Characteristics, Upon Presentation, of a Cohort of Hispanic Patients with Birdshot Retinochoroidopathy

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Objective: To describe the characteristics, upon presentation, of a cohort of Hispanic patients with birdshot retinochoroidopathy.

Methods: A retrospective chart review of Hispanic patients with birdshot retinochoroidopathy of was performed. The demographic and clinical characteristics were analyzed.

Results: Nine patients who met the research criteria for a diagnosis of birdshot retinochoroidopathy were identified and included in the analysis, all of whom were HLA-A29 positive. The median age of the cohort upon presentation was 52 years; 89% of the patients were female, and all were Hispanics. Ninety-four percent of the eyes had an initial visual acuity of 20/50 or better, while 72% had measured 20/25 or better. Sixty-one percent of the eyes had retinal vasculitis, which was bilateral in 83% of the cases. Thirty-three percent of the patients had, upon presentation, evidence of cystoid macular edema, which was always bilateral. All the eyes had the typical birdshot lesions, at presentation.

Conclusion: Birdshot retinochoroidopathy can be found in Hispanic patients. Our study suggests that the characteristics upon presentation in Hispanics may be similar to those of Caucasian cohorts. [*P R Health Sci J 2020;39:249-253*]

Key words: Birdshot retinochoroidopathy, Hispanics, HLA-A29, Retinal vasculitis, Posterior uveitis

Ryan and Maumenee first described birdshot retinochoroidopathy (BSRC) in 1980 (1). It is a chronic, most commonly bilateral, autoimmune posterior uveitis with a very distinctive phenotype, yet with a heterogeneous clinical presentation (1–3). It is a rather rare condition affecting 6 to 7.9% of patients with posterior uveitis (4). It most commonly affects subjects from 35 to 70 years of age and has a slight female predominance (5). BSCR is distinguished by its multiple ovoid, cream-colored, or depigmented spots scattered throughout the fundus, mainly around the optic disc and radiating out towards the midperiphery (1,2). see Figures 1A and 1B. As described by Ryan and Maumenee, it resembles a "pattern seen with birdshot in the scatter from a shotgun" (1). Other common clinical features include vitritis, retinal vasculitis, and cystoid macular edema (2,5,6). see Figures 1C and 1D.

In 1982, Nussenblatt et al. first described BSRC's association with the HLA-A29 antigen, which has been reported in 80% to 100% of affected patients (2,7–9). BSRC has the highest known HLA class I disease association, with the HLA-A29 genotype conferring a relative risk that is reported to be as high as 224:1, in some series (8). Modern understanding of disease genetics reveals that there are 2 main subtypes of HLA-A29, HLA-A29.1, and HLA-A29.2, associated with BSRC (4,10,11).

The frequencies of the HLA-A29.1 and HLA-A29.2 alleles are 0.7% and 3.3%, respectively, in the United States, non-Hispanic Caucasian population (4). Conversely, the frequencies of the HLA-A29.1 and HLA-A29.2 alleles in the United States Hispanic population are 0.35 and 4.17%, respectively (4). Despite the similar relative frequency of the HLA-A29.2 allele in both populations, for reasons not clearly understood, BSRC remains underreported in Hispanics. In 2012, Rodriguez-Garcia and Almanzar-Santos described their experience managing 6 Mexican patients with BSRC, of which 5 were tested, and confirmed to be HLA-A29 positive (12). The first English-language report of a Hispanic patient with HLA-A29-associated BSRC occurred as recently as 2016, and to our knowledge, there have not been any further reports in Hispanics (4).

