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Birdshot Retinochoroidopathy: Prognostic Factors of Long-term Visual Outcome

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Abstract:

Purpose: To determine the prognostic factors of long-term visual outcome in Birdshot Retinochoroidopathy (BRC).
Methods:
Design: Retrospective case series.
Study population: Successive HLA-A29+ BRC patients whose latest visit was between May and August 2013 at a single tertiary centre (Pitié-Salpétrière Hospital, Paris).
Observation procedure: Endpoint visual status (remission or deterioration) was determined for each patient based on clinical and ancillary data from the latest visit including optical coherence tomography (OCT), automated visual field (AVF) and angiograms.
Main outcome measure: Epidemiological, clinical, OCT, AVF, angiographic and electrophysiological data at baseline were correlated to final visual status.
Results: 55 patients were included. Mean observation period was 8 years (range: 0.6-23). Mean disease duration was 9.8 years (range: 1.2-32.7). Female-to-male sex ratio was 1.6. Factors of good visual prognosis (Remission vs Deterioration) included at baseline: late age of disease onset (49.5 vs 45 years, p=0.05), presence of vitreous inflammatory reactions>2+ (35.9% vs 6.2%, p=0.04), vascular leakage on fluorescein angiograms (FA) (44.4% vs 12.5%, p=0.03) absence of macular pigment epithelium atrophy on FA (88,9% vs 62,5%, p=0.05) and presence of macular oedema on OCT (33.3% vs 6.2%, p=0.04). Preserved electro-oculography light peak and Arden ratio (p=0.06), and presence of choroidal spots on ICG angiograms (80% vs 53.3%, p=0.08) seemed associated with the best prognoses.
Conclusion: This study suggests a series of prognostic factors of long-term visual outcome in BRC. Keeping in mind the insidious evolution of the disease, knowledge of such prognostic factors should help tailor the treatment and monitoring of Birdshot patients.

-Original Article-

Birdshot Retinochoroidopathy: Prognostic Factors of Long-term Visual Outcome.

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Introduction:

Birdshot Retinochoroidopathy (BRC) is a rare form of posterior autoimmune uveitis that is mainly characterized by the presence of deep, hypo-pigmented ovoid spots in the fundus and nodular lesions at the choroidal level[1-3].
If the disease is indeed chronic, there has been a couple of reports supporting its relative self-limitation after resolution of the initial bout of inflammation, and this was mainly based on the stability of visual acuity (VA) overtime[4-6].
However, there is now evidence of the possibility of subclinical evolution towards retinal atrophy and blindness[7-10]. Additionally further analysis of a recent study suggested no evidence of strong correlations between VA and other descriptive variables of disease activity[11], amongst which electroretinograms (ERG) and visual fields[12].

Today a spectrum of treatment options for BRC ranging from surveillance to highly aggressive corticosteroid and immunosuppressive treatments, are commonly employed, rather than targeted treatments based on the result of evidence-based medicine[1]. Consequently, patient care and visual outcome appear to depend heavily on the attending physician's opinion, which can vary depending on their country of origin and degree of specialization. As a result of this, the need for prognostic factors to guide medical management becomes increasingly evident.
The objective of this work was to search for prognostic factors of long-term visual outcome to help adapt the treatment and monitoring of BRC patients in a more standardised fashion.

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 hospital-based retrospective study reviewed the files of consecutive HLA-A29 positive BRC patients[13] whose latest visit was between May and August 2013 at a tertiary referral centre (Pitié Salpétrière Hospital, Paris).

For each patient, demographic data, medical and treatment history were recorded. Clinical parameters were collected at baseline for both eyes and included: best corrected visual acuity (BCVA) (decimal scale converted to Logarithm of the Minimum Angle of Resolution (LogMAR)), quantification of anterior segment cells (Laser cell flaremeter analyser, Kowa FC 1000®, Tokyo, Japan) and vitreous inflammatory reaction[14]; and analysis of fundus features. Ancillary parameters included: Optical coherence tomography (OCT) central macular thickness (OCT Cirrus, Carl Zeiss Meditec, Inc, Jena, Germany), fluorescein (FA) and infracyanin green (ICG) angiograms, electro-oculograms (EOG) and full field (ff) electroretinograms (ERG) following the protocols of the International Society for Clinical Electrophysiology of Vision (WIN 8000F monitor, Metrovision, Perenchies, France) and automated visual field (AVF) parameters including mean deviation (MD) and pattern standard deviation (PSD) (24-2 and 10-2 programs, Zeiss-Humphrey, San Leandro, USA).

