Multiple evanescent white dot syndrome: clinical course and factors influencing visual acuity recovery

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ABSTRACT

Objective To report the demographics and the clinical course of patients with multiple evanescent white dot syndrome (MEWDS) and to investigate for those factors which influence visual acuity (VA) recovery.

Methods This is a retrospective single-centre observational study. Electronic medical records and retinal imaging of patients with a diagnosis of MEWDS with a minimum follow-up of 3 months were reviewed. Patients were categorised into three groups according to the VA at presentation and at the last visit: group 1 >0.48 logarithm of the minimum angle of resolution (LogMAR), group 2 ≤0.48 and ≥0.18 LogMAR and group 3 <0.18 LogMAR. All patients had non-invasive multimodal imaging including optical coherence tomography, near-infrared reflectance imaging and blue fundus autofluorescence at presentation and during follow-up.

Results A total of 51 eyes from 51 patients (41 women, mean age 29.8±7.8 years) were included. Significantly more patients presented in the autumn (X^2=8.69, p=0.034). The percentage of eyes recovering vision to 0.0 LogMAR or better was 80.3% (41/51). Worse presenting vision and young age at presentation were independent significant predictive variables for poorer final VA (p=0.002 and p=0.02, respectively). No imaging features were significantly predictive of complete versus incomplete recovery, but disc hyperfluorescence on fluorescein angiography was more common in those with incomplete recovery.

Conclusions Although the majority of cases have a benign prognosis, the clinical spectrum of MEWDS includes incomplete visual recovery. In our series, poor presenting VA and young age were associated with poor VA outcome. Further study is warranted to confirm these findings.

INTRODUCTION

Multiple evanescent white dot syndrome (MEWDS) was first described in 1984 by Jampol *et al*[1] as a typically unilateral self-limiting condition characterised by multiple small, ill-defined white dots at the level of the retinal pigment epithelium (RPE) or outer retina with a distinct granular appearance in the fovea. The lesions may be subtle and fade within the first few weeks of the disease. White dots may be sometimes absent or barely visible on fundus examination,[2] especially when the condition is seen in the resolving phase.[2 3] In these cases, non-invasive retinal imaging, including optical coherence tomography (OCT) and fundus autofluorescence (FAF), is very helpful for the diagnosis and monitoring of the condition.[4] Atypical features with coexisting chorioretinal diseases have been described,[5] and these often explain a persistent reduction in vision. The primary location of the condition has been the source of debate for a long time, but recent publications with new imaging technology (OCT-angiography (OCT-A)) have demonstrated that the choriocapillaris is not involved in acute cases indicating that the RPE–photoreceptor interface is the primary site.[6 7] It is suspected to be the result of a viral-like infection, possibly with an immune-mediated mechanism, in a genetically susceptible person.[8 9] It has thus been defined as a 'common cold of the retina' by Tavallali and Yannuzzi.[10]

It is known that this condition typically occurs in young healthy women, but this has not been documented in large case series. The only population-based study published on white dot syndromes included six cases of MEWDS[11] and the largest case series published so far included 34 patients.[6] The visual prognosis is considered excellent,[10] but it has never been studied in a large case series.

Aim of our study was to investigate the demographics of patients presenting with MEWDS and to investigate those factors, including multimodal imaging features, which may influence visual acuity (VA) recovery.

METHODS

This is a single-centre retrospective study conducted in patients affected by MEWDS seen by the uveitis service at Moorfields Eye Hospital NHS Foundation Trust from February 2011 to December 2017.

The study was performed in accordance with the tenets of the Declaration of Helsinki. Approval from the local Institutional Review Board was obtained.

Chart review and electronic medical review of patients with clinical features of MEWDS were analysed. Appropriate search terms were used to electronically search all records from February 2011 to December 2017 in order to identify cases where a diagnosis of MEWDS was considered. The authors then considered all cases and refined the diagnosis using accepted clinician consensus criteria, as first described by Jampol.[1] These included (a) acute onset of unilateral or (rarely) bilateral visual symptoms in a previously healthy subject, (b) absence of any chronic systemic underlying conditions and (c) recognised phenotypic ocular features, which included foveal granularity and/or white dots, or imaging changes on autofluorescence (hyperautofluorescent dots), fluorescein (early wreath-like hyperfluorescent lesions) and indocyanine green