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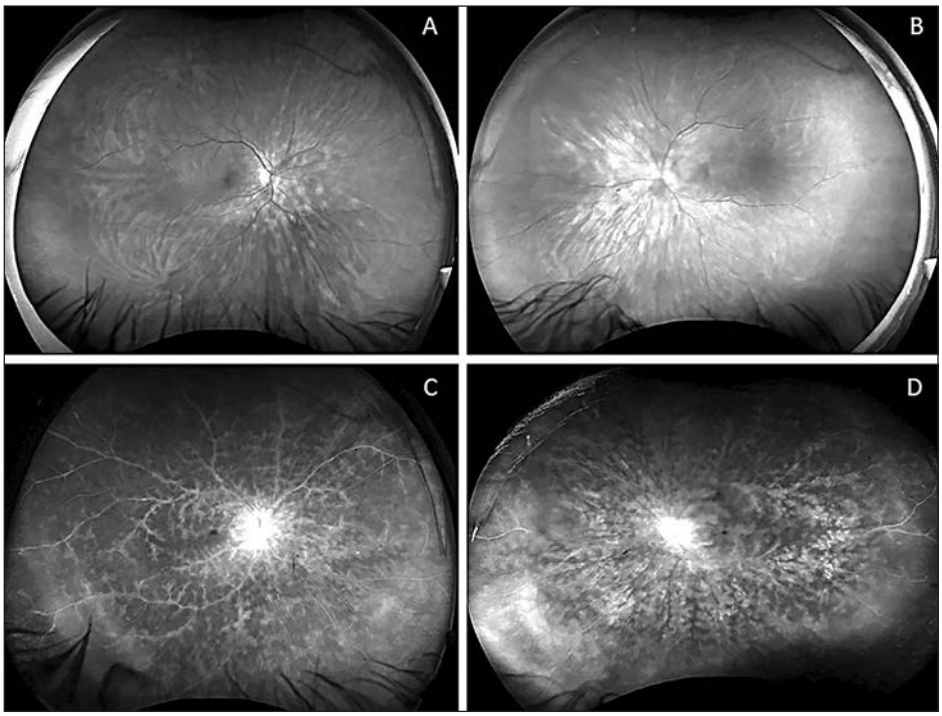

Figure 1. A 52-year-old man with HLA-A29-positive birdshot retinochoroidopathy. Ultra-widefield color fundus photographs revealing the typical cream-colored, elongated choroidal lesions, which are located mainly surrounding the optic disk and irradiating towards the periphery, on the right and left, A and B, respectively. Ultra-widefield fluorescein angiogram, late phase, revealing disk hyperfluorescence, macular leakage, and perivascular leakage heralding the presence of active inflammation with macular edema and retinal vasculitis, on the right and left, C and D, respectively.

BSRC is a potentially blinding disease that often requires the use of systemic immunosuppressors to achieve proper disease control and prevent both the recurrence of edema and the progression of visual field loss (2). Further establishing the existence of BSRC in Hispanic populations is of utmost importance as doing so will help to define this disease better. Therefore, we must report the clinical characteristics of BSRC in the patients of our uveitis practices, which practices serve a predominantly Hispanic population living in the United States Commonwealth of Puerto Rico.

Methods

Medical records covering from July 2006 through May 2019 were reviewed. The records were located in the medical records databases of the Medical Services Administration of Puerto Rico, outpatient clinics of the University of Puerto Rico Medical Sciences Campus Department of Ophthalmology, and 2 private uveitis practices. Charts of patients with a diagnosis of BSRC were selected for analysis. The BSRC ascertainment was made using the diagnostic criteria outlined in 2006 during an international conference exploring the condition (9). (see Table 1). Patients not meeting these criteria were excluded from the analysis.

All the patients had been personally examined by either 1 or both of 2 well-experienced academic uveitis specialists who established, in those patients, the diagnosis of BSRC. Before this diagnosis was established, all the patients underwent an extensive systemic workup to rule out other possible etiologies of retinochoroiditis and retinal vasculitides, such as syphilis, tuberculosis, and sarcoidosis; no evidence of these or other systemic conditions was found.

Table 1. Birdshot Chorioretinopathy: Diagnostic criteria for research purposes

Required characteristics	1. Bilateral disease 2. Presence of at least three peripapillary "birdshot lesions"* inferior or nasal to the optic disk in one eye 3. Low-grade anterior segment intraocular inflammation (defined as ≤1+ cells in the anterior chamber†) 4. Low grade vitreous inflammatory reaction (defined as ≤2+ vitreous haze‡)
Supportive findings	1. HLA-A29 positivity 2. Retinal vasculitis 3. Cystoid macular edema
Exclusion criteria	1. Keratic precipitates 2. Posterior synechiae 3. Presence of infectious, neoplastic, or other inflammatory diseases that can cause multifocal choroidal lesions§

*Cream-colored, irregular or elongated, choroidal lesions with indistinct borders, the long axis of which is radial to the optic disk. Typical lesions are illustrated in Figure 1. †As defined by the Standardization of Uveitis Nomenclature (Sun) Working Group (13). ‡As defined by Nussenblatt and associates (14). § patient should be evaluated for the following disorders by appropriate history taking, physical examination, or laboratory tests: sarcoidosis with panuveitis or posterior uveitis; intraocular lymphoma; acute posterior multifocal placoid pigment epitheliopathy (APMPPE); multifocal choroiditis and panuveitis; punctate inner choroidopathy (PIC); multifocal evanescent white dot syndrome (MEWDS); pars planitis syndrome; posterior scleritis; sympathetic ophthalmia; Vogt-Koyanagi-Harada disease (chronic stage); syphilis; tuberculosis (15). Reprinted from Am J Ophthalmol, 141(1), Levinson RD, Brezin A, Rothova A, Et Al, Research Criteria for the Diagnosis of Birdshot Chorioretinopathy: Results of an International Consensus Conference, pages no 185-7, copyright (2006), with permission from Elsevier.

