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A case series study on exploring the role of HLA B27 among patients with retinitis pigmentosa and uveitis and short-term treatment response

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Purpose. *We present a case series of retinitis pigmentosa associated with uveitis and share our clinical observations and insights on this co-occurrence.*

Materials and methods. *This prospective, non-controlled case series included 7 patients with retinitis pigmentosa (14 eyes) who presented with concurrent signs of uveitis.*

Results. *Among 173 patients with retinitis pigmentosa, 7 (4 males, 3 females) presented with signs of intermediate uveitis; 3 of them also had mild anterior uveitis. No sex predilection was observed. The mean age at uveitis diagnosis was 26.9 years (range 19–37). RP had been diagnosed more than 10 years earlier in 4 patients, 3 years earlier in 1 patient, and 2 years earlier in another; only 1 patient was diagnosed with both RP and uveitis during the current study. In addition to typical RP features, patients showed vitreous cells graded 1+ to 2+, and vitreous haze of 0.5+ to 1+. Cystoid macular edema was found in 5 patients. None reported acute onset of floaters, blurred vision, or central vision loss, and no systemic complaints were recorded. HLA-B27 positivity was identified in 5 patients (2 males, 3 females); 2 of them were subsequently diagnosed with low-activity ankylosing spondylitis, while the others were classified as having HLA-B27-associated uveitis. The remaining 2 patients were considered to have either idiopathic uveitis or significant inflammatory activity related to RP. All patients received anti-inflammatory treatment.*

Conclusions. *The potential association with HLA-B27 should be taken into account in RP patients presenting with signs of anterior or intermediate uveitis, regardless of sex or the absence of acute uveitis symptoms and systemic manifestations.*

Key words:
retinitis pigmentosa, anterior uveitis, intermediate uveitis, HLA-B27 positive uveitis, retina, uveitis

Introduction. Retinitis pigmentosa (RP) is a heterogeneous group of inherited disorders affecting photoreceptors and the retinal pigment epithelium (RPE) which gradually leads to nyctalopia and visual field constriction. The total prevalence of RP among the general population is variably reported 1 case for each 2500-7000 persons, affecting all races and both genders equally. [8, 13, 19].

RP can lead to blindness, causing an emotional and economic burden particularly among young adults. [5, 23]. Patients who develop cystoid macular edema (CME) face the most unfavorable consequences as it leads to central vision impairment. CME can occur 50% of RP cases [1, 14, 15] due to a combination of pathogenetic factors, including breakdown of the blood-retinal barrier, failure (or dysfunction) of the pumping function of the retinal pigment epithelium (RPE), Müller cell oedema and dysfunction, antiretinal antibodies and vitreous traction [24].

Inflammation has recently been implicated as a critical mechanism responsible for the progressive nature of neurodegeneration [4]. Recent basic and clinical studies suggest the importance of chronic inflammation in the pathogenesis of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and retinal degenerative diseases. Although, the primary causes of RP are now recognized as genetic defects in photoreceptors or the retinal pigment epithelium. Recent studies emphasize the role of sustained chronic inflammatory response as a confounding factor in the pathogenesis of RP [29].

Co-presence of uveitis in patients with RP is uncommon, but it has been reported in the literature [9]. In these patients, the uveitis may vary in intensity and localization within the uveal track. So far, Fuch's heterochromic uveitis (FHU) has been most common type of uveitis reported in association with RP, [7, 9, 10, 14, 17, 25, 26, 27] based mostly on sporadic cases or small case series. To our knowledge, the study by Majumder P.D. et al. represents the largest numbers of RP patients with uveitis involving 22 consecutive patients identified over a period of 30 years [10].

In this study we present a case series of bilateral uveitis in patients with RP and share our prospective observations

of exploring for possible risk factors of co-occurrence and potential role of Human Leukocyte Antigen B27 (HLA-B27).

Materials and methods

This was a single center, prospective, non-controlled case series study approved by the State Institution "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine" Research Ethics Board. The study involved a total of 173 patients with RP who were followed by our center for 2 years. Seven patients were identified with coexisting uveitis and further studied upon signed informed consent.

