

# Visual Acuity in Birdshot Retinochoroidopathy Evaluation



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- **PURPOSE:** To determine the statistical correlation between visual acuity (VA) and various quantitative parameters relevant to birdshot retinochoroidopathy (BRC) evaluation.
- **DESIGN:** Hospital-based retrospective observational study.
- **METHODS:** SETTING: Institutional. STUDY POPULATION: Consecutive HLA29+ BRC patients were included between May and August 2013 at a single tertiary center (Pitié-Salpêtrière Hospital, Paris). OBSERVATION PROCEDURES: Demographic data and quantitative parameters relevant to BRC at baseline were collected: VA, degree of anterior and posterior inflammatory reaction, foveal thickness measured by optical coherence tomography (OCT), Arden ratio, and electrooculography (EOG) light peak. MAIN OUTCOME MEASURES: Correlation between VA and the other parameters of the ipsilateral and fellow eye was performed using Spearman rank correlation coefficients.
- **RESULTS:** Fifty-five patients were included. Mean VA was 6/9.5 in the right eye (OD) and 6/12 in the left eye (OS). Mean foveal thickness was 240  $\mu\text{m}$  OD (range: 112–606) and 251  $\mu\text{m}$  OS (range: 85–662). Mean Arden ratio was 159% OD and 160% OS. EOG light peak was 714 mV OD (range: 316–1379) and 746 mV OS (range: 272–1652). VA of a given eye was moderately correlated with VA of the contralateral eye ( $r = 0.4$ ). On the contrary, all other parameters showed a strong correlation between both eyes (all  $r > 0.7$ ,  $P < .01$ ). Overall, none of the studied parameters was correlated with its VA (all  $r < 0.5$ ).
- **CONCLUSION:** In BRC, visual acuity alone does not seem to fully reflect the disease severity in terms of clinical or ancillary quantitative findings at baseline. (Am J Ophthalmol 2015;160(4):817–821. © 2015 by Elsevier Inc. All rights reserved.)

Accepted for publication Jul 4, 2015.

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**B**IRDSHOT RETINOCHOROIDOPATHY (BRC) IS A chronic bilateral posterior form of autoimmune uveitis, characterized by the presence of distinctive hypopigmented choroidal lesions.<sup>1–4</sup> Although BRC is a potentially blinding pathology, evolution toward retinal atrophy and blindness occurs in a subclinical fashion.<sup>5–7</sup> As a consequence, disease evaluation and monitoring should not be neglected and must be as complete and objective as possible, including both clinical and ancillary tests.

Among the ancillary parameters, automated visual fields (AVF)<sup>8–10</sup> and electroretinograms (ERG), especially the 30 Hz ERGs,<sup>11,12</sup> have shown their reliability and efficiency as evaluation and monitoring tools. However, ophthalmologists continue to experience difficulty in managing patients with BRC owing to the variability and labor-intensive methodology of AVF and ERG in detecting subtle change in disease activity, as opposed to large changes (ie, significant loss of functional vision).

While many BRC specialists agree on the fact that treatment algorithms based on visual acuity (VA), vitreous inflammatory reaction, or retinal vascular leakage of fluorescein alone are ineffective<sup>8–12</sup> and that many uveitis experts do not consider VA to be an optimal descriptive mechanism for activity in BRC, such statements have never been statistically investigated. This is particularly relevant for VA that seems to be widely used by the nonspecialists as a decisional tool.

This study was designed to determine the statistical correlation between VA and various clinical and ancillary quantitative parameters relevant to BRC evaluation.

## METHODS

INSTITUTIONAL REVIEW BOARD APPROVALS FOR RETROSPECTIVE chart reviews were obtained commensurate with the respective institutional requirements prior to the beginning of the study. Described research was approved by the Ethics Committee of the French Society of Ophthalmology and adhered to the tenets of the Declaration of Helsinki. Fully informed consent was obtained for all patients.