For each patient, endpoint visual status was defined and corresponded

to one of the two following categories: Remission or deterioration, based on clinical and ancillary tests from the latest visit (Table 1).

Main outcome measure:
Epidemiologic, clinical, OCT, AVF, angiographic and electrophysiological data at baseline were collected and compared between the groups based on their final visual status.

Statistical analysis:
It was demonstrated previously[11] that there is a strong correlation between both eyes for multiple parameters in BRC except for visual acuity (VA). As a result, data was analysed by patient rather than in terms of eyes. In turn, quantitative variables were established based on the worst value between the right and left eye and for qualitative variables, presence of abnormal values in at least one eye was considered for each patient. Baseline quantitative parameters were described and compared between the two groups (remission versus deterioration) using Mann-Whitney-Wilcoxon test, while comparisons for qualitative parameters used Fisher-exact test. P values of less than 0.05 were considered statistically significant. Statistical analyses were performed using R 3.0.2 (R Development core team, 2013, Vienna, Austria)[15].

Results:

Baseline characteristics:
Fifty-five Caucasian patients were included. Female to male sex ratio was 1.6 (62% females, 38% males). Mean age at diagnosis was 49.1 years (range: 30.3-73.9). At baseline, mean disease duration was 2.8 years (range:0-24.4). Mean follow-up duration was 8 years (range: 0.6-22.9). At endpoint, mean disease duration was 9.8 years (range: 1.2-32.3).

Medical history consisted of high blood pressure in 27% of cases, hypercholesterolemia in 16.4% of cases, type 2 diabetes in 5.4% of cases, autoimmune diseases in 5% of cases, and neurological conditions in 7.3% of cases (1 case of meningioma sparing visual tracts, 1 case of idiopathic epilepsy, 1 case of non-compressive pituitary adenoma and 1 case of congenital deafness).

Clinical and ancillary data at baseline are listed in Table 2 and 3. Birdshot lesions were initially seen in 72% of cases on fundus examination. Additionally, 58% of patients displayed optic nerve swelling while 81% showed vasculitis upon funduscopic examination. No significant cataract was noted initially. Overall, 25% of patients had macular oedema on OCT (central macular thickness>250 microns or presence of ‘logettes’). Regarding visual fields, foveal thresholds were in the normal range for all patients at baseline.

Endpoint characteristics:
Characteristics at endpoint are displayed in Table 2. In summary, visual acuity was stable overall during follow-up (no statistical difference between baseline and endpoint values) and no patent cataract was noted except in 3 patients who underwent cataract surgery. Prevalence of

macular oedema decreased at endpoint as compared to baseline (26.9% versus 6,5% OD and 32.7% versus 15,2% OS, respectively for baseline versus endpoint). We also noticed that 5 patients, who presented with architectural modifications and decreased macular thickness at baseline, could recover normal retinal anatomy on OCT. Interestingly, alteration of mean deviation overtime seemed more obvious on the 10-2 than the 24-2 AVF, regardless of the presence of macular oedema. It was also observed that no neovascular membrane was diagnosed on OCT or FA.

During the follow-ups, 100% of patients received systemic corticosteroid treatments for a mean duration of 7 years (range: 0.3-16.6). Time interval between disease onset and initiation of systemic corticosteroids was on average 2.9 years (range: 0-24.2). 42 of 55 patients (76%) received immunosuppressive treatments (Mycophenolate Mofetil, Azathioprine, Ciclosporin, Interferon alpha 2a,Cyclophosphamide and Methotrexate in respectively 44.4%, 13.2%, 9.4%, 28.3%, 1.9% and 1.9% of cases) for a mean duration of 4.8 years (range: 0.4-21.4), after an average of 5.2 years after diagnosis was made (range: 0.3-24.8). Intermittent local steroid injections were administered punctually as adjuncts to systemic treatments to treat unilateral relapses. 7.5% of patients received intravitreal injections while 18.8% received periocular injections of corticosteroids.

