MORPHOLOGY AND FUNCTIONAL CHARACTERISTICS IN ADULT VITELLIFORM MACULAR DYSTROPHY

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Purpose: Detailed morphologic and functional evaluation of adult vitelliform macular dystrophy (AVMD).

Methods: The records of 61 consecutive AVMD patients (inclusion criterion: vitelliform lesion smaller than one disk diameter at least in one eye) were evaluated retrospectively regarding visual acuity, color vision, perimetry, retinal pigment epithelium (RPE) autofluorescence, fluorescein angiography, electro-oculography, full-field and multifocal electroretinography, and molecular genetic evaluation of the VMD2 and RDS/peripherin genes.

Results: The mean age of subjects was 54.6 years. Visual loss was variable (median, 0.6; range, 1.25–0.05). Color vision and visual field were normal in about half of the patients but presented defects with high variability in the remaining patients. Autofluorescence findings showed increased fluorescence within the foveal yellow lesion in 76%. In the majority of eyes, the amplitude of the 30 Hz flicker response of the full-field electroretinogram (72%) and the central P1 amplitude of the multifocal electroretinogram (63%) were reduced. Mutational analyses revealed a potentially disease-associated mutation in the RDS/peripherin gene in one patient.

Conclusion: AVMD is characterized by late onset, slow progression, good prognosis, and high variability of morphologic and functional abnormalities resulting frequently in misdiagnosis. Autofluorescence findings indicate lipofuscin accumulation in the yellow lesion. Electroretinography revealed a generalized cone system dysfunction with increasing severity toward the fovea.

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The differential diagnosis of macular disorders in adults includes a variety of acquired and inherited disorders. In general, age-related maculopathy is suspected in patients older than 50 years of age, whereas inherited disorders are more frequent in the first two decades of life. However, some inherited macular disorders manifest in older adults. In our department, adult vitelliform macular dystrophy (AVMD) is the most frequent macular dystrophy in patients older than 40 years of age. The clinical features of AVMD were first described by Gass in 1974.[1] The typical ophthalmoscopic finding in AVMD is a solitary, round or oval, slightly elevated, yellow, subretinal lesion of the fovea, ranging from one-third to one disk diameter in size and often accompanied by a central pigmented spot. The onset is usually between 30 and 50 years of age. The patients may report mild visual blurring and

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Table 1. Adult Vitelliform Macular Dystrophy Studies Arranged by Number of Patients and the Different Terms and Abbreviations for this Disorder

Study	No. of Patients	Terms and abbreviations used
Glacet-Bernard et al, 1990[3]	85	Adult macular vitelliform degeneration
Greaves et al, 1990[4]	81	Adult vitelliform macular degeneration (AVMD)
Theischen et al, 1997[5]	49	Adult vitelliform macular degeneration (AVMD)
Sabates et al, 1982[6]	42	Pseudovitelliform macular degeneration (VMD)
Vine & Schatz, 1980[7]	33	Adult-onset foveomacular pigment epithelial dystrophy (AOFPED)
Burgess et al, 1987[8]	31	Adult(-onset) foveomacular vitelliform dystrophy (AOFVD)
Benhamou et al, 2003[9]	14	Adult(-onset) foveomacular vitelliform dystrophy (AOFVD)
Brecher & Bird, 1990[10]	12	Adult(-onset) vitelliform macular dystrophy
Epstein & Rabb, 1980[11]	10	Adult vitelliform macular degeneration (AVMD)
Gass, 1974[1]	9	Peculiar foveomacular dystrophy
Battaglia Parodi et al, 1996[12]	8	Adult(-onset) foveomacular vitelliform dystrophy (AOFVD)
Kingham & Lochen, 1977[13]	6	Vitelliform macular degeneration
Marmor, 1979[14]	6	Vitelliform lesions in adults
Saito et al, 2003[15]	6	Adult(-onset) vitelliform macular dystrophy (AVMD)
Bloom et al, 1981[16]	5	Adult vitelliform macular degeneration (AVMD)
Salinas Alamán et al, 2003[17]	4	Adult(-onset) foveomacular vitelliform dystrophy (AOFVD)
Fishman et al, 1977[18]	3	Pseudovitelliform macular degeneration (VMD)
Hodes et al, 1984[19]	3	Pseudovitelliform macular dystrophy
Dubovy et al, 2000[20]	3	Adult-onset foveomacular pigment epithelial dystrophy (AOFPED)
Snyder et al, 1978[21]	2	Vitelliform macular lesion
Skalka, 1981[22]	2	Vitelliform macular lesion
Patrinely et al, 1985[23]	1	Foveomacular vitelliform dystrophy: adult type (FVDAT)
Giuffre & Lodato, 1986[24]	1	Macular vitelliform lesions/vitelliform dystrophy of the RPE
Jaffe & Schatz, 1988[25]	1	Adult-onset foveomacular pigment epithelial dystrophy (AOFPED)
Dufek & Penn, 1998[26]	1	Adult(-onset) foveomacular vitelliform dystrophy (AOFVD)
Battaglia Parodi et al, 2000[27]	1	Adult(-onset) foveomacular vitelliform dystrophy (AOFVD)
Yamaguchi et al, 2001[28]	1	Adult(-onset) foveomacular vitelliform dystrophy (AOFVD)