All RP patients routinely underwent a complete ophthalmologic examination including best-corrected visual acuity (BCVA) (Snellen, ft), slit-lamp examination, and dilated fundus examination, electroretinography (ERG), dilated digital fundus photos, optical coherence tomography (OCT) (Spectralis, Heidelberg Engineering, Heidelberg, Germany). All patients underwent visual field testing using standard automated perimetry (Humphrey 30-2 protocol). The RP diagnosis was relied on the patients' complaints (such as history of night blindness) visual field constriction, and marked reduced or non-recordable a- and b-wave amplitudes on ERG, in addition to characteristic of fundus changes (bone spicules, diffuse granularity or stippling and pigment clumping, attenuated retinal vessels, optic disc pallor).

The uveitis was classified and graded according to the Standardization of Uveitis Nomenclature Working Group (SUN) and National Institute of Health (NIH) criteria while entering the study [18]. RP patients with coexisting uveitis signs underwent additional examination, such as a complete blood count, erythrocyte sedimentation rate, urine analysis, syphilis serology, HLA-B27, antinuclear antibodies, chest x-ray, brain MRI and patients suspected autoimmune conditions were referred to a rheumatologist.

All RP patients got standard neuroprotective, trophic, vasodilative treatment, and photobiomodulation. In addition to this treatment, patients with uveitis received periocular dexamethasone injections and systemic oral methylprednisolone, as recommended by the provider when necessary. In some cases, sub-tenon triamcinolone injection (STI) was performed as previously described [20, 30].

Results

Among 173 RP patients screened, 7 patients (4 males, 3 females) were enrolled in the study for the presence of uveitis. All cases had bilateral intermediate uveitis with (n=3) or without (n=4) signs of slight anterior uveitis. In addition to classic picture of RP, all patients had NIH criteria for vitreous cells 1+ or 2+, and for vitreous haze 0.5+ or 1+. Five patients had CME and one of these patients also had papilledema with optic nerve drusen.

In 4 patients, the diagnosis of RP preceded the diagnosis of uveitis for more than 10 years. In one patient, RP preceded for 3 years, and in another for 2 years. In a study cohort 1 patient had RP and uveitis diagnosed first time together. Clinically, all 7 patients had typical RP complaints with deterioration in central vision over the past year and complaints of floaters and blurred vision. This was in conjunction with complaints of visual fields impairment, poor mesopic and night vision for more than 3 years (4 of them even more than 10 years). None of the 7 patients had ophthalmalgia or acute onset of floaters, blurred vision, or acute onset of deterioration in central vision. All 7 had no signs of FHU and were negative for infectious disease work-up.

Interestingly, HLA-B27 antigen was positive in 5 (2 males, 3 females) out of these 7 patients. 37 years old female and 19 years old male were further evaluated by rheumatologist for arthralgia, and mild morning stiffness of the lower back, respectively. Both were diagnosed with ankylosing spondylitis with low disease activity. Neither of these patients had CME or anterior uveitis. The remaining 3 cases were considered as HLA-B27 positive uveitis. Two patients who were HLA-B27 negative were considered as either idiopathic uveitis or inflammatory component of RP.

As shown in Table 1, five patients with CME with (n=3) or without (n=2) positive HLA-B27 were treated with subtenon triamcinolone injection (STI). Two out of 5 developed ocular hypertension after the STI and required antihypertensive medication. Patients who were diagnosed with ankylosing spondylitis were treated with systemic disease modifying agents in collaboration with rheumatologist.

Table 2 summarizes the treatment response at one month follow-up after start of treatment. We observed improvement in all patients except one who didn't come to appointed visit. This included improvement of BCVA and resolution of active anterior uveitis. CME resolved in 1 patient, who got triamcinolone STI, other patients had partly resolved CME. Among patients with intermediate uveitis, two achieved remission with oral methylprednisolone, while the others showed partial improvement in disease severity.