Endpoint visual status: Among the 55 studied patients, 39 (71%) remitted during the follow-up (1 cured, 18 in complete remission, 20 in partial remission), while 16 deteriorated (Table 1).

Prognostic value of baseline characteristics on visual evolution: Baseline characteristics according to final visual status are displayed in Table 4. Follow-up duration was not found to be different between the groups (deterioration: median=8.1years [InterQuartile-Range (IQR): 5.8 - 11.9]; remission: median=4.9years [IQR: 3.1 – 11.1], p=0.22]). Besides, patients in the remission group were slightly older at diagnosis than those in the deterioration group. In fact, early disease onset seemed associated with unfavourable visual outcomes, regardless of disease duration (deterioration: median=45.2years [IQR: 40.9-51] versus remission: median=49.5years [IQR: 45.3-54.6], p=0.05). On the other hand, we found no significant difference in terms of past medical history or gender and final visual status.

Clinically speaking, patients in the deterioration group had less overt signs of posterior segment inflammation on initial presentation than those in the remission group (vitreous inflammatory reaction≥2+: 7% versus 37%; presence of macular edema in at least one eye: 6% versus 33% respectively for deterioration and remission groups, p=0.04). Similarly, presence of macular leakage on FA was associated with good outcomes (deterioration group: 13% versus remission group: 44%, p=0.03). Whatever the disease duration, Birdshot lesions on ICG angiogram were initially found in 80% of remission cases versus 53% of deterioration cases (p=0.08). Furthermore, macular RPE (retinal pigment epithelium) atrophy on FA was diagnosed in 11.1% of remission cases versus 37.5% of deterioration cases at baseline (p=0.05). However, this observation

was not consistent with OCT findings, since decreased central macular thickness (<130microns) was not statistically associated with endpoint visual status (57.6% versus 53.8% respectively for the remission and deterioration groups). Taken together, these observations argue for the possible involvement of RPE in determining the visual outcome. Regarding electrophysiology, EOG light peak values in the worst eye at baseline were lower in the deterioration group as compared to the remission group (deterioration, median=417millivolts, IQR: 362-531; remission, median= 638millivolts, IQR: 440-1032; p=0.06). Similarly, decreased Arden ratio seemed to be associated with the worse outcomes (median baseline values: 158% versus 137% respectively for the patients in the remission versus deterioration groups, normal value being >180%, p=0.06). Regarding perimetry, *Full Field* and 30Hz Flicker ERG, no statistical correlation with the final outcome was noted. Regarding treatments, treatment duration was not correlated with final status (p=0.11 and 0.16 respectively for systemic corticosteroids and immunosuppressive treatments). Type of immunosuppressive treatment was not neither predictive of the final outcome.

Discussion:

Birdshot Retinochoroidopathy is a rare form of posterior uveitis that is characterized by the variability of its phenotypes and unpredictability of its evolution, which makes standardization of patient care very challenging. In fact, no consensus regarding treatments (type or duration) or surveillance modalities has been defined to date[1]. In addition, a study by Tomkins-Netzer et al. recently demonstrated that patients who received intermittent or short-term treatments showed more substantial deterioration of their peripheral visual fields overtime as compared to those who received long-term immunosuppression[16]. Such statements further highlight the importance of immunosuppression in BRC and more particularly its duration, keeping in mind the cumulative side effects of some molecules.

Our results focused on a series of parameters whose initial characteristics seemed to discriminate the patients according to their final visual outcome. As such, these parameters correspond to potential prognostic factors. On one hand, early age of disease onset was associated with poor outcomes regardless of disease duration. On the other hand, we could not prove any relation between delayed initiation of treatments and final prognosis, despite numeric difference of average figures between the groups for both corticosteroid and immunosuppressive treatments. Such an absence of statistical significance can be explained by the size of the studied groups and further studies on larger samples should be able to answer this important question. While it has been suggested by others that prolonged treatments can increase the likelihood of the preservation of visual function versus intermittent treatments[16], and whilst all patients in this study received as deemed necessary, long-term immunosuppression in accordance with these previous results, we were not able to prove any

correlation between treatment duration and final outcome.