angiography (early to late hypofluorescent lesions). Note that the presence of easily identifiable white dots on clinical exam was not an essential criterion for the diagnosis. Patients with incomplete records or other ocular comorbidities were excluded from the statistical analysis. Minimum follow-up from presentation required for inclusion was 3 months. The following epidemiological data were collected for every patient: gender, ethnicity, age at presentation, prodromal illness, season at presentation, eye affected and refraction of the patient. Any cases where the condition was bilateral were recorded, whether simultaneous presentation or sequential involvement, and any recurrence of disease was recorded, as well as any steroid treatment prescribed. The treatment with oral steroids was decided at clinician discretion at the presentation, typically starting with 60 mg prednisolone for average body weight and proceeding with slow tapering. However, as it was a retrospective study, the treatment regimen was not protocolised. The following symptoms reported by the patient at presentation were recorded: blurred vision, photopsia, floaters, scotoma and distortion. Duration of the symptoms (in days) before the first examination was also recorded. Best-corrected visual acuity (BCVA) was recorded at presentation and at the last follow-up visit. For the cases with simultaneous involvement, the worst eye was considered for the statistical analysis, while for the cases with sequential involvement, the first affected eye was considered.

Snellen VA was converted into logarithm of the minimum angle of resolution (LogMAR). Patients were grouped into three categories according to the presenting VA and the same three categories at the last follow-up. These categories had a clinical meaning, corresponding with moderate-to-severe vision loss, mild vision loss and normal vision.[12]

The three categories of VA at presentation were as follows: group 1 >0.48 LogMAR (worse than Snellen equivalent 6/18), group 2 ≤0.48 and ≥0.18 LogMAR (Snellen equivalent 6/18 to 6/9) and group 3 <0.18 LogMAR (Snellen equivalent 6/6 or better). Patients were grouped in the same three categories according to the VA at the last follow-up. We defined 'incomplete' VA recovery when the patient's acuity had not recovered to 6/6 Snellen at the last follow-up (group 3).

MEWDS features were graded in different retinal imaging modalities. Foveal granularity, presence, location (limited to the macular area, surrounding the optic disc and extending beyond the arcades) and appearance (isolated or confluent) of dots were evaluated.

Non-invasive multimodal retinal imaging, including colour fundus photography (CFP), spectral-domain OCT (SD-OCT), near-infrared reflectance (NIR) imaging and blue FAF, was available for all patients at presentation (figure 1). Where available, fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) were also reviewed. CFP was acquired with a fundus camera (TRC 501; Topcon Medical Systems) at presentation and at follow-up. SD-OCT, NIR and FAF were acquired at presentation and during follow-up with the scanning laser ophthalmoscopy of the Heidelberg system (HRA-OCT Spectralis, Heidelberg Engineering, Heidelberg, Germany). FFA and ICGA were acquired on the Heidelberg system or on the Topcon system (TRC-50DX, Topcon, Tokyo, Japan) or on the Optos system (200Tx, Optos R, Marlborough, Massachusetts, USA). SD-OCT subfoveal scan was assessed for any alterations of the outer retinal layers, within the 3 mm ETDRS circle diameter provided by the Heidelberg Eye Explorer software. The retinal reflective bands imaged by SD-OCT were defined according to international consensus,[13] in which the four hyper-reflective bands in the outer retina represent the external limiting membrane, the photoreceptor ellipsoid zone (EZ), the interdigitation zone (IZ) and the RPE/Bruch's complex in order from inside to outside. Integrity of SD-OCT retinal bands at the onset and in the course of disease and corresponding VA was assessed.