metamorphopsia. Generally, the visual loss is slowly progressive. Additional characteristic features include a central nonfluorescent spot surrounded by an irregular ring of hyperfluorescence in fluorescein angiography.[1,2] In contrast to juvenile vitelliform macular dystrophy (Best disease), the electro-oculogram (EOG) shows normal or only slightly reduced findings in patients with AVMD.

Since 1974, further cases of AVMD have been reported in few large and multiple small clinical series (Table 1)[1,3–28] and some of the patients have been followed for periods ranging from 1 to 20 years.[3–8,11,18,19,23] These studies revealed variability in the appearance and progression of AVMD and unfortunately have generated a number of different terms and abbreviations for this disease.

It is still undefined whether AVMD is a single entity with high variability of clinical expression or a heterogeneous group of disorders with variable clinical, angiographic, and histopathologic features. In addition, the basis of the yellow color of the central lesion and a possible inheritance are still controversial. Limited knowledge exists about the electrophysiologic findings in AVMD patients. To date a full-field electroretinogram (ERG) has been performed in only 17 patients[13–15,18,19,21,22,28] and a multifocal electroretinogram only in seven patients.[15,28] The diagnostic value of the in vivo measurement of retinal pigment epithelium (RPE) autofluorescence and its comparison to the more invasive fluorescein angiography has not been examined. Therefore, we present the results of a large group of AVMD patients who underwent extensive functional testings and in vivo fundus autofluorescence.

Patients and Methods

In our retrospective analysis, the records of 61 AVMD patients consecutively seen at the Department of Ophthalmology at the Benjamin Franklin Clinic from April 1994 to April 2003 were reviewed. The main inclusion criterion was the presence of a central, yellow, subretinal lesion smaller than one disk diameter at least in one eye.

All examinations were performed after informed consent was obtained after explanation of the procedures. The research adhered to the tenets of the Declaration of Helsinki. All patients underwent a complete eye examination including best-corrected Snellen visual acuity, slit-lamp, fundus ophthalmos-

copy, and photography. Color vision was tested with the desaturated Panel D15 test (n = 40 patients). Visual field testing was performed with Goldmann (n = 24) or automatic perimetry (n = 3). Fluorescein angiography was done in 46 patients.

Autofluorescence imaging of the fundus was performed on 13 patients. The in vivo measurement of autofluorescence of the RPE was carried out with a confocal Scanning Laser Ophthalmoscope (Heidelberg Retina Angiograph, Heidelberg Engineering, Germany). Argon laser light (488 nm) was used to excite RPE autofluorescence. A wide band-pass filter with a cut-off at 500 nm was inserted in front of the detector. A 30-degree field-of-view mode was used. The image resolution was 512 × 512 pixels. The maximal illumination of a 10 × 10 degree field of view was approximately 2 mW/cm^2. Six pictures per second were recorded. After focusing on the structure of interest, at first reflectance images (standard red-free) and then autofluorescence images were recorded. Between 4 and 12 single images were averaged, depending on the fixation of the patient.

Electrophysiologic testing included EOG (n = 11 patients), full-field ERG (n = 22), and multifocal ERG (n = 47). The same technician recorded all examinations. The recording equipment remained the same during all evaluations. Recording of EOG and full-field ERG was done according to ISCEV standards[29,30] and multifocal ERG according to the ISCEV guideline.[31] The recording protocols have been described in detail elsewhere.[32,33] The EOG was recorded with a ramp test method.[34] Full-field ERG recordings were done with maximal dilated pupils using a Nicolet Spirit and Ganzfeld (Nicolet, Madison, Wisconsin, USA). Stimulus duration was 0.1 msec. After 30 minutes of dark adaptation, four stimuli with increasing intensity (maximum light intensity: 10 cd·s/m^2) were used for recordings in the dark. Light-adapted recordings were performed after 10 minutes of light adaptation in the presence of white background light of 30 cd/m^2 with white stimuli of maximum light intensity. No averaging was done. For comparison, age-related normal ranges for amplitudes and implicit times were determined by calculation of the median values and the 95% confidence intervals from single eyes of 70 probands. Multifocal ERGs were recorded and analyzed with the VERIS system. Recording was performed with maximal dilated pupils following the full-field ERG using a Jet contact lens electrode. Refractive errors were corrected. For stimulation, a black and white pattern of 61 or 103 hexagons was presented on a monitor (200 cd/m^2 for white, 99.3% contrast). Duration of data acquisition was 4 minutes divided into eight sessions of 30 seconds. Data analysis (first-order kernel) was performed with the VERIS system.[35] The response elicited by the central hexagon (ring 1) and summated responses elicited by concentric rings of hexagons surrounding the center (rings 2–5) were evaluated. Based on manually controlled cursor placement, amplitudes and implicit times were determined for the first positive component (P1) of each trace. Amplitudes were expressed relative to their respective area (nV/deg^2). The normal ranges for these amplitudes and implicit times were defined by calculation of the median values and the 95% confidence intervals in one eye of 15 age-similar probands. Multifocal ERG stimuli location and anatomical areas correspond roughly as follows: ring 1 to the fovea, ring 2 to the parafovea, ring 3 to the perifovea, ring 4 to the near periphery, and ring 5 to the central part of the middle periphery.