Discussion

Central vision loss due to uveitis and/or macular edema in RP patients is a devastating consequence, since these patients already suffer from pre-existing peripheral vision impairment. This brings a challenge to distinguish the microenvironmental changes and understand the convoluted progression of disease pathogenesis for targeted treatment and avoid vision loss.

In this study we presented our tertiary center experience on RP associated with uveitis. Out of 173 patients with RP, seven had co-existing uveitis. This is compatible with a report by D. Damla Sevgi et al. on five patients who presented with RP-like retinal pigmentary changes, which were eventually attributed to longstanding uveitis. This study demonstrates that uveitis can mimic RP in atypical cases. Described patients were in age from 33 to 66 years old. Retinal pigmentary changes were bilateral in three cases and unilateral in two cases. All patients had nega-

Table 1. RP patient's characteristics at enrollment to the study

Patient N	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Gender	F	M	M	M	M	F	F
Age (years)	28	30	19	19	24	31	37
Family rheumatologic history +/-	-	-	-	-	-	-	+
Complaints of visual fields impairment, bad mesopic and night vision (years)	+ More than 10 years	+ About 5 years	+ About 3 years	+ About 3 years	+ More than 10 years	+ More than 10 years	+ More than 10 years
Complaints of deterio-ration in central vision over the past year +/-	+	+	+	+	+	+	-
Complaints of floaters and blurred vision +/-	+	+	+	+	+	+	+
RP diagnosis was made in this visit/before	Before	In this visit	Before	Before	Before	Before	Before
The duration of the already known diagnosis RP (years)	More than 10 years	N/a	2 years	3 years	More than 10 years	More than 10 years	More than 10 years
Anterior uveitis +/-	+ OU	+ OU	+ OU	-	-	-	-
Keratic precipitates +/-	+	+	+	-	-	-	-
SUN criteria for anterior chamber cells	0.5+	0.5+	0.5+	0	0	0	0
SUN criteria for anterior chamber flare	0	0	0	0	0	0	0
Intermediate uveitis +/-	+ OU	+ OU	+ OU	+ OU	+ OU	+ OU	+ OU
NIH criteria for vitreous haze	0.5+	0.5+	1+	1+	0.5+	0.5+	0.5+
NIH criteria for vitreous cells	1+	1+	2+	2+	2+	1+	2+
CME +(μ) /-	-	+ OD:785 OS:537	+ OD:569 OS:603	+ OD:840 OS:789	+ OD:535 OS:594	+ OD: 713 OS: 614	-
BCVA	OD:20/40 OS:20/40	OD:20/400 OS:20/25	OD:20/40 OS:20/40	OD:20/80 OS:20/50	OD:20/25 OS:20/30	OD:20/200 OS:20/200	OD:20/40 OS:20/40
Cataract +/-	+	-	+	+	+	+	+
Ocular hypertension	+	-	-	-	-	-	-
Other ocular pathology	-	-	OU: optic nerve drusen, papilledema	-	-	-	-
Uveitis ethiology	HLA-B27-associated	Idiopathic?/ inflammatory component of RP	HLA-B27-associated	HLA-B27-associated	Idiopathic?/ inflammatory component of RP	HLA-B27-associated	HLA-B27-associated
Systemic complaints	none	none	none	Slight back stiffness in the morning	Diminished hearing, behavioral problems	none	Arthralgia
Systemic diagnosis	none	none	none	Ankylosing spondilitis	Usher syndrome, schizophrenia	none	Ankylosing spondilitis
Anti-inflammatory treatment modalities	Oral methil-prednisone	STI	STI	Oral methil-prednisone, sulfasalazin,STI	STI	STI	Oral methil-prednisone, sulfasalazine

Table 2. Treatment response of RP patients with uveitis at one month follow-up.