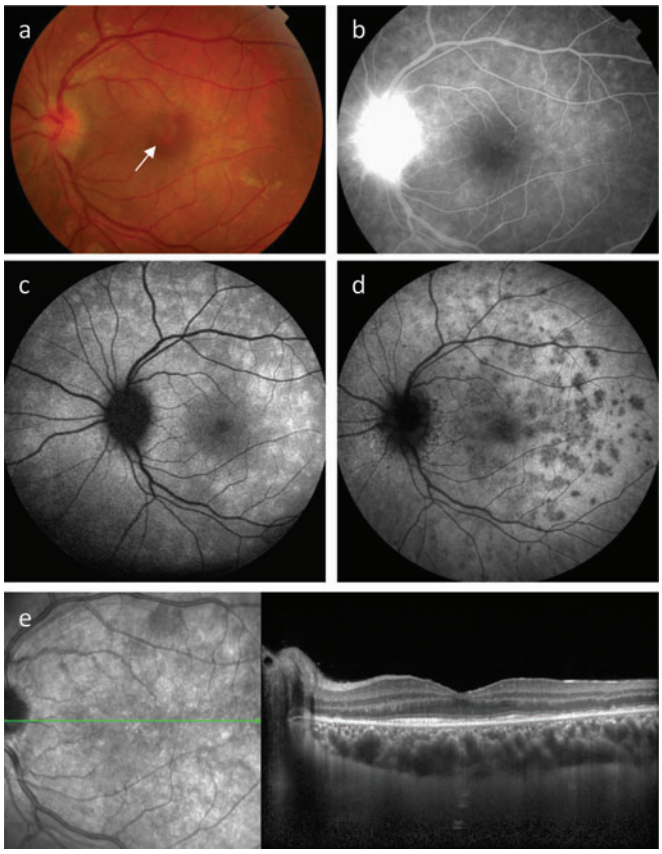

Figure 1 Representative case of retinal imaging of multiple evanescent white dot syndrome in the left eye. Fundus colour photograph (A) shows foveal granularity (arrow),multiple white dots at the posterior pole and optic disc with blurred margins. Fundus fluorescein angiography late frame (B) shows wreath-like hyperfluorescent lesions and dye leakage from a 'hot disc'. Blue fundus autofluorescence (AF, C) shows increased AF signal in correspondence of the dots. Indocyanine green angiography (D) late frame shows hypofluorescence of the dots. Simultaneous acquisition of near-infrared reflectance (NIR) imaging and enhanced depth optical coherence tomography (OCT, E) shows foveal granularity on NIR and interruptions of the ellipsoid zone on OCT.

The grading was done by the same investigator (FB) under the guidance of the senior members of the team (CP and MW).

The data were tested for normality and means were compared using Student's t-test and analysis of variance. Proportions were compared using the χ^2 test (unpaired data) and the McNemar test (paired data).

To evaluate the joint effect of initial VA and age, an exact logistic model was fitted to the data, considering final VA as the dependent variable and initial VA and age as the independent variables.

A significance level of 5% was always adopted. All the analyses were performed using R 3.5.1 (R Core Team 2018. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Seventy-two eyes from 68 patients were scrutinised. Twenty-one patients had coexisting chorioretinal diseases, such as choroidal

neovascularisation or multifocal choroiditis, which could have affected the final visual outcome and were therefore excluded from our analysis. Fifty-one patients met the inclusion criteria of MEWDS without overlapping atypical features and at least 3 months of follow-up, with documented VA at presentation and at the last follow-up.

Characteristics of patients are summarised in table 1: 41 patients (80.4%) were women and 36 (70.6%) were of Caucasian origin. Mean age at presentation was 29.8±7.8 years (range 17–51 years) and was significantly lower in the group of patients with worse final VA (p=0.012). None of the patients included had history of amblyopia.

In five patients, the condition was bilateral (9.8%, 5/51) of which two (40%, 2/5) had simultaneous and three (60%, 3/5) had sequential eye involvement during the course of the disease. In six patients (11.7%), the condition recurred; 12 patients (23.5%) were aware of a preceding viral illness. Two patients (3.9%) were pregnant at presentation.

The mean presenting VA was 0.28±0.24 LogMAR (range −0.1 to 1.0 LogMAR) and the mean final VA was −0.01±0.12 LogMAR (range −0.2 to 0.18 LogMAR). The percentage of eyes recovering vision to 0.0 LogMAR or better was 80.3% (41/51).

The incidence of the condition was significantly higher in the mid-seasons (32 cases, 62.7%, in autumn and spring). χ^2 test was done to assess a possible 'seasonality' of this disease and showed a significantly different incidence of MEWDS according to the seasons, with significantly greater incidence in the autumn with 18 cases (35.3%) (X^2=8.69, p=0.034) (online supplemental figure 1).

No significant difference was found in relation to visual recovery in terms of gender, ethnicity, reported previous viral illness, refractive status, laterality or recurrence. Presenting symptoms were not significantly associated with the final VA when considering both each symptom individually and the total number of symptoms reported (0–5 symptoms). Six patients (11.8%) received systemic oral steroid treatment and their final VAs were not significantly different from those who did not receive treatment (p>0.5). When evaluating differences between patients with complete VA recovery versus those without VA recovery, in terms of the duration of symptoms, no significant difference between the means was found (p=0.51). In addition, age at presentation was significantly associated with poorer final VA (p=0.012), with younger patients showing a higher risk of a poor outcome (table 1).