Genetic analysis of VMD2 was performed in 11 patients (IDs #909, #1033, #1050, #1159, #1202, #1220, #1255, #1284, #1373, #1419, #1829) by directly sequencing the 10 coding exons of the gene as described previously.[36] Mutation screening of the RDS/peripherin gene was done in 10 other patients by SSCP analysis (IDs #458, #645, #712, #939, #946, #978, #1139, #1163, #1205, #1273) and direct DNA sequencing as described previously.[37] The 609_625del17 deletion mutation in patient #645 was verified by cloning of polymerase chain reaction products and subsequent DNA sequencing of single bacterial colonies.

Results

Our study included 61 patients (120 eyes; 2 eyes had been enucleated because of malignant melanoma). There were 40 female and 21 male subjects, ranging in age from 26.4 to 78.1 years (mean, 54.6 years) at the time of the first visit. The majority of patients (n = 56) were single cases with an unremarkable family history. Two patients were sisters, and there was one mother-son pair. One patient had a mother (not included in this study) who presented with bilateral foveal choriocapillaris atrophy that could be an advanced stage of AVMD. Thirteen patients (25 eyes) have been followed for a mean time of 3.4 years (range, 0.9–6.4 years). Most of the patients had a reduced visual acuity with slow progression (n = 47). Additional complaints were metamorphopsia (n = 11), decreased reading vision (n = 9), mild photophobia (n = 8), central/paracentral visual field defects (n = 5), and blurred vision (n = 4). The duration of the symptoms before the first eye examination ranged from 3 weeks (n = 1) to more than 10 years (n = 3). The majority of patients had noticed symptoms within

Table 2. Fundus Findings at the Time of the First Eye Examination

	Fundus Findings	Number	
		Bilateral	Unilateral
Patients with bilateral yellow lesion (n = 43)	Yellow lesion	43	—
	Pigmented spot	9	8
	RPE alterations	13	—
	RPE atrophy	2	1
	>1 yellow lesion w/o pigmented spot	2	2
	Drusen	3	—
	Paracentral naevus	—	2
Patients with unilateral yellow lesion (n = 18)	Yellow lesion	—	18
	Pigmented spot	—	8
	2 pigmented spots	—	1
	RPE alterations	2	3
	RPE atrophy	3	2
	Hyperpigmented areas	1	1
	>1 yellow lesion w/o pigmented spot	—	3
	Normal fundus	—	8

RPE, retinal pigment epithelium.

the last 12 months before the first examination. It should be noted that 8 patients had no symptoms and their condition was detected during routine eye examination. At the time of the follow-up eye examination, patients had slowly progressive visual loss (n = 9, followed 0.9–6.4 years), decreased reading vision (n = 4, followed 1.4–6.4 years), need for magnifying reading glasses (n = 1, followed 6.4 years), mild photophobia (n = 2, followed 1.2 and 1.6 years), metamorphopsia (n = 1, followed 3.0 years), and night vision loss (n = 1, followed 6.4 years); however, 3 patients did not notice any changes (followed 2.0–4.6 years).

Of 47 patients with a referral diagnosis, only 3 patients were suspected to have AVMD. Seven patients were diagnosed with Best disease and 3 with other dystrophies. At least 15 patients were diagnosed with age-related macular degeneration; in some of these cases, choroidal neovascularization was suspected. In the remaining patients, macular holes or cysts, idiopathic central serous chorioretinopathy, unspecific macular disease, or optic atrophy was diagnosed.