This was a hospital-based retrospective study that reviewed the files of all consecutive HLA-A29-positive BRC patients seen for the latest time for a routine visit between May and August 2013 at a single tertiary referral

**TABLE 1.** Baseline Demographic and Clinical Characteristics of 55 Patients With Birdshot Retinochoroidopathy

Demographic Characteristics and Patient History	Mean	95% CI	SD
Patient age (y)	38.7	[13–83]	15.8
Female/male sex ratio	1.6	-	-
Disease duration at baseline (y)	2.8	[0.1–24.4]	4.7
Medical therapy before and at baseline			
Oral corticosteroids	29%	-	-
Immunosuppressive treatments	5.5%	-	-
Clinical characteristics			
Visual acuity <sup>a</sup> OD	6/9.5	[6/126–6/6]	6/10
Visual acuity <sup>a</sup> OS	6/12	[6/600–6/6]	6/15
Anterior chamber flare OD (ph/ms)	18	[0.1–157]	31
Anterior chamber flare OS (ph/ms)	23	[0.1–373]	68
Vitreous inflammatory reaction <sup>b</sup> OD	1.2	[0–3]	0.6
Vitreous inflammatory reaction <sup>b</sup> OS	1.2	[0–3]	0.6
OCT central foveal thickness OD (μm)	240	[112–606]	115
OCT central foveal thickness OS (μm)	251	[85–662]	125
Arden ratio OD	159%	[106–218]	32
Arden ratio OS	160%	[103–235]	37
EOG light peak OD (mV)	714	[316–1379]	319
EOG light peak OS (mV)	746	[272–1652]	346
24-2 <sup>c</sup> MD OD	-7.723	[-29.18 to 11.9]	7.2
24-2 <sup>c</sup> MD OS	-7.923	[-27.96 to 10.3]	7.2
10-2 <sup>c</sup> MD OD	-4.726	[-19.7 to 7.3]	6.3
10-2 <sup>c</sup> MD OS	-5.951	[-14.7 to -0.14]	4

CI = confidence interval; EOG = electrooculogram; MD = mean deviation; OCT = optical coherence tomography; OD = right eye; OS = left eye; Ph = photons; SD = standard deviation.

Information was available for all 55 patients unless otherwise indicated.

<sup>a</sup>Visual acuity was measured on a decimal scale and then converted to a Snellen scale.

<sup>b</sup>Vitreous inflammatory reaction was clinically determined based on the Standardization of Uveitis Nomenclature criteria.<sup>14</sup>

<sup>c</sup>Automated perimetry performed with the Humphrey visual field analyzer, using the 24-2 and 10-2 programs.

center (Pitié Salpêtrière Hospital, Paris). All patients met criteria for diagnosis of birdshot retinochoroidopathy that had been previously defined by an international group of uveitis specialists.<sup>13</sup> Additionally, exhaustive evaluation to exclude the infectious and other inflammatory causes of uveitis that can mimic BRC was performed for all patients: Parameters including history and clinical presentation, specific infectious serologies, pulmonary function

tests, salivary glandular biopsy, targeted ancillary tests, and clinical examination by an internal medicine specialist were systematically performed to exclude differential diagnoses.

For each patient, demographic data including age, sex, ethnicity, and medical history were recorded at baseline. Quantitative parameters relevant to BRC were collected at baseline for both eyes and included the following clinical parameters: best-corrected visual acuity (BCVA) measured with a decimal scale, then converted to a Snellen scale; quantification of anterior segment cells and vitreous inflammatory reaction; and the following ancillary parameters: central foveal macular thickness as measured by optical coherence tomography (OCT), quantitative electrophysiological data including Arden ratio and electrooculography (EOG) light peak; and automated perimetry data (mean deviation). Anterior segment cells were quantified using a laser cell flaremeter analyzer (Kowa FC 1000; Kowa, Tokyo, Japan) (normal value <8 photon units/ms). Vitreous inflammatory reaction was clinically determined based on the Standardization of Uveitis Nomenclature criteria.<sup>14</sup> OCT analyses were performed using a Cirrus device (Carl Zeiss Meditec, Inc, Jena, Germany). Electrooculograms integrating the protocols recommended by the International Society for Clinical Electrophysiology of Vision and were obtained using a WIN 8000F monitor (Metrovision, Perenchies, France). Automated perimetry was performed with the Humphrey visual field analyzer, using the 24-2 and 10-2 programs (Zeiss-Humphrey, San Leandro, California, USA).

All outcomes were from a single clinical visit (the first visit in our unit). Correlation between VA and the other quantitative parameters of the same eye was analyzed.