Analysing VA grouped into three categories, worse presenting vision was a highly significant prognostic factor (McNemar test; p<0.001) for poorer final VA (table 2: no affected eye's VA deteriorated over follow-up).

The exact logistic regression model to evaluate the joint effect of initial VA and age in determining the final VA showed that, after having adjusted for the effect of age, initial VA remained a significant prognostic factor for the final VA (p=0.002); the odds of not having a complete recovery when initial VA was >0.48 were much higher compared with patients with a better presenting VA; the estimate of the adjusted OR was 12.16 (with a 95% CI of 1.76 to 147.84). In this multivariate analysis, age at presentation remained a significant effect (p=0.020); for example, a 5-year decrease in age at onset of the disease conferred a 2.04 OR of poorer outcome in younger patients with respect to older patients' (with a 95% CI of 1.11 to 4.34). From a clinical point of view, at a cut-off age of 25 years, the odds of poor functional outcomes for younger subjects (up to 25 years old) are 8.5 times those of older subjects. Table 3 shows that foveal granularity was detected in about 70% of the cases at presentation in both CFP (70.3%, 26/37) and NIR imaging (70.8%, 34/48). Moreover, it was still found in about 40% of the cases after 3 months of follow-up and with no significant difference between the cases with complete (34.8%, 8/23 on CFP and 40.0%, 14/35 on NIR) and incomplete VA recoveries (66.7%, 2/3 on CFP and 50.0%, 5/10 on NIR). SD-OCT showed alterations mainly in the EZ and IZ (up to 100% of the cases at

Table 1 Demographic, epidemiological and clinical features at presentation of patients included in the study

	Total sample		Complete VA recovery		Incomplete VA recovery		
	n	%	n	%	n	%	P value
Gender							0.67
Female	41	80.4	32	78.0	9	90.0	
Male	10	19.6	9	22.0	1	10.0	
Ethnicity							0.78
Caucasian	36	70.6	27	65.9	9	90.0	
African	3	5.9	3	7.3	0	0.0	
Asian	5	9.8	5	12.2	0	0.0	
Other	7	13.7	6	14.6	1	10.0	
Prodromal illness/ pregnancy							0.19
No	25	49.0	18	43.9	7	70.0	
Yes	12	23.5	12	29.3	0	0.0	
Unknown	12	23.5	9	22.0	3	30.0	
Pregnant	2	3.9	2	4.9	0	0.0	
Symptoms							
Photopsias	24	47.1	20	48.8	4	40.0	0.73
Blurred vision	35	68.6	26	63.4	9	90.0	0.14
Floaters	9	17.6	6	14.6	3	30.0	0.35
Scotoma	17	33.3	15	36.6	2	20.0	0.46
Distortion	2	3.9	2	4.9	0	0.0	0.97
Steroid treatment							0.99
No	45	88.2	36	87.8	9	90.0	
Yes	6	11.8	5	12.2	1	10.0	
	Mean	SD	Mean	SD	Mean	SD	P value
Age at presentation (years)	30.0	7.8	31.3	7.4	25.0	7.6	0.012
Visual acuity at presentation (LogMAR)	0.28	0.24	0.23	0.23	0.49	0.14	0.001
Duration of symptoms (days)	16.6	28.3	14.7	22.9	24.6	44.8	0.51

LogMAR, logarithm of the minimum angle of resolution; VA, visual acuity.

Table 2 Number of eyes divided by categories of visual acuity at presentation and at 3 months of follow-up

		Visual acuity at 3-month follow-up			
		>0.48 LogMAR	≤0.48 and ≥0.18 logMAR	<0.18 LogMAR	
					P=0.003
Visual acuity at presentation	>0.48 LogMAR	0	7	8	
	≤0.48 and ≥0.18 LogMAR	0	3	21	
	<0.18 LogMAR	0	0	12	

LogMAR, logarithm of the minimum angle of resolution.

