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Clinical pathogenesis of macular holes in patients affected by Retinitis Pigmentosa

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Abstract. – ***Background*. To define the main clinical mechanisms involved in the pathogenesis of macular holes (MH) in patients affected by Retinitis Pigmentosa (RP).**

***Methods*. 236 RP subjects were enrolled in this study and ophthalmologically examined according to a standard FIARP (Italian Federation of the RP Associations) protocol. The prevalence of posterior vitreous detachment (PVD) as well as all types of RP-related macular abnormalities – especially vitreoretinal interface alterations (VRIA), cystoid macular edema (CME), "bull's eye maculopathy" (BEM) and MH – was reported; statistical analyses and correlations were assessed by means of Student *t* test and Pearson χ^2.**

***Results*. VRIA and CME were observed in 26.15% and 9.45% of the cases respectively and resulted significantly associated with MH, since they were constantly present in 22 of the 25 eyes affected by MH (88%) ($\chi^2 = 50.4$; $p < 0.01$). In particular, in 9 of these cases (40.9%) MH was correlated to both CME and VRIA, while in 11 (50%) and 2 (9.1%) eyes CME or VRIA were present separately. A normal biomicroscopic macular appearance, PVD and BEM were found in 26.81%, 6.6% and 21.54% of the cases respectively.**

***Conclusions*. Further studies involving a larger number of patients are required to complete these preliminary results. However, the present investigation seem to confirm the data already reported in the literature, i.e. that pathogenesis of MH in RP is strictly correlated to the presence of VRIA, cellophane maculopathy and cystic foveal degeneration with CME.**

Key Words:

Cystoid macular edema, Macular hole, Retina, Retinitis Pigmentosa, Vitreoretinal interface, Vitreous.

Introduction

Retinitis Pigmentosa (RP) is characterized, in its most typical form, by night blindness, visual field constriction and electroretinographic response alterations of various degrees. Pale "waxy" optic disc pallor, attenuation of the retinal arteries and a typical intraretinal "bone spicule" pigmentation involving the equatorial retina represent hallmarks of this inherited degenerative retinal disorder[1-3]. Central vision is usually spared until comparatively late in the disease when posterior subcapsular cataract and cystoid macular edema (CME) may occur[4-7]. In particular, the persistence of CME over prolonged periods of time may lead to a legal blindness due to retinal pigment epithelium atrophy ("bull's eye maculopathy"or BEM) and partial or full thickness macular holes (MH)[1-7].

Vitreous degeneration, vitreoretinal interface alterations (VRIA) with epiretinal membrane formation ("cellophane maculopathy") as well as CME seem to represent the most important factors able to determine MH[1-6]. However, the exact cause of MH development in RP patients is still uncertain.

It was therefore the purpose of this paper to analyse the main clinical mechanisms involved in the pathogenesis of MH in RP.

Subjects and Methods

A total amount of 236 RP subjects (472 eyes) (116 M and 120 F; mean age: 38.5 ± 14.9 years) were selected from our patient population and retrospectively studied.

The diagnosis of RP was based on the clinical, genetic and instrumental criteria established by Marmor et al.[8]. Only patients affected by a typical rod-cone degenerative disorder and presenting a clearly identified inheritance pattern (autosomal dominant, autosomal recessive or X-linked) were enrolled.

Cone-rod dystrophies and RP syndromic forms (i.e., Usher or Laurence-Moon-Bardet-Biedl) were excluded from this investigation. Other therapies in progress (e.g., systemic corticosteroids, thiazide diuretics, digitalis, nonsteroidal anti-inflammatory agents, anticoagulants) as well as age-related macular degeneration, diabetes, smoking (> 10 cigarettes daily), pregnancy, aphakia or pseudophakia, intraocular pressure > 22 mmHg, refractive error > ± 4 D, history of vitreoretinal surgery, previous retinal occlusive disorders or other systemic diseases (e.g., tyroid pathologies; cancer; vasculitis; obliterating peripheral arteriopathies) were also exclusion criteria.