The fundus findings are summarized in Table 2. In 43 patients, a central yellow lesion was present in both eyes, and in 18 patients only in one eye (Figure 1). Two of these 18 patients had only one eye and the remaining 16 fellow eyes showed no central yellow lesion. Of 104 eyes with a central yellow lesion, 35 eyes had a pigmented spot in the center of the lesion additionally. Most of the yellow lesions were about one-half disk diameter in size; all lesions were less than one disk diameter in size. Other fundus findings included variable RPE alterations or atrophy. In eight fellow eyes, the fundus was normal. Fundus ophthalmoscopy during follow-up eye examination (25 eyes) revealed (1) no changes in comparison to the first eye examination (13 eyes, followed 0.9–5.3 years), (2) reduced diameter of the central pigmented spot (1 eye, followed 3.0 years), (3) disappearance of the central pigmented spot (2 eyes, followed 4.4 and 5.3 years), (4) increased diameter of the yellow lesion (3 eyes, followed 4.6–6.1 year), (5) disappearance of the yellow lesion with remaining RPE atrophy (5 eyes, followed 1.4–6.4 years), and (6) additional drusen (1 eye, followed 4.6 years) (Figure 1).

Details of functional evaluation are given in Table 3. Visual acuity varied between 1.25 and 0.05 (mean 0.62 ± 0.26, median 0.60). Comparing both eye examinations, visual acuity was unchanged in 10 eyes

Fig. 1. **A**, Fundus photograph: Characteristic yellow lesion with pigmented spot (female patient, age 50 years; visual acuity, 0.5). **B**, Fluorescein angiography with characteristic blockade and surrounding hyperfluorescent ring (same patient as in part A). **C**, Fundus photograph: Characteristic yellow lesion with larger area of pigmentation (male patient, age 78 years; visual acuity, 0.5). **D**, Fluorescein angiography with atypical hyperfluorescent flecks (same patient as in part C). **E**, RPE autofluorescence with typical increased fluorescence within the lesion (same patient as in part C). **F**, RPE autofluorescence with irregular increased fluorescence in a patient with a typical yellow lesion (male patient, age 35 years; visual acuity, 1.0). **G**, Fundus photograph: Characteristic yellow lesion with pigmented spot (female patient, age 41 years; visual acuity, 0.5). **H**, Fundus photograph: Regression of the yellow lesion and progression to RPE atrophy in a larger area (same patient as in part G; age, 47 years; visual acuity, 0.2).