Table 3 Retinal imaging analysis of foveal granularity on colour fundus photograph (CFP) and near-infrared reflectance imaging, affected outer retinal layers on optical coherence tomography (OCT), disc swelling on CFP and disc hyperfluorescence on fluorescein angiography at presentation and at 3-month follow-up

	Presentation							3-Month follow-up						
	Total		Complete VA recovery		Incomplete VA recovery			Total		Complete VA recovery		Incomplete VA recovery		
Sign or imaging characteristic	N	%	n	%	n	%	P value	N	%	n	%	n	%	P value
Foveal granularity														
Colour fundus photograph	26/37	70.3	20/30	66.7	6/7	85.7	0.65	10/26	38.5	8/23	34.8	2/3	66.7	0.54
Near-infrared reflectance	34/48	70.8	27/39	69.2	7/9	77.8	>0.9	19/45	42.2	14/35	40.0	5/10	50.0	0.72
Affected external retina layers on OCT														
RPE-Bruch's membrane complex	22/49	44.9	18/40	45.0	4/9	44.4	>0.9	3/50	6.0	3/40	7.5	0/10	0.0	>0.9
Interdigitation zone	42/49	85.7	33/40	82.5	9/9	100.0	0.32	16/50	32.0	12/40	30.0	4/10	40.0	0.71
Ellipsoid zone	41/49	83.7	32/40	80.0	9/9	100.0	0.32	14/50	28.0	12/40	30.0	2/10	20.0	0.7
External limiting membrane	33/49	67.3	25/40	62.5	8/9	88.9	0.24	5/50	10.0	4/40	10.0	1/10	10.0	>0.9
Disc swelling														
Colour fundus photograph	6/37	16.2	5/30	16.7	1/7	14.3	>0.9	0/26	0.0	0/23	0.0	0/3	0.0	>0.9
Disc hyperfluorescence														
Fluorescein angiography	17/34	50.0	11/26	42.3	6/8	75.0	0.22	N/A		N/A		N/A		

RPE, retinal pigment epithelium; VA, visual acuity.

presentation) and some residual alterations persisted at the 3-month follow-up in a significant number of patients: 30% (12/40) of patients with complete VA recovery and up to 40% (4/10) of patients with incomplete VA recovery even though the VA recovery was already complete (figures 1 and 2). However, it was not possible to find any significant difference between the two groups. Of note, from a descriptive point of view, a hyperfluorescent disc on FA at presentation was much more frequent in the cases with incomplete recovery (75.0%, 6/8) than in the cases with complete recovery (42.3%, 11/26); however, this finding did not reach the statistical significance (p=0.22). The mean age of those patients with hyperfluorescent discs was 27.4±9.1 years.

Table 4 shows that autofluorescence was the test most frequently performed in the clinical practice (44 cases, 86.2%) for showing the dots and diagnosing MEWDS, while FA was performed in 34 cases (66.6%) and ICGA only in 28 cases (54.9%). On ICGA, the dots appeared hypofluorescent, more isolated and well defined, while on blueautofluorescence (BAF) and FA, they appeared hyperautofluorescent or hyperfluorescent and more frequently confluent or with a mixed pattern. BAF showed involvement of the RPE most frequently at the macula and peripapillary area. ICGA was able to show extension of the dots in the mid-periphery in a greater proportion of patients compared with those who had only BAF. Representative cases are shown in figure 3.