• **STATISTICAL ANALYSES:** Correlations between each pair of quantitative parameters were estimated using Spearman rank correlation coefficients. Each correlation coefficient was tested against the null hypothesis of absence of correlation ( $\rho = 0$ ). *P* values of .05 or less were considered statistically significant. Correlations were considered to be strong when correlation coefficients were >0.5 and very strong when correlation coefficients were >0.8. Statistical analyses were performed using R 3.0.2 (R Development core team, 2013, Vienna, Austria).<sup>15</sup>

## RESULTS

FIFTY-FIVE HLA-A29-POSITIVE BRC PATIENTS WERE INCLUDED. Mean disease duration at baseline was 2.8 years (range: 0.1–24.4 years). Female-to-male sex ratio was 1.6. Demographic and clinical data at baseline are listed in Table 1. At baseline, 36 of 55 patients (66.6%) were naive of any treatment. 16 of 55 patients had previously received oral corticosteroids while only 3 of 55 (5.4%) had received immunosuppressive treatments (oral cyclosporine, intravenous immunoglobulins,

and oral mycophenolate mofetil, respectively). Mean BCVA was 6/9.5 in the right eye (OD) (range: 6/126–6/6) and 6/12 in the left eye (OS) (range: 6/600–6/6). Mean anterior chamber flare values reached 18 photon units (ph)/ms OD (range: 0.1–157 ph/ms) and 23 ph/ms OS (range: 0.1–373 ph/ms). Most patients had moderate vitreous inflammatory reaction (mean 1.2 +, range: 0–3). Mean OCT central foveal thickness was 240  $\mu\text{m}$  OD (range: 112–606  $\mu\text{m}$ ) and 251  $\mu\text{m}$  OS (range: 85–662  $\mu\text{m}$ ). Mean Arden ratio was 159% OD (range: 106%–218%) and 160% OS (range: 103%–235%), whereas the normal value is  $>180\%$ . Mean EOG light peak was 714 mV OD (range: 316–1379 mV) and 746 mV OS (range: 272–1652 mV), showing frequent EOG impairment.

Table 2 shows the 2-by-2 correlation coefficients between each pair of parameters. VA did not seem to be significantly correlated with any other parameter of the study (all correlation coefficients  $<0.5$ ). Additionally, except for visual acuity, all quantitative parameters related to a given eye seemed strongly correlated with the same parameter in the fellow eye (eg, flare on the right eye with flare on the left eye:  $r = 0.821$ ,  $P < .001$ ).

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## DISCUSSION

REGARDING BIRDSHOT RETINOCHOROIDOPATHY, CORNERstones for patient evaluation seem to be mainly clinical because they are expected to provide immediate information about disease activity. Among them, VA, anterior segment cellularity, vitreous inflammatory reaction, and the presence of macular edema are usually assessed.<sup>1–9,16–18</sup> Although the medical strategy can reliably be based on the presence of intraocular signs of inflammation, our study suggested that VA was not significantly correlated with the clinical inflammation or the other quantitative descriptive parameters of the disease that have been described (EOG, OCT foveal thickness, 24-2 and 10-2 perimetry mean deviation). This is in accordance with previous reports that stated absence of correlation between VA and the commonly accepted evaluation tools of the disease (eg, ERG, perimetry).<sup>8–12</sup> Similarly, Oh and associates suggested in a descriptive observational study that perimetry and ERG worsened progressively despite apparently preserved VA.<sup>5</sup> Visual function encompasses various parameters that central VA is far from summarizing.<sup>14,19,20</sup> Keeping in mind the potentially disastrous visual outcome of BRC,<sup>6</sup> solid knowledge about the usefulness of disease descriptive tools needs to be mastered. A few reports have previously suggested the absence of validity of VA as a descriptive variable<sup>4,5,8–12</sup>; however, none has ever used statistics to specifically reinforce this finding.