The data obtained from the review of medical records of BSRC patients were prospectively entered into a new database for analysis. The database included demographic and clinical data. Descriptive statistical analysis was performed using the Google Sheets® software program. The frequencies of the clinical and demographic variables upon presentation were tabulated to facilitate analysis. The University of Puerto Rico, Medical Sciences Campus Internal Review Board reviewed and approved this protocol.

Subjective complaints such as photopsia or floaters were tabulated whenever documented in the history section of a given patient's medical chart. Anterior uveitis was defined as the presence of a 0.5 or higher grade of white blood cells in the anterior chamber, as defined by the standardization of uveitis nomenclature (SUN) working group criteria (13). Vitritis was defined as any evidence of vitreous cells on a slit lamp examination. For this study, the assessment of cystoid macular edema was made exclusively through optical coherence tomography. In addition, vasculitis was assessed whenever it was present on either fundus drawings, photographs, or fluorescein angiograms. Finally, birdshot lesions were assessed whenever 3 or more such lesions were present on either fundus drawings or photographs or by the presence of hypocyanescent spots on indocyanine green (ICG) angiography.

Results

Our group identified a total of 12 patients with a diagnosis of BSRC, of which 3 were excluded from the analysis as they did not meet the BSRC research criteria as outlined in 2006 by a group of specialists attending an international conference aimed at determining such criteria (9). The disease onsets of the identified patients spanned 11 years, from 2007 through 2018. The clinical characteristics have been summarized (see table 2). The median age at presentation was 52 years, with a range of 41 to 63 years. Eight out of 9 patients were female (88.9%). All the patients were Hispanics and lived in the United States Commonwealth of Puerto Rico. All the patients were HLA-A29 positive.

At presentation, 89% of the patients complained of floaters, and 56% complained of photopsia. All the patients had bilateral disease. All the eyes in the analysis had a visual acuity of 20/60 or better; 94% had 20/50 or better and 72% had 20/25 or better. Thirty-three percent of the patients had at least 1 eye with anterior uveitis, which was bilateral in 33% and present in 22% of the eyes. The anterior uveitis grade was 1+ in 75% of the eyes and 0.5+ in 25% of the eyes. None of the eyes had keratic precipitates, iris nodules, or anterior or posterior synechiae.

Eighty-nine percent of the patients had evidence of active vitritis; this was bilateral in 88% of the patients and present in 83% of the eyes. Sixty-seven percent of the patients had evidence of retinal vasculitis; this was bilateral in 83% of the patients and present in 61% of the eyes. All the patients had evidence of typical BSRC lesions on both eyes. Cystoid macular edema was present in 33% of the patients and occurred in 33% of the eyes; when present, it was always bilateral.

Table 2. Demographic and clinical characteristics of patients with birdshot retinochoroidopathy

	N=9
Patient-specific characteristics at presentation	
Median age, years (range)	52 (42-63)
Sex, % female	89
Race, % Hispanic	100
HLA-A29 positive, %	100
Bilateral disease, %	100
Floaters (symptom), %	89
Flashers (symptom), %	56
Anterior uveitis, %	33
Active vitritis, %	89
Retinal vasculitis, %	67
Birdshot lesions, %	100
CME, %	33
Eye-specific characteristics at presentation	
Number of eyes	18
20/25 or better, %	72
20/50 or better, %	94
20/60 or better, %	100
Anterior uveitis, % (% bilateral)	22 (33)
Active vitritis, % (% bilateral)	83 (88)
Retinal vasculitis, % (% bilateral)	61 (83)
Birdshot lesions, % (% bilateral)	100 (100)
CME, % (% bilateral)	33 (100)

Discussion

BSRC has been previously cited in the literature as being a disease that almost exclusively affects Caucasian adults (16). However, recent case reports have started to challenge that notion, establishing the fact that BSRC may be present in patients of Hispanic descent or black race (4,12,17). Our cohort of Hispanic patients with HLA-A29-positive BSRC living in the United States Commonwealth of Puerto Rico should help further establish the presence of this disease outside the previously discerned racial and ethnic confines.

Similar to what has been observed in other primarily Caucasian cohorts, the median age at presentation for our patients was in the sixth decade of life (2,5). Furthermore, our cohort was predominantly female, and all the patients had bilateral disease, which concurs with the expected features of the disease (2,9,16). Most of the eyes presented with 20/50 or better visual acuity, with over 70% having 20/25 or better vision, suggesting that either our patients had been detected early or they had a milder variant of this disease.

