acquired with a well-defined, standardized protocol and were evaluated by two readers independently. The autofluorescence systems used for this study have no internal reference standards, which limits the interpretation of the obtained FAF signal. Newer FAF systems will provide quantitated AF, which improves the determination of the signal. Our study definition of activity was based on vitreous haze, which was not statistically associated with any FAF finding; in contrast, the presence of vitreous cells ≥0.5+ was weakly related to several FAF patterns (Table 3). The presence of cells may be a more sensitive predictor of RPE damage than haze in people with BSCR. Furthermore, signs of intraocular inflammation may not reflect all disease activity at the tissue level. Therapeutic indications for treatment could have biased relationships between clinical findings and treatment. Because our institutions are all tertiary referral centers, study participants may not be representative of all individuals with BSCR.

Our study raises several issues that should be pursued in future studies. The fact that there are statistical relationships between FAF findings and signs of intraocular inflammation and between FAF findings and visual function suggests that FAF findings might be a marker that could help to guide treatment. Such a determination will require a longitudinal study. The possibility of direct drug effects on the RPE and FAF findings should also be considered. Quantification of FAF signals, as mentioned above, may provide additional information about relationships. In addition, possible relationships between the retinal vasculature and RPE can be explored further with additional testing techniques (angiography, electrophysiologic studies).

In conclusion, a number FAF abnormalities are widespread in eyes with BSCR, and the relationship between these abnormalities and intraocular inflammation suggests that the RPE has a role in disease pathophysiology. Our study has also shown that FAF abnormalities are markers of vision dysfunction. Although cross-sectional studies cannot confirm cause and effect relationships, we found some evidence to support the assumption that FAF abnormalities progress from granular hypoautofluorescence to confluent hypoautofluorescence and possibly that disease progresses centripetally toward the fovea, raising the possibility that FAF imaging can be used clinically to monitor patients for disease progression during treatment.

Investigative Ophthalmology & Visual Science

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