This study showed the weak correlation between VA and the other quantitative descriptive parameters of

BRC. We demonstrated that the VA of a considered eye could be preserved while obvious inflammatory signs, including vitreous inflammatory reaction and OCT foveal thickness, or latent signs of visual dysfunction, including EOG and perimetry impairment, could simultaneously show underlying disease activity. Interestingly, unlike what was shown previously,<sup>5–15,17,18,21–27</sup> we did not find any strong correlation between VA at baseline and OCT foveal thickness (Spearman correlation coefficient  $<0.5$ ). We noticed that a great proportion of patients initially displayed either signs of vitreous inflammation (45 of 55 patients with vitreous haze  $>0.5+$ ) or preliminary signs of macular atrophy (23 of 55 patients), which probably biased the correlation between VA and OCT thickness. Furthermore, at baseline only 11 patients (20%) had macular edema, which could also have interfered with the detection of such correlation. On the other hand, no prominent cataract was noted at baseline. Our cohort included patients at different stages of BRC, suggesting that statistical conclusions are relevant regardless of disease duration and severity. We also looked at the correlations between each eye for all parameters. We found that all variables showed a strong correlation between both sides (all correlation coefficients  $>0.7$ ). This provided statistical confirmation for disease symmetry except for VA, suggesting a discrepancy between this variable and the other parameters. Further studies should be performed to confirm these findings.

There are limitations to our study that need to be pointed to. First, our VA values ranged between 6/600 and 6/6; however, no obvious cause for poor vision (eg cataract, corneal opacities, etc) other than BRC itself explained such poor figures in some of our patients. This was probably the result of a recruitment bias because our center is a tertiary structure specializing in uveitis. The main result of this study was the lack of statistically significant correlation between VA and other indications of disease activity. Nonetheless, it must be noted that in medical empirical studies, it is inadequate to think that strict statistical independence between 2 variables can be proved. Besides, we cannot dismiss the risk of a type 2 error. Thus, to be accurate, we can only claim that the study data do not suggest significant correlation between visual acuity and the other parameters. One of the main flaws of this work is the absence of more typical BRC evaluation techniques such as color vision, contrast sensitivity, angiograms, and ERG. These were not performed on the same devices for a significant part of the study sample, which made them very hard to compare. In addition, if we had decided to assess the correlation for all ERG variables, it would have required us to estimate polychoric correlations, which—in combination with the proportion of unusable data—would have led to very poor estimates. Further analyses are currently being performed and should extend our results to ERG.

In summary, our data statistically suggested that visual acuity alone does not seem to fully reflect the

**TABLE 2.** Spearman Correlation Coefficients Between Visual Acuity and Various Quantitative Descriptive Parameters of Birdshot Retinochoroidopathy at Baseline