One of the most interesting and novel findings was that presence of overt signs of posterior segment inflammation on initial presentation (including clinical, OCT, FA and ICG observations[17]) seemed predictive of the best outcomes. In fact, we noticed that the patients who displayed the largest amounts of vitreous inflammation at baseline (≥2+), received corticosteroid treatments earlier than those with less prominent vitritis (on average 603 days versus 1265 days respectively, p=0.04) (data not shown). Similarly, presence of macular RPE atrophy on FA seemed associated with the poorest outcomes, and initiation of corticosteroid and immunosuppressive treatments was delayed in the group of patients who displayed such signs at baseline (3154 versus 632 days for corticosteroids, p=0.016 and 3505 versus 1568 days for immunosuppressive treatments, p=0.05). Overall, based on these observations, the results of this work might be explained by the possibility of multiple disease phenotypes (with relative indolence of the active and readily presenting disease phenotypes as opposed to the insidious slowly progressive not as obviously presenting disease forms) and differential medical behaviour depending on initial presentation. The prognostic value of RPE atrophy was furthermore corroborated by the fact that decreased EOG light peak and Arden ratio at baseline appears associated with the worst outcomes. To our knowledge, this is the first study that investigated the prognostic value of EOG in BRC.

Regarding visual fields; if multiple studies previously investigated their utility in Birdshot monitoring, none has specifically questioned their prognostic value. Furthermore, there remains no consensus regarding which type of perimetry to use in BRC[18-19]. Within this study, we were not able to find any relation between 24-2 or 10-2 MD values and final patient outcome. Additionally, foveal thresholds and PSD figures were missing for part of the sample group at baseline, therefore no satisfactory analysis could be performed for these values.

Analysis of the *Full Field* ERG was not statistically conclusive, as neither b-wave (amplitude or implicit time) or b/a ratios, in terms of amplitude at baseline seemed predictive of the final outcome. Nevertheless, these results do not contradict what was previously reported in the literature i.e. the value of *Full Field* ERG as evaluation and monitoring tool in BRC[20-23]. Similarly, amplitude or implicit time of the 30 Hz ERG Flicker b-wave at baseline could not discriminate patients according to their final outcome. Holder et al showed that 30 Hz Flicker implicit time was an important monitoring tool for BRC[20]. However, in our study, we could not prove its prognostic value and further multi-centric studies in larger samples would likely be required to demonstrate conclusively.

Interestingly, Chiquet et al recently correlated multifocal ERG findings with various clinical parameters and suggested their potential value as evaluation and monitoring tools[24.] In our study, no conclusion could be made regarding the prognostic value of multifocal ERG (data not shown).

There are limitations to our study that need to be highlighted. Firstly, our study was conducted in a third-line care unit specialized in uveitis; therefore, we cannot exclude the possibility of a selection bias

with patients being possibly more severely affected than in non-specialized centres. Additionally, our results need to be moderated by the retrospective design of the study and its limited sample size. Multivariate analyses did not provide any further evidence.

The objective of this study was to point to potential predictive factors of disease evolution, the validity of which can only be confirmed through further prospective studies that are specifically designed to evaluate those factors. From these results, we can however postulate that this study proposes novel and valuable prognostic tools that may be able to help with therapeutical decisions on an everyday basis. Cited literature shows similar trends as our results demonstrating the accuracy of these prognostic factors.

In summary, this study focused on a series of clinical and ancillary parameters that are potential predictive factors of long-term visual outcome in Birdshot Retinochoroidopathy. Prospective multi-centric studies should be able to confirm these findings, especially in consideration of the insidious evolution of the disease, knowledge of such prognostic factors can only help further tailor the treatment and monitoring of Birdshot patients.

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Table I: Endpoint visual status: study categories.