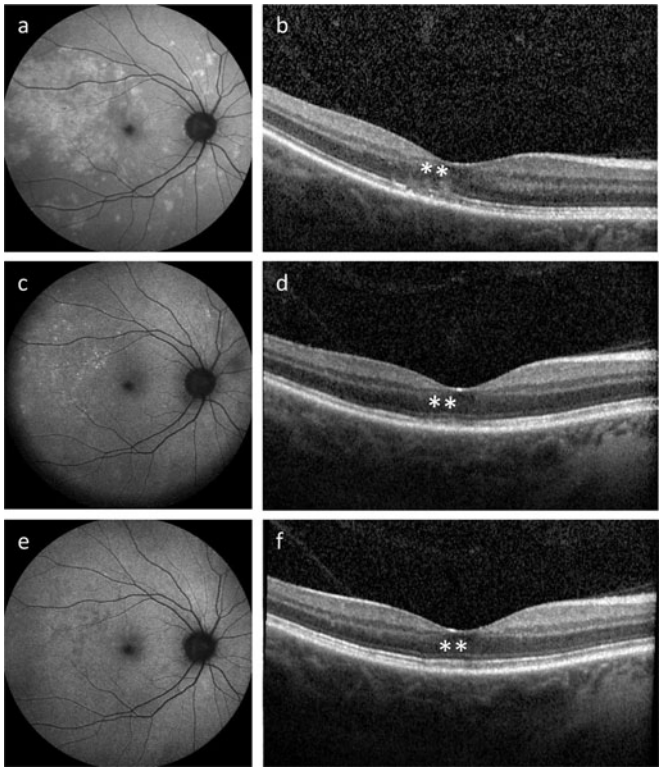

Figure 2 Representative case of retinal imaging of multiple evanescent white dot syndrome in the right eye. At baseline, blue fundus autofluorescence (AF, A) shows increased AF signal in correspondence of the dots; optical coherence tomography (OCT, B) scan shows focal interruption of the ellipsoid zone (EZ, white asterisks) with ill-defined hyper-reflectivity at the level of the affected outer retina layers. Four weeks after presentation, blue fundus AF (C) shows reduction of the hyper-AF dots; OCT scan (D) shows overall improvement of the outer retinal integrity with persistent focal interruption of the EZ (white asterisks). Twelve weeks after presentation, AF (E) shows disappearance of the hyper-AF dots; OCT scan (F) shows overall improvement of the outer retinal integrity but persistence of focal interruption of the EZ (white asterisks).

DISCUSSION

This study represents, to our knowledge, the largest case series of patients affected by MEWDS published in the literature so far. In our series, we confirm that MEWDS is predominantly a disease of young women as 80.4% were women, with a mean age of 29.8 ±7.8 years, presenting typically after a viral prodrome (less than one-third of the cases in our series), with a variety of visual symptoms (photopsia, blurred vision, floaters and scotoma). We have found an interesting seasonality of this disease, with most cases presenting in the mid-seasons, especially in the autumn (p=0.03). Interestingly, autumn is the season just preceding the peak of common influenza-like viral illnesses.[14] MEWDS is

Table 4 Morphology and location of dots on the different multimodal retinal imaging techniques at presentation

			Dot morphology						Dot location					
	Done at presentation		Isolated		Confluent		Mixed		Macula		Peripapillary		Mid-periphery	
Imaging modality	n	%	n	%	n	%	n	%	n	%	n	%	n	%
BAF	44	86.2	11	25.0	10	22.7	22	50.0	41	93.2	38	86.4	29	65.9
FA	34	66.6	12	35.3	6	17.6	15	44.1	28	82.4	24	70.6	21	61.8
ICGA	28	54.9	16	57.1	1	3.6	10	35.7	24	85.7	25	89.3	20	71.4

BAF, blue autofluorescence; FA, fluorescein angiography; ICGA, indocyanine green angiography.

considered a benign condition with excellent prognosis for invariable spontaneous visual recovery. This is the first study actually focusing on visual recovery and shows that not all the patients recover completely, in terms of VA. Interestingly, we found that almost 10% of cases were bilateral at presentation or at recurrence, which occurred in 11.7% of the cases overall. Bilateral simultaneous involvement has been reported very rarely in MEWDS.[15 16] However, these atypical presentations did not correlate with visual recovery. Our case series showed that the VA at first examination was highly predictive of eventual VA recovery. For example, those patients presenting with VA worse than 0.48 LogMAR were much more likely to have an incomplete recovery. VA recovery showed also a significant correlation with the age of the patients at presentation, with a mean age significantly lower (25.0±7.6 years) in the group of patients with incomplete recovery. This finding could be explained by the possible stronger immune reaction in the younger patients affected by MEWDS, as we know that there is relative immune senescence with increasing age.[17] In our series, only six patients (11.8%) were treated with systemic steroids but their final visual outcome was not significantly different from those who did not receive treatment ($p>0.5$). Our results do not support that routine use of systemic steroids, and in any case, the majority, but not all, of the MEWDS cases recover good vision.[10] However, the number of treated patients was very low. Nevertheless, our results may influence future treatment strategies as we have at least identified some risk factors for incomplete recovery—primarily those with poor presenting VA and conceivably young patients, these subgroups of patients could be targeted for treatment. These treatments could include systemic steroids but validating efficacy with robust trials will be very challenging, given the rarity of the disease.