The necessary ethical approvals were obtained by the University Commitee and the study was conducted in compliance with the Declaration of Helsinki.

All patients underwent a careful ophthalmological examination according to a standard FIARP (Italian Federation of the RP Associations) protocol[9]. In particular, vitreal static and dynamic biomicroscopy was performed on fully dilated pupils (one drop of tropicamide 0.5% + phenylephrine 1% in both eyes) by means of a Haag-Streit 900 slit-lamp and high positive power precorneal lenses (Super Field and +78D Volk Lenses). The examination angle ranged from 14° to 20° and the slit-lamp beam amplitude measured 12 mm. Vitreal alterations were carefully classified according to our 6-level grading, elsewhere described in greater detail[9].

Biomicroscopy combined with binocular indirect ophthalmoscopy and fluorescein angiography (Heidelberg Retina Angiograph) allowed a full examination of the retina. As already done in our most recent paper[7], the ETDRS classification of clinically significant macular edema[10] was followed in order to determine the correct area of CME to be graded and, inside this area, all angiograms were graded by one examiner only (E.M.V.) according to the previously published Fishman's classification of macular edema in RP[11].

The prevalence of posterior vitreous detachment (PVD) as well as all types of RP-related macular abnormalities – especially VRIA, CME, BEM and MH – was reported. Statistical analyses and correlations were assessed by means of Student t test and Pearson χ^2 (Apple Macintosh, StatView II program). Statistical significance was expressed in terms of p values at 0.01 or less.

Results

Among a total amount of 472 eyes, only 455 of them were statistically considered since pseudophakia was present in 17 eyes. The distribution and percentages of all the vitreoretinal features found in our patients have been graphically shown in Figure 1 and, in greater detail, in Table I. Normal macula (26.81% of the cases), BEM (21.54%), CME (9.45%), VRIA (26.15%) and mixed forms (15.39%) have been observed. PVD was diagnosed in 6.6% of the total number of cases (30 of 455 eyes), a percentage that increases to 16.8% if considering only those presenting VRIA with or without cellophane maculopathy (178 eyes; Table I: E+G+H+I).

A total number of 25 eyes (5.5%) were affected by partial or full thickness MH, being VRIA and CME significant pathogenetic factors since they were constantly present in 22 of them (88%) ($\chi^2 = 50.4$; $p < 0.01$). In particular, in 9 of these cases (40.9%) MH was correlated to both CME and VRIA, while in 11 (50%) and 2 (9.1%) eyes CME or VRIA were present separately. MH was identified as isolated vitreoretinal pathology in 3 cases only (0.66% or 12% if considering, respectively, the total number of eyes or only those affected by MH).

Moreover, among a total number of 57 eyes presenting both VRIA and CME (Table I: H+I), MH was diagnosed in 9 of them (15.79%) compared to 11 (20.37%) of 54 eyes (Table I: D+F) and 2 (1.65%) of 121 eyes (Table I: E+G) presenting CME or VRIA separately.

Discussion

Despite the remarkable clinical impact of MH both on the natural history of the disease and on the ordinary life of RP patients, the pathogenesis of this important retinal complication is still poorly understood.