	VA <sup>a</sup> OD	VA <sup>a</sup> OS	AH Flare OD	AH Flare OS	Vitreous Inflamm <sup>b</sup> OD	Vitreous Inflamm <sup>b</sup> OS	OCT CFT OD	OCT CFT OS	Arden OD	Arden OS	EOG LP OD	EOG LP OS	10-2 MD <sup>c</sup> OD	10-2 MD <sup>c</sup> OS	24-2 MD <sup>c</sup> OD	24-2 MD <sup>c</sup> OS
VA <sup>a</sup> OD	—	0.48	0.41 <sup>d</sup>	0.24	-0.03 <sup>d</sup>	-0.06	0.27 <sup>d</sup>	0.14	-0.17 <sup>d</sup>	-0.35	-0.20 <sup>d</sup>	-0.03	-0.07 <sup>d</sup>	0.06	-0.07 <sup>d</sup>	-0.03
VA <sup>a</sup> OS	<.001	—	0.08	-0.08 <sup>d</sup>	-0.28	-0.27 <sup>d</sup>	0.03	0.10 <sup>d</sup>	-0.18	-0.40 <sup>d</sup>	0.17	0.27 <sup>d</sup>	-0.20	-0.08 <sup>d</sup>	-0.34	-0.39 <sup>d</sup>
AH Flare OD	.03	.68	—	0.82	0.00	0.10	0.24	0.38	-0.22	-0.13	0.29	0.00	-0.31	0.16	-0.10	0.15
AH Flare OS	.20	.69	<.001	—	0.02	0.18	0.22	0.28	-0.16	-0.04	0.00	-0.17	-0.03	-0.01	0.14	0.19
Vitreous Inflamm <sup>b</sup> OD	.85	.04	.98	.91	—	0.89	-0.06	-0.04	-0.34	-0.22	0.16	0.09	-0.14	-0.20	-0.07	-0.03
Vitreous Inflamm <sup>b</sup> OS	.65	.05	.61	.36	<.001	—	-0.15	-0.09	-0.30	-0.19	0.14	0.02	-0.25	-0.40	-0.23	-0.14
OCT CFT OD	.07	.87	.25	.29	.70	.32	—	0.77	0.04	0.06	-0.16	0.08	-0.08	0.17	0.34	0.29
OCT CFT OS	.36	.52	.07	.18	.77	.57	<.001	—	-0.01	0.12	0.04	0.19	0.08	0.42	0.42	0.42
Arden OD	.41	.38	.48	.62	.10	.15	.85	.95	—	0.72	0.25	0.11	0.60	0.20	0.36	0.39
Arden OS	.08	.05	.70	.91	.29	.36	.79	.59	<.001	—	0.19	0.16	0.30	0.00	0.57	0.73
EOG LP OD	.39	.49	.50	>.999	.49	.56	.53	.89	.28	.43	—	0.91	-0.40	-0.40	0.67	0.62
EOG LP OS	.90	.25	>.999	.69	.71	.92	.76	.46	.65	.50	<.001	—	-0.80	-0.80	0.82	0.69
10-2 MD <sup>c</sup> OD	.77	.39	.27	.92	.54	.29	.75	.73	.35	.68	.75	.33	—	0.57	0.50	0.25
10-2 MD <sup>c</sup> OS	.80	.74	.56	.97	.37	.07	.47	.06	.78	>.999	.75	.33	.01	—	0.49	0.63
24-2 MD <sup>c</sup> OD	.67	.03	.65	.52	.64	.15	.03	.01	.16	.02	.02	.00	.02	.02	—	0.82
24-2 MD <sup>c</sup> OS	.87	.01	.49	.35	.87	.38	.08	.01	.12	.00	.03	.01	.27	.00	<.001	—

AH = aqueous humor; Arden = electrooculography Arden ratio; EOG LP = electrooculography light peak; MD = mean deviation; OCT CFT = central foveal thickness provided by optical coherence tomography; OD = right eye; OS = left eye; VA = visual acuity; Vitreous Inflamm = vitreous inflammatory reaction.

Above the diagonal are the raw values for Spearman correlation coefficients; below the diagonal are the corresponding *P* values.

<sup>a</sup>Visual acuity was measured on a decimal scale and then converted to a Snellen scale.

<sup>b</sup>Vitreous inflammatory reaction was clinically determined based on international criteria.<sup>14</sup>

<sup>c</sup>24-2 and 10-2 mean deviation on automated perimetry performed with the Humphrey visual field analyzer.

<sup>d</sup>Correlation coefficients between visual acuity and the other parameters on the same eye.

severity of disease in terms of clinical or ancillary quantitative findings at baseline. Based on these preliminary results, we suggest that evaluation of BRC patients should include complete clinical and ancillary tests including automated perimetry, OCT, electrophysi-

ology, and angiograms. Other technologies, such as choroidal changes using OCT enhanced-depth imaging,<sup>28</sup> are currently being investigated as a way to evaluate BRC disease activity and should be considered in future studies.

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ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported. The authors indicate no funding support. All authors attest that they meet the current ICMJE requirements to qualify as authors.

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### **Biosketch**

Dr Sara Touhami is a Resident in Ophthalmology with a subspecialisation in retinal pathology and ocular inflammation. After completing her Masters Degree at the Pasteur Institute of Paris on the genetic predispositions to malaria, she worked at the University College of London, and the Massachusetts Institute of Technology where she acquired some experience on stem cells and bioengineered devices. She is now currently pursuing a PhD degree in the field of retinal inflammation and AMD.



### **Biosketch**

Dr Christine Fardeau works at la Pitié-Salpêtrière Hospital in the department of Ophthalmology led by Pr P Le Hoang, international expert in uveitis. She has been the reporter for the official labelling of the Paris Uveitis Center as “Reference Center of Rare Diseases” and has participated to many international publications. She also has been one of the leaders and the principal investigator for a randomized controlled trial assessing the efficacy of interferon alpha treatment in uveitis.