In our statistical analysis, we evaluated also the joint effect of initial VA and age in determining the final VA with an exact multivariate logistic model, and this has further strengthened our results. The estimate of the adjusted odds of a poor functional outcome when initial VA was >0.48 was about 13 times those of patients with a better presenting VA ratio; the wideness of the associated CI is due to the relatively small number of observations. A limitation of this study is that the only parameter that we could use retrospectively to evaluate retinal function is the VA, but there are other parameters like contrast sensitivity or tests like electrophysiology and microperimetry which are not usually performed in the common clinical practice and have been used in other case series.[18 19] These tests could be useful particularly for those patients who, even with a complete VA recovery, complain that the vision in the affected eye is not the same as it was before and some visual disturbances persist. But this was not objective of our study.

Regarding multimodal imaging, there are several published studies focused particularly on understanding the pathogenesis and the primary location of the condition, which is still subject of debate (Marchese *et al*[20]); Zicarelli *et al*[21] observed on SD-OCT a hypertransmission sign underneath the RPE, possibly due to changes in RPE intracellular melanin, supporting the RPE pivotal role of the condition. ICGA early to late hypofluorescent lesions consist of altered reflectivity of the damaged RPE, as also Gaudric *et al*[22] speculate.

Foveal granularity, deeply studied on multimodal imaging by Mantovani *et al*[23] and named also 'Jampol dots' on adaptive optics studies showing hyper-reflective patches in background of healthy photoreceptors,[24] is a characteristic feature, almost pathognomonic for MEWDS.[1 7 25 26] It can be the only presenting sign[2] or it may persist long after the resolution of the other lesions.[1 7 25 26] In our case series, foveal granularity was still present in about 40% of the cases at the 3-month follow-up, but it was not possible to find any significant difference between the cases with complete and incomplete VA recovery. We can speculate that higher number of cases would be needed in order to obtain statistically significant results in the analysis.

The disruption of the outer retina layers on the OCT did not give any statistically significant result in predicting the final visual outcome in our patient groups as we found persistent alterations of 30% of patients with complete VA recovery and up to 40% of patients with incomplete VA recovery. The typical alterations of the ellipsoid layer are well known from the previous literature[7 26 27] as well as from the granular appearance of the RPE in some cases.[18] We evaluated IZ also, which seems to be altered similar to EZ, but to a slightly less extent.

Our findings may seem to be in contrast with other studies reporting very frequent recovery of the outer retinal layers during the course of the disease. However, no systematic longitudinal grading of the outer retinal layers on high-resolution OCT has been reported in the current literature.[26 28]

Of note, Li *et al* reported persistent focal disruption of the outer retinal layers with the old-generation OCT in one patient (14.3%) of the seven patients, despite all of them having complete BCVA recovery.[28] Marsiglia *et al* in their series used different OCT machines for the grading of the outer retinal layers. Therefore, differences in OCT machines, acquisition and grading protocol of the tomographic scan may account for the different results of the subjective interpretation of the outer retinal layers' integrity.[26]

We found that FAF is the test most frequently performed after OCT and there is no consistent perfect correlation between FAF, FFA and ICGA findings. Sometimes the dots were better visualised on ICGA, being isolated and well defined, while FAF showed more lacy and confluent patterns. ICGA often showed more extended dots beyond the arcades, but maybe we can speculate that ICGA, and particularly wide-field ICGA, was performed more frequently in cases of widespread involvement of RPE on BAF, so that there is potential bias. Furthermore, angiographic tests were performed sometimes at different times after the onset of symptoms, in a rapidly evolving condition; this could maybe explain the different findings. Interestingly, we observed