According to the literature, VRIA, cellophane maculopathy, BEM and CME are

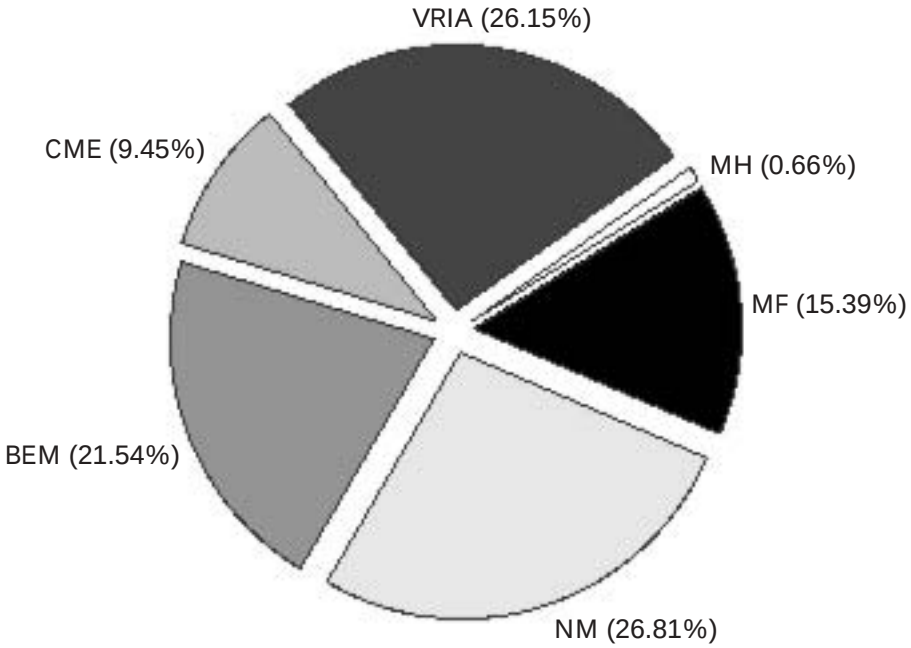

Figure 1. Distribution and percentages of the vitreoretinal features found in the examined eyes (NM = normal macula; BEM = "bull's eye" maculopathy; CME = cystoid macular edema; VRIA = vitreoretinal interface alterations; MH = macular hole; MF = mixed forms).

commonly associated with RP and seem to represent the most important factors able to determine MH[1-6,12,13]. In 1977, Fishman et al., in a retrospective study conducted on 110 RP patients, reported that 63% of these cases presented a BEM, 20% a CME and/or VRIA and 17% a normal macular appearance[4]. Similar results were also found in a second paper, even though performed on 31 subjects only, where the following percentages were described: 58% BEM; 19% CME and/or VRIA; 23% normal macula[5]. Thereafter, Pruett confirmed these findings in a large clinical study that statistically assessed 383 RP eyes: 42% BEM; 14% CME; 20% VRIA; 24% normal macula[6].

Regarding MH, both Fishman et al. and Pruett found a partial or full thickness MH in the late phases of the disease only and always associated with cystic degeneration of the macular area and preretinal gliosis[4-6]. Moreover, according to a very recent paper that histologically and cytologically studied this issue, these epiretinal membranes con-

Table I. Different associations found in the examined eyes between retinal and vitreal alterations (+ = presence; – = absence).

Macular hole	*Cystoid macular edema*	*Bull's eye" "maculopathy*	*Vitreoretinal interface alterations*	*Eyes*	
+	–	–	–	3 (0.66%)	A
–	–	–	–	122 (26.81%)	B
–	–	+	–	98 (21.54%)	C
+	+	–	–	11 (2.42%)	D
+	–	–	+	2 (0.44%)	E
–	+	–	–	43 (9.45%)	F
–	–	–	+	119 (26.15%)	G
–	+	–	+	48 (10.55%)	H
+	+	–	+	9 (1.98%)	I
Total				**455**	

tain many cells, including macrophages, Müller cells, glial cells and fibroblasts, suggesting that an immune- and RP-related degeneration of the vitreous body may represent a main cause of MH[12].

Observations from this study seem to confirm these findings, even though lower percentages of BEM and CME and a higher percentage of normal macula were found compared to the above mentioned papers. However, this difference may probably be due not only to the younger age of our patients (38.5 ± 14.9 years) but also to the more accurate classification used that allowed us to identify pure and mixed forms and to differentiate, contrary to Fishman et al., between CME, VRIA and MH.

In summary, our investigation may not be considered conclusive, because of the relatively small number of patients enrolled and their young mean age. However, even though further studies are required to determine the main clinical mechanisms involved, our results confirm the data already reported in the literature, i.e. that pathogenesis of MH in RP subjects seem to be strictly correlated to the presence of VRIA, cellophane maculopathy and micro/macrocystic foveal degeneration with CME.

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