Patient N	1	2	3	4	5	6	7
Subjective improvement in visual fields, mesopic and night vision	-	+	N/a	+	-	-	-
Subjective improvement in central vision	+	+	N/a	+	+	+	+
Active anterior uveitis +/-	-	-	N/a	-	-	-	-
Active Intermediate uveitis +/-	+	+	N/a	+	+	-	-
CME +(μ) /-	-	- OD:209 OS:219	N/a	+ OD:428 OS:314	+ OD:459 OS:507	+ OD: 489 OS: 467	-
BCVA	OD:20/32 OS:20/45	OD:20/60 OS:20/22	N/a	OD:20/30 OS:20/25	OD:20/20 OS:20/20	OD:20/125 OS:20/125	OD:20/34 OS:20/28
Ocular hypertension	-	-	N/a	+ (probably associated to STI)	-	+ (probably associated to STI)	-
Anti-inflammatory treatment modalities	Continuation of oral methilprednisone	Oral methilprednisone	N/a	Continuation of oral methilprednisone, sulfasalazine	Topical nepafenac	Oral methilprednisone	Continuation of oral methilprednisone, sulfasalazine

tive family history. In differential diagnosis between RP and RP-like retinal pigmentary changes the authors relied on significant retinal vascular leakage or deep multifocal leakage on FA, which is significantly more common in uveitis than inherited retinal diseases. Also, authors got good response to steroids or other immunomodulators which testified towards uveitis. And another clue to the uveitis authors identified as perivascular pigmentation localization [22].

Of course, we considered possibility of RP-like mimicking uveitis. But in our cases patients were much younger (19 to 37 years vs. 33 to 66). We found no sexual predilection, and the mean age at the time of diagnosing uveitis was 26.9 years (range 19 to 37 years). RP changes were bilateral. They had complaints of visual fields impairment, bad mesopic, and night vision for more than 3 years (4 of them even more than 10 years). Herewith they developed complaints of deterioration in central vision only over the past year. All patients had typical for RP impairment in ERG. Also, all patients met criteria of typical RP fundus changes (retinal vessel attenuation, waxy pallor optic disc, and bone spicule pigmentation [12]). Pigmentation didn't have perivascular localization. So, we didn't suggest retinal changes as consequence of uveitis and tilt toward coexistence RP and uveitis.

We believe, in our study, the etiology of uveitis, differs from previously studies. In the study by Chowers I. et al on 338 patients with RP, it was found that 4 patients (1.2%) had the typical findings of FHU [7]. The largest study on this issue was conducted by Parthopratim et al, who analyzed 8364 PR-patients in a more than 30 year period. They found uveitis in 32 eyes of 22 RP-patients, so the prevalence of uveitis in RP-patient was 0.26%. The anterior uveitis was the most common in their study (18 eyes), followed by intermediate uveitis (14 eyes). Authors defined that among 18 eyes with anterior uveitis, 5 had typical feature of FHU and 3 eyes presented with acute non-granulomatous anterior uveitis [10]. In turn, we diagnosed intermediate uveitis in all our patients, and 3 of them also had anterior uveitis. In general, the majority of reports about RP association with uveitis focused on FHU. These reports are not so large like mentioned above [3, 9, 17, 21, 26, 27, 28]. None of our patients had signs of FHU and all cases were bilateral. In comparison, our study, suggests positive for HLA-B27 antigen can be a risk factor for uveitis among patients with RP. Furthermore, these patients may be prone to develop ankylosing spondylitis.

We did not find any publications on the HLA-B27 positive uveitis associated with RP. HLA-B27 is present about 8% of the population in Eastern Europe. Thus, in our hands finding HLA-B27 in 5 out of 173 patients or 2.89% is not surprising. In fact, this number is likely to increase close to 8% if all 173 were to be tested for HLA-B27. This is compatible with the previous report from 1981 on HLA typing in RP. Accordingly, there was no significant difference in the frequency of any HLA (A, B, C) antigen, when comparing autosomal dominant and recessive RP patients with a control population [16]. The study was conducted on 173 patients, and it is obvious that patients with uveitis were not included in the study, so our data does not go against this study. However, what is interesting with our data is that 5 out of 7 or 71.43% of patients with RP and uveitis were HLA-B27 positive. It is also interesting that in all 5 patients, the signs and symptoms of RP preceded