Category	Definition	N	%
Remission	= Cure+Complete Remission+Partial Remission.	39	70,91
Cure	Complete remission >5 years after treatment withdrawal.	1	1,82
Complete Remission	No direct signs of intraocular inflammation : • No active vitritis (0+)[a]. • Quiet *FA (no vasculitis, no vascular leakage, no hyperfluorescence of the choriocapillaris, no optic disc swelling).* • Quiet ICG-A *(no active dark spots, no choroidal vessel dilation, no late hypercyanescence of the posterior pole).* • No ME or CME. No indirect signs of intraocular inflammation : • Absence or stabilization of AVF abnormalities (**δ** MD≤10%/year). • No macular atrophy on OCT or FA.	18	32,73
Partial Remission	Stabilized VA (<1 line loss) But persistent insidious activity in at least one eye: • Slow AVF deterioration (**δ** MD>10%/year). • Mild vitritis or improvement of vitritis[a]. • FA: hyperfluorescence of the choriocapillaris. • ICG-A: persistent dark dots (≤5). • Choroidal neovascularization. • Decreased ME on OCT (by at least 20%, in the absence of macular atrophy).	20	36,36
Deterioration	Clinical and/or subclinical deterioration in at least one eye that does not fit any other category.	16	29,09

N= Number of patients in each category, %= Proportion of patients in each category. VA= Visual acuity. [a]Vitreous inflammatory reaction was clinically determined based on the Standardization of Uveitis Nomenclature criteria. OCT= Optical Coherence Tomography. ME= macular oedema, CME= cystoid macular oedema. FA= Fluorescein Angiogram, ICG-A= Indocyanin green Angiogram, AVF= Automated visual Field. MD: Mean Deviation. **δ:** Variation.

Table II: Birdshot Retinochoroidopathy: Prognostic Factors of Long-term Visual Outcome: Baseline and endpoint characteristics.

Variables	Baseline		Endpoint	
	OD	OS	OD	OS
Quantitative variables (Mean± SD)				
BCVA	0.21 ± 0.25	0.29 ± 0.42	0.18 ± 0.3	0.32 ± 0.5
Anterior chamber flare (ph/ms) [a]	18.2 ± 31.3	23.7 ± 68.3	3 ± 2.1	4 ± 1.5
Vitreous inflammatory reaction (+) [b]	1.2 ± 0.6	1.2 ± 0.7	0.5 ± 0.3	0.5 ± 0.4
OCT central macular thickness (microns)	240.1 ± 114.6	251.7 ± 125.2	230 ± 54	236 ± 71.6
10-2 MD (decibels) [c]	-4.7 ± 6.3	-5.9 ± 4.1	-8.4 ± 9	-7.3 ± 6.9
24-2 MD (decibels) [c]	-7.7 ± 7.3	-7.9 ± 7.2	-8 ± 8	-6.8 ± 7.9
Qualitative variables n (%)				
Vasculitis on FA	44 (84.6%)	45 (86.5%)	18 (38.3%)	21 (44.6%)
Macular leakage on FA	14 (26.9%)	17 (32.7%)	3 (6.5%)	7 (15.2%)
Macular RPE atrophy on FA[d]	9 (17.3%)	8 (15.4%)	12 (25.5%)	12 (25%)
Birdshot spots on ICG[e]	36 (72%)	36 (72%)	7 (18.9 %)	8 (21.6%)

OD: Right eye. OS: Left eye. BCVA: Best-corrected visual acuity in LogMAR (Logarithm of the Minimum Angle of Resolution). SD: Standard deviation. Ph/ms: Photon-unit per millisecond. [a] Normal value < 8photon units/millisecond. [b]Vitreous inflammatory reaction was clinically determined based on the Standardization of Uveitis Nomenclature criteria[14]. OCT: Optical coherence tomography. MD: Mean Deviation. [c]Automated perimetry performed with the Humphrey visual field analyzer, using the 24-2 and 10-2 programs. %: proportion of eyes. FA: Fluorescein angiogram. ICG: Infracyanin green angiogram. [d]Autofluorescence. [e]On ICG: Birdshot spots are hypocyanescent during early and intermediate stages of the angiogram.

Table III: Birdshot Retinochoroidopathy: Prognostic Factors of Long-term Visual Outcome: Electrophysiology: characteristics at baseline.