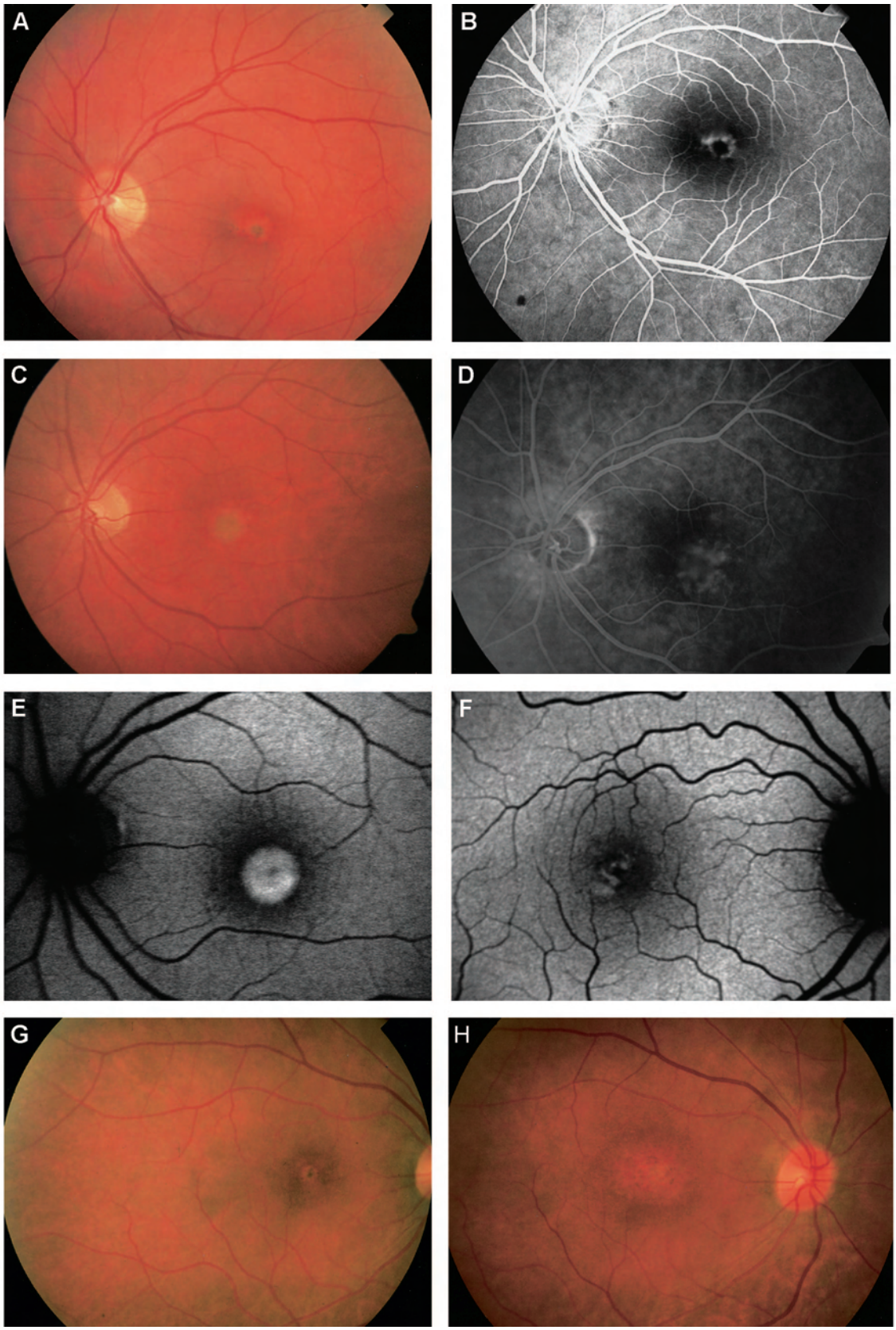

Fig. 1. *Continued*

Table 3. Results of Functional Evaluation: Visual Acuity, Color Vision, and Perimetry

		All eyes	With yellow lesion	No yellow lesion
Visual acuity, first examination	Number of eyes	120	104	16
	Median	0.60	0.60	0.90
	Range	1.25–0.05	1.0–0.1	1.25–0.05
Visual acuity, follow-up examination	Number of eyes	25	18	7
	Median	0.40	0.45	0.20
	Range	1.0–0.05	1.0–0.05	1.0–0.1
Color vision,* first examination	Number of eyes	75	64	11
	Normal	38	31	7
	Mild errors	10	10	0
	Moderate errors	6	6	0
	Severe errors	21	17	4
Perimetry, first examination	Number of eyes	53	45	8
	No scotoma	28	23	5
	Central scotoma	25	22	3

* The data of the males with congenital color vision deficiency are not included.

(followed 0.9–4.6 years), reduced in 11 eyes (difference of 0.06–0.4; followed 1.4–5.3 years), and improved in four eyes (difference of 0.1–0.2; followed 3.1–4.4 years). Color vision testing was performed in 79 eyes. Two male subjects showed a congenital red-green color vision defect and were not included in the subsequent evaluation. In 38 eyes, color vision was normal. The results of color vision testing revealed unspecific errors in variable severity without any typical axis of confusion in the remaining 37 eyes (Table 3). No major changes in color vision were observed in 10 eyes during follow-up of 1.2 to 6.4 years. Visual field testing was performed in 53 eyes and revealed normal findings in 28 eyes. A central scotoma was present in the remaining 25 eyes; however, an absolute central scotoma was observed only in four eyes. During follow-up, a central scotoma developed in two eyes (followed 1.2 years) and the findings did not show major changes in the other four eyes (followed 1.4–6.4 years). With respect to the morphologic findings, eyes with a yellow lesion tended to have lower visual acuity, more color vision deficits, and slightly more visual field defects compared to fellow eyes without yellow lesions at first examination. At last examination, however, eyes without a yellow lesion had a lower visual acuity compared to eyes with a yellow lesion. This may be because those eyes without a yellow lesion include normal fellow eyes as well as late stages with regressed vitelliform lesions.

Results of fluorescence evaluation are summarized in Table 4. Fluorescein angiography was carried out in 87 eyes. All patients had central RPE alterations in at least one eye. Normal fluorescein angiographic findings were observed in five eyes. None of the patients had any leakage. Forty-seven eyes showed the typical central nonfluorescent spot with a surrounding irregular ring of hyperfluorescence (Figure 1). Additional alterations in fluorescein angiographic findings were

Table 4. Findings of Fluorescein Angiography and in vivo Autofluorescence at First Eye Examination

	Number		
	All eyes	With yellow lesion	No yellow lesion
Fluorescein angiography	87	76	11
Normal	5	1	4
Nonfluorescent spot with hyperfluorescent ring	47	46	1
RPE window defect	23	17	6
Central hyperfluorescence	12	12	0
RPE autofluorescence	25	22	3
Increased level foveal	19	19	0
Additional small spot of reduced autofluorescence	8	8	0
Reduced level foveal	4	2	2
No central changes	2	1	1

RPE, retinal pigment epithelium.

Table 5. Full-field Electroretinography (ERG): B-Wave Amplitudes at First Eye Examination

Full-field ERG (n = 43 eyes)	Maximum mixed response	Single cone response	30 Hz flicker response
Reduced in number of eyes (%)	12 (27.9)	18 (41.9)	31 (72.1)
Reduction to %*	80.5–66.4	80.5–59.8	88.8–54.4
Mean, %	74.5 ± 4.1	72.3 ± 6.2	72.4 ± 9.8
Yellow lesion in number of eyes	10	15	27

* Values are given in percentage of the median of the corresponding age-related norm.