uveitis for years. HLA- B27, a surface antigen expressed on every nucleated cell, is known to be associated with immunopathogenesis of arthritis and inflammatory bowel disease though molecular mimicry and cellular immunity [6]. Therefore, it is likely that presence of HLA-B27 in patients with RP can be a confounding factor that promotes ocular inflammation and progression of eye disease. However, it is likely that other host factors and/or environmental influences, such as certain infections, also play a pivotal role to augment the effects of HLA-B27 in the setting of RP.

Concerning the remaining 2 patients with uveitis of unknown etiology, we cannot exclude that vitritis was a manifestation of the inflammatory reaction in RP. This data is consistent with Yoshida N. et al paper. They reported occasional or more cells in the vitreous cavity in 61.5% (313 eyes) of 509 eyes with RP; 1+ or more cells in 37.3% (190 eyes). Authors also detected increased levels of a variety of proinflammatory cytokines and chemokines in the aqueous humor and vitreous fluid of RP patients. Our observations support the concept that sustained chronic inflammatory reaction occurs in patients with RP and is closely related to the disease pathogenesis [29].

Parthopratim Dutta Majumder et al emphasize that majority of the patients tend to have milder inflammation in anterior chamber and vitreous, and are usually asymptomatic which might be a reason for undiagnosed. In their study, only three RP-patients had prominent symptoms of acute uveitis [10]. Similar in our series there were no acute uveitic patients. It's very important to remember that uveitis in RP patients has a tendency to non-acute manifestation. We have to accurately collect history and clinical testing in order to not miss unspecific symptoms.

As a limitation to our study the main factors are the absence of genetic analysis in RP patients and low number of patients. In addition, The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine is a level 3-4 center, so there is a rare disease collaborative initiative is needed for better patient care. Unique position of Filatov`s Institute to accept patients with different level of complexity gives us an opportunity to provide country wide observational study. Treatment of RP and uveitis is a challenge to a provider. Current approaches include stem cell therapy, gene therapy and retinal implant, but more studies needed to provide evidence-based therapy that will include many specifics of combined diseases, as many methods are under development and quite expensive.

Various methods for management of RP-associated CME includes oral and topical carbonic anhydrase inhibitors, oral, topical, intravitreal and periocular steroids, topical non-steroidal anti-inflammatory medications, laser photocoagulation, vitrectomy with internal limiting membrane peeling, oral lutein and intravitreal anti-vascular endothelial growth factor injection, but there are no studies yet providing high-level evidence for RP-CME treatments [2, 11, 24]. In our case series we focused on the treatment of uveitis and the treatment of macular edema as a complication to the combined risk factors. Summarizing the analysis, 3 patients were prescribed for systemic immunosuppressive drugs and 5 patients got STI. After one month of treatment all patients had BCVA improvement and decrease of uveitis inflammation. CME resolved in 1 patient and partially resolved in 6 patients. To enhance data sensitivity for risk factor analysis, further study with a larger number of participants is needed.

Conclusions. In patients with combined RP and anterior or intermediate uveitis, even in the absence of acute symptoms or systemic manifestations, the possibility of an HLA-B27 association should be considered, regardless of sex. This case study demonstrates the effectiveness of a multidisciplinary diagnostic approach, combining both local (topical) and systemic anti-inflammatory therapies, including corticosteroids or other immunomodulators to effectively manage inflammation and prevent vision loss.

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Abbreviation. *BCVA – best-corrected visual acuity; CME – cystoid macular edema; ERG –electroretinography; FHU – Fuch's heterochromic uveitis; NIH – National Institute of Health; RP – retinitis pigmentosa; RPE – retinal pigment epithelium; SD-OCT – spectral-domain optical coherence tomography; STI – subtenon triamcinolone injection; SUN – Standardization of Uveitis Nomenclature Working Group.*

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