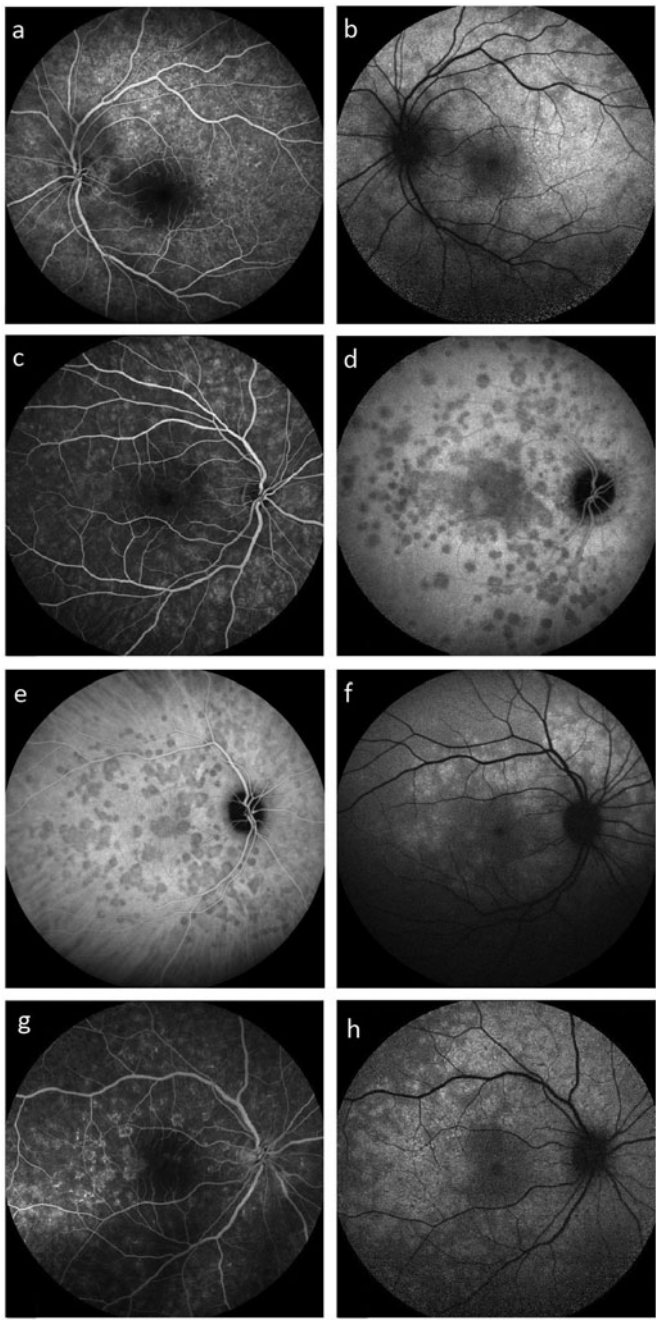

Figure 3 Representative cases of different dot morphologies in patients presenting with multiple evanescent white dot syndrome. Case 1 (A, B) shows confluent dots on fluorescein angiography (FA) and blue autofluorescence (BAF). Case 2 (C, D) shows isolated dots on FA and mixed dots (confluent at the posterior pole and isolated in the mid-periphery) on indocyanine green angiography (ICGA). Case 3 (E, F) shows isolated dots on ICGA and mixed dots on BAF. Case 4 (G, H) shows isolated dots on FA and confluent dots on BAF.

that, from a descriptive point of view, an hyperfluorescent disc on FFA at presentation was more frequent in the cases with incomplete recovery (75.0%) than in the cases with complete recovery (42.3%). This finding was, however, not significant, but this may have been a type II statistical error as a consequence of the rarity of this disease and the challenges of obtaining large number of patients in the study. We can speculate that maybe disc hyperfluorescence is an additional marker of more severe inflammatory involvement; in such cases, there is a greater likelihood of failure to recover completely the VA. The mean age of patients with hyperfluorescent discs was closest to the younger ages of those who had an incomplete recovery, and this supports the concept of stronger immune reaction in younger patients. This is an interesting finding and we believe that this needs to be further explored in future studies. Persistence of enlarged blind spot on visual field test[28] and evidence of irreversible decrease of the ganglion cell layer (GCL) and inner plexiform layer in MEWDS[29] may support the view of a relationship between the severity of the optic disc involvement at presentation and the incomplete VA recovery. In our study, we did not evaluate the GCL, but we can hypothesise that a significant decrease in GCL could concur with the incomplete visual recovery, as a result of the optic disc inflammatory involvement.

There are a number of limitations to our study. It is retrospective and, as a consequence, not all patients had complete imaging. In addition, the study was performed before the widespread introduction of OCT-A. This new technology, along with the other imaging techniques, has demonstrated that the choriocapillaris appears unaffected in acute cases, suggesting that the RPE is the primary site of involvement.[6 7 20–22] While we acknowledge that the absence of OCT-A is a limitation in our study, we believe that it does not invalidate our findings. Another limitation is that we cannot exclude recruitment bias in our study population. The study was retrospective and included patients attending the tertiary centre, which may inevitably have been weighted