RPE window defects and central hyperfluorescence. In five eyes, fluorescein angiography did not reveal any changes during follow-up eye examination (1.6–5.3 years). Autofluorescence imaging of the fundus was performed in 25 eyes. A yellow lesion was present in 22 of these eyes, with central pigmentation in 6 eyes. In 19 of these 22 eyes, an increased level of autofluorescence within the clinically visible yellow lesion compared to the background signal was observed (Figure 1). Of these 19 eyes, 8 eyes had an additional small spot of reduced autofluorescence in the center of the area with increased autofluorescence. Only two of these eight eyes presented a clinically visible pigmentation in the center of the yellow lesion. In two other eyes, a reduced level of autofluorescence within the clinically visible yellow lesion compared to the background signal was present. Although one eye presented with a central yellow lesion, no central changes in fundus autofluorescence were visible. However, this eye showed multiple small irregularities of autofluorescence in the posterior pole and midperiphery. One eye had no yellow lesion and an inconspicuous fundus autofluorescence. The patient with the longest follow-up (6.4 years) presented at the second eye examination RPE atrophy in both eyes corresponding to an oval area of reduced autofluorescence surrounded by a small line of increased autofluorescence; in the midperiphery, multiple small irregularities of autofluorescence were visible. No follow-up data on RPE autofluorescence were available.

An EOG was recorded in 21 eyes. A normal light increase (≥160%) was present in six patients in both eyes and in three patients in one eye. Two of these eyes had no yellow lesion. A slightly reduced light increase (149–155%) was observed in two patients in both eyes and in two other patients in one eye. All six eyes with a reduced EOG light increase had a foveal yellow lesion. There was no patient who underwent EOG twice.

A full-field ERG was recorded in 43 eyes (Table 5). A central yellow lesion was present in 39 of these eyes. The b-wave amplitude of the maximum rod-cone response was slightly reduced in 12 eyes and the single flash cone response in 18 eyes. The 30 Hz flicker response, however, was reduced in the majority of the eyes (31 eyes). Four patients (8 eyes) underwent full-field ERG during follow-up eye examination. Three of these patients did not show any changes in comparison to the first examination (followed 1.6–6.1 years). One patient presented with a markedly reduced full-field ERG after 6.4 years of follow-up. At the initial examination, her b-wave amplitudes at dark- and light-adapted single flash stimulation and the amplitude at 30 Hz flicker stimulation were borderline, reduced to approximately 70% of the age-related median. Six years later, the same parameters were reduced to approximately 30% of the age-related median.

Multifocal ERGs were recorded in 86 eyes. A central yellow lesion was present in 74 of these eyes. In 72 eyes, a multifocal ERG was obtained with 61-hexagon stimulation, and in 14 eyes with 103-hexagon stimulation. Details of the ringwise analysis of P1 amplitude and implicit time are given in Table 6. During follow-up eye examination, seven patients (12 eyes) underwent multifocal ERG. Ten eyes did not present any marked changes in multifocal ERG (followed 0.9–3.0 years). In two eyes of two patients (followed 1.2 and 6.4 years), P1 amplitudes of all rings were markedly reduced, the smallest P1 amplitudes were recorded in the eye of the patient followed more than 6.4 years.

DNA samples of 21 patients were analyzed for mutations in the VMD2 (n = 11) or RDS/peripherin gene (n = 10). A disease-associated sequence alteration was detected in only one patient, however. This patient carried a 17 bp deletion in exon 2 (609_625del17) of the RDS/peripherin gene. The mutation results in a frameshift in codon 203 (Arg203fs) and leads to premature translation termination further eight codons downstream. This patient had central yellow lesions in both eyes.

Discussion

In the present retrospective study we report a detailed evaluation of the morphologic and functional findings in a consecutive series of 61 patients with

Table 6. Multifocal Electroretinography (ERG) (61 hexagons): P1 Amplitude and Implicit Time at First Eye Examination

Multifocal ERG (n = 72 eyes)	Ring 1	Ring 2	Ring 3	Ring 4	Ring 5
P1 amplitude					
Reduced in number of eyes (%)	45 (62.5)	33 (45.8)	16 (22.2)	10 (13.9)	6 (8.3)
Reduction to %*	54.0–16.6	65.1–21.9	59.3–21.7	55.1–18.0	51.5–17.1
Mean, %	40.4 ± 10.9	50.5 ± 12.1	49.1 ± 11.2	44.6 ± 12.0	41.2 ± 13.3
P1 implicit time					
Increased in number of eyes	22 (30.5)	21 (29.2)	25 (34.7)	31 (43.1)	27 (37.5)
Increased to %*	114.0–128.4	114.8–135.3	115.3–133.5	115.3–136.4	114.8–135.3
Mean, %	116.8 ± 3.7	119.1 ± 5.2	119.1 ± 5.1	119.4 ± 5.4	119.7 ± 5.2

* Values are given in percentage of the median of the corresponding age-related norm. For simplicity, only the results for 61 hexagons stimulation are displayed.