Quantitative variables (Mean +/- SD)	OD	OS
Full field ERG b-wave AMP (millivolts)[a,b]	67.8 +/- 43.7	69.4 +/- 43.3
Full field ERG b-wave IT (milliseconds)[a,b]	40.7 +/- 5.08	42.2 +/- 4.7
Full field ERG b/a (AMP) ratio [a,b]	3 +/- 1.25	2.9 +/- 2.7
30 Hz Flicker b-wave AMP (millivolts)[c]	70.6 +/- 45	63.9+/- 42.3
30 Hz Flicker b-wave IT (milliseconds)[c]	29 +/- 6.3	34.6 +/- 13.6
EOG Arden ratio[a]	159 +/- 31.8	160 +/- 36.6
EOG light peak (millivolts)[a]	713.5 +/- 319.4	745.5 +/- 346.2

OD: Right eye. OS: Left eye. SD: Standard Deviation. AMP: Amplitude. IT: Implicit time. Hz: Hertz. ERG: Electroretinogram. EOG: Electro-oculogram. Arden ratio: normal values are >180%. [a]ERG and EOG followed the latest protocols recommended by the International Society for Clinical Electrophysiology of Vision (ISCEV). [b]Photopic responses in scotopic environment were recorded for full field electroretinograms. Abnormal values for b-wave amplitude and implicit time were respectively <80 millivolts and > 40 milliseconds. [c] Abnormal values for 30 Hz Flicker b-wave amplitude and implicit time were respectively <100 millivolts and > 30 milliseconds.

Table IV: Birdshot Retinochoroidopathy: Prognostic Factors of Long-term Visual Outcome: Comparison of baseline characteristics according to final visual status (deterioration versus remission).

Quantitative characteristics at baseline	Deterioration (n=16)		Remission (n=39)		p-value
	Median	IQR	Median	IQR	
Age at diagnosis (years)	45	[40.9-51]	49.5	[45.3-54.6]	0.05
Follow-up duration (years)	8.1	[5.8-11.9]	4.9	[3.1-11.1]	0.22
Disease duration (years)	11	[8-14.5]	8.5	[4.4-11.4]	0.11
Time interval between diagnosis and initiation of corticosteroid treatment (years)	1.5	[0.9-2.4]	1	[0.3-3.4]	0.34
Time interval between diagnosis and initiation of immunosuppressive treatment (years)	2.5	[2.1-8]	2.7	[1.6-6.5]	0.65
Treatment duration (steroids and/or immunosuppressive treatments) (years)	9.5	[6.8-12.8]	4.7	[2.7-9.9]	0.07
EOG light peak in the worst eye (mV)	417	[362-531]	638	[440-1032]	0.06
EOG Arden ratio in the worst eye	137	[125-148]	158	[138-177]	0.06

Qualitative characteristics at baseline	Deterioration	Remission	p-value
	n (%)	n (%)	
Vitreous inflammatory reactions≥2+ in at least one eye[a]	1 (6.2%)	14 (35.9 %)	0.04
Presence of macular oedema on OCT in at least one eye[b]	1 (6.2%)	13 (33.3%)	0.04
Macular leakage on FA in at least one eye	2 (12.5%)	16 (44.4%)	0.03
Macular RPE atrophy on FA in at least one eye[c]	6 (37.5%)	4 (11.1%)	0.05
Vasculitis on FA in at least one eye	14 (87.5%)	32 (88.9%)	1
Birdshot spots on ICG in at least one eye[d]	8 (53.3%)	28 (80.0%)	0.08

IQR: interquartile range. EOG: Electro-oculogram. FA: Fluorescein angiogram. ICG: Infracyanin green angiogram. OCT: Optical coherence tomography. RPE: Retinal pigment epithelium. %: Proportion of patients. [a]Vitreous inflammatory reaction was clinically determined based on the Standardization of Uveitis Nomenclature criteria[14]. [b] Macular oedema was defined by central macular thickness> 250microns and/or in the presence of logettes on OCT. [c]Autofluorescence . [d]On ICG: Birdshot spots are hypocyanescent during early and intermediate stages of the angiogram.