We found prevalences, at presentation of anterior uveitis, vitritis, and cystoid macular edema, that were similar to those of other predominantly Caucasian cohorts (2). The most common presenting symptom in our cohort was floaters, whereas approximately half of the patients had flashes. All the patients in our analysis had the typical birdshot lesions, as well

as bilateral disease, both being features that are required to meet the meet the research criteria for the diagnosis of BSRC that were determined during the conference described earlier (9).

We excluded 3 patients from the analysis. These patients had a clinical assessment of BSRC made by the senior author that did not strictly meet the BSRC research diagnostic criteria. The first patient was excluded due to the lack of typical BSRC lesions on either eye. This female patient complained of photopsia and had vitritis, retinal vasculitis, and bilateral peripheral visual field constriction; in addition, she was positive for HLA-A29. After an extensive workup to rule out other potential etiologies, an assessment of early BSRC was made, and the patient was treated with oral prednisone and mycophenolate mofetil (MMF), which resulted in the resolution of her symptoms. This patient had followed a chronic disease course of over 9 years and had recurrences whenever taken off of steroids and MMF.

The second patient was an HLA-A29-positive female who had typical BSRC lesions; however, due to the unilateral nature of her disease, she did not meet the diagnostic criteria for research (9). This female patient also had received treatment with oral prednisone and MMF, which treatment had resulted in disease stability. Despite having been treated with MMF, her disease followed a chronic course, with flares occurring whenever the prednisone was tapered to dosages below 7.5mg per day. Whether these 2 patients would have eventually progressed to a full-blown disease manifestation with BSRC lesions on both eyes, might never be known because they received aggressive treatment for this potentially blinding and devastating disease.

A third patient was excluded due to his having anterior chamber cell grades of 2+ in the right eye and 3+ in the left eye; however, this male patient was HLA-A29 positive, had bilateral 1+ vitritis and multiple typical BSRC lesions that were found most frequently in the inferonasal quadrants of both eyes. He did not have granulomatous keratic precipitates or anterior chamber synechiae. This patient was treated with MMF and high dose oral corticosteroids, which were gradually tapered off over several months. After 1 year of therapy, he achieved remission. None of the excluded patients had keratic precipitates, iris nodules, or anterior or posterior synechiae, in either eye.

The term Hispanic refers to persons who are of Latin American descent in particular; those who are of Cuban, Puerto Rican or Mexican origin (18). As Puerto Rico has a predominantly Hispanic population, it is not customary in our local medical culture to make notes with regards to skin color, particularly for patients who have been identified as native Spanish speakers. However, genetics studies have found that in general terms, the Puerto Rican population is a mestization with varying degrees of European/Mediterranean, sub-Saharan African, and Taino Native American ancestry, as evidenced by mitochondrial DNA studies (19-21). Most of the patients in our cohort likely had a variant of the aforementioned racial mix.

As is the case with the results of any retrospective study, ours should be interpreted with caution. Our study may reflect referral bias, as less severe cases of BSRC may have been managed elsewhere by other specialists. Conversely, the combined practices of the 2 senior authors probably receive the majority of uveitis referrals on the island of Puerto Rico. Our study is also limited by the relatively small sample size compared with series from centers that receive nationwide referrals and perhaps serve more highly populated states.

Resumen

Objetivo: Describir las características en la presentación de una cohorte de pacientes hispanos con retinocoroidopatía en perdigonada. Métodos: Se realizó una revisión retrospectiva de expedientes médicos de pacientes hispanos con retinocoroidopatía en perdigonada. Se analizaron las características demográficas y clínicas. Resultados: Nueve pacientes que cumplieron con los criterios de investigación para el diagnóstico de retinocoroidopatía en perdigonada fueron identificados e incluidos en el análisis; todos los cuales fueron positivos para HLA-A29. La edad media de presentación fue de 52 años; el 89% de los pacientes eran mujeres, todos hispanos. El noventa y cuatro por ciento de los ojos tenían una agudeza visual inicial de 20/50 o mejor, mientras que el 72% midió 20/25 o mejor. El 61% de los ojos tenía vasculitis retiniana, que fue bilateral en el 83% de los casos. El treinta y tres por ciento de los pacientes tenían evidencia de edema macular cistoide en la presentación, el cual siempre fue bilateral. Todos los ojos tenían las típicas lesiones en perdigonada. Conclusiones: La retinocoroidopatía en perdigonada se puede hallar en pacientes hispanos. Nuestro estudio sugiere que las características en la presentación en hispanos podrían ser similares a las de las cohortes caucásicas.

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