AVMD. Considering the increasing relevance of correct diagnosis of macular disorders in the adult population and the fact that the first patient included in this study was diagnosed 20 years after the initial description of the disorder,[1] it is noteworthy that, in spite of the characteristic ophthalmoscopic features, only 3 of 47 patients with a referral diagnosis were suspected to have AVMD. A possible reason for the limited knowledge of this disorder is the huge variety of terms that have been used for its description and that seem to indicate different disease entities (Table 1).

In several respects, we could confirm findings reported in previous large series.[3–10] The patients reported variable visual disturbances, but 13% of the patients had no symptoms. Visual acuity was variable as well but never below 0.05. In addition to the foveal yellow lesion, RPE alterations and RPE atrophy were seen frequently. As also noted in other studies, we have seen in some cases more than one yellow lesion, parafoveal drusen,[2,5,7,12,15,18] and paracentral drusen.[11,12,19,23] RPE detachment,[21,27] stellate retinal folds,[28] and subretinal neovascularizations[3,7,27] were not observed. Previously not reported was the occurrence of nevi, other hyperpigmentations, and malignant melanomas in four eyes with AVMD, although the relevance of this finding remains unclear. In half of the eyes with a yellow lesion, fluorescein angiography revealed the typical nonfluorescent spot with a ring of hyperfluorescence. The EOG was normal in most cases.

Thus far, detailed functional evaluation has been reported only in a limited number of patients.[11,14,15,18,19,23,28] In our series, the functional findings were variable but in most cases were in accordance with a mild to moderate macular dysfunction. The visual field was normal in half of the eyes. Small central scotomas of approximately 5 degrees in diameter were the most frequent finding in the other half of the eyes. Visual field defects had no obvious correlation with the presence of a central pigmented spot in the yellow lesion. Color vision deficiencies were variable, but, unexpected for a macular disorder, a normal color vision in the desaturated Panel D15 test was observed in 50.7% of eyes. In three patients, blue-yellow defects were reported.[14,18] In our series, color vision defects were nonspecific without any typical axis of confusion.

The major finding in the full-field ERG was the reduction of the 30 Hz flicker response amplitude in 72% of eyes, indicating a cone system dysfunction. Previous studies reported mostly normal ERGs in 17 patients, but these were recorded in different studies with various and partially unknown methods.[13–15,18,19,21,22,28]

In recent years, the multifocal ERG has been established for the evaluation of macular function.[32,38] So far, seven patients with AVMD have been examined.[15,28] In our series, P1 amplitude reduction was most frequent in the multifocal ERG in ring 1, corresponding to the fovea. The frequency of P1 amplitude reduction was increasingly diminished toward the periphery, consistent with a disorder predominantly affecting the fovea. An increase in P1 implicit time was less frequent compared to amplitude reduction. Although in our experience the multifocal ERG is a sensitive tool for evaluation of macular function, multifocal ERG amplitudes and implicit times were normal in 17.4% of eyes. Probably the functional disturbance is too limited to always be measurable with the multifocal ERG using 61 or 103 hexagons as a stimulus. These findings are in contrast to those of Saito et al,[15] who recorded multifocal ERGs with a similar technique and described a generalized reduction of the multifocal ERG amplitudes with normal implicit times in 11 of 12 eyes of six patients. In the present study, a comparable generalized reduction of the multifocal ERG amplitudes was only seen in 14% of eyes. With respect to the larger number of eyes, the results of this study more likely represent the variability of multifocal ERG findings and retinal functional disturbance in AVMD.

The most typical finding in RPE autofluorescence imaging of the fundus was an increased level of

autofluorescence corresponding to the clinically visible yellow lesion compared to the background signal. It is well established that autofluorescence is derived from lipofuscin in the RPE,[39] and in vivo recording of RPE autofluorescence provides information about the levels and distribution of lipofuscin of the RPE. The high level of autofluorescence seen in our patients indicates an abnormal accumulation of lipofuscin granules in the RPE. This is compatible with histopathologic findings of a massive increase of lipofuscin within RPE cells and macrophages in atrophic outer retina and with the conclusion that lipofuscin with or without RPE atrophy may account for the vitelliform appearance.[20,23] In contrast to our findings, Gass[1] and Jaffe,[25] who studied eyes that had a central yellow lesion with a pigmented spot, did not find an increase of lipofuscin. Jaffe concluded that the yellow zone corresponds to thinned RPE overlying periodic acid-Schiff-positive, sub-RPE material. This discrepancy between different histopathologic studies could be explained by the fact that our autofluorescence findings also were variable between patients. An increased level of autofluorescence within the clinically visible yellow lesion compared to the background signal has been reported from one group previously, but no clear documentation has been published.[40] In addition, this group observed that the entire fundus of patients with AVMD showed abnormally high autofluorescence, suggesting a generalized abnormality of the RPE even though on biomicroscopy the visible lesions were focal.

Although there were characteristic ophthalmoscopic, fluorescein angiographic, and RPE autofluorescence features of AVMD, it was not possible to predict from the ophthalmoscopic findings the results of fluorescein angiography or autofluorescence. Patients with a yellow lesion presented either with a typical fluorescein angiography, a central hyperfluorescence, or a RPE window defect. A typical fluorescein angiography was seen in patients with (1) a yellow lesion and increased autofluorescence with a central hypofluorescent spot, (2) a yellow lesion with a pigmented spot and an increased autofluorescence, or (3) a yellow lesion and a reduced autofluorescence. An increased autofluorescence with a hypofluorescent spot in the center was observed in patients with a yellow lesion as well as in patients with a yellow lesion with a pigmented spot. The lack of correlation can be explained by heterogeneity of the subretinal deposited material causing different findings in autofluorescence and fluorescein angiography. It has been shown that there are at least 10 different fluorophores with different absorption and emission characteristics contributing to the autofluorescence of the RPE.[41]

The natural course of AVMD was variable in our series and may contribute to the difficulty in correctly diagnosing AVMD. For example, two patients of similar age who were followed for 6 years demonstrate the two extremes. One of these patients presented with a slight increase in the diameter of the yellow lesion without marked changes in visual acuity, color vision, and full-field ERG. The other patient suffered an ongoing visual loss and progression from a yellow lesion to central chorioretinal atrophy and a marked amplitude reduction in full-field ERG and multifocal ERG. During follow-up, the ophthalmoscopic picture remained unchanged in half of the patients. Minor variations were seen in most of the other patients, but in some patients the yellow lesions had been slowly absorbed and replaced with an atrophic area in the RPE. These findings are in accordance with previous reports.[3,4,6–8,11,18,19,23] Similarly, in the majority of patients, progression of functional loss was limited. The central RPE atrophy may be the main reason for the lower visual acuity in our patients at follow-up examination. Only five patients presented a visual loss of more than two lines; of these, visual loss was unilateral in three patients.

Initially, Gass presumed an autosomal dominant inheritance for AVMD.[1] There are only two descriptions of three-generation pedigrees supporting an autosomal dominant inheritance.[10,16] In the present study, no family with evident autosomal dominant inheritance was observed; however, there were two small pedigrees of two affected family members each. Similar small uninformative pedigrees have been reported.[3,7,18,19,24,42] The majority of our patients were single cases with an unremarkable family history, as were the majority of cases reported so far. Because the condition was detected in several of our patients during routine eye examination, it is possible that other affected family members could be identified only by detailed family examination. Molecular genetic analysis of the VMD2 and the RDS/peripherin gene in part of our patient cohort indicate that mutations in these genes may constitute only a minor cause for AVMD. Only in one patient was a deletion in the RDS/peripherin gene detected. This deletion causes a frame shift that results in a largely truncated polypeptide. The same mutation has been previously reported to segregate in a large Spanish family with autosomal dominant macular dystrophy[43] and was also found in another German patient with AVMD (SK, BW, unpublished results). Several reports have shown that AVMD can be associated with mutations in the RDS/peripherin gene.[37,44,45]

In summary, AVMD is characterized by late onset, slow progression, and high variability of morphologic and functional alterations. Diagnosis should include careful ophthalmoscopy and can be aided by RPE autofluorescence. In some cases, fluorescein angiography is more informative. In spite of the obvious macular involvement, retinal function is often normal or only slightly reduced. Functional tests were useful to determine the actual degree of retinal involvement but were not helpful in predicting progression of functional loss. Counseling of patients should assure them of a usually good prognosis but include information about a possible loss of central visual function.

Autofluorescence findings indicate that lipofuscin accumulates in the yellow lesion in the majority of cases. However, it still remains unclear whether AVMD is a single entity or a common degenerative feature of separate disorders, such as age-related macular degeneration[3,4,11,20,27] or pattern dystrophy.[5,24,26] The heterogeneity of clinical and histopathologic findings may support the presence of separate disorders. However, it has been shown that mutations in some genes (e.g., RDS/peripherin) can be associated with a high variation of clinical appearance. Further studies will be necessary to solve this issue.

Key words: adult vitelliform macular dystrophy, autofluorescence of the retinal pigment epithelium, full-field electroretinography, multifocal electroretinography, RDS/peripherin gene, VMD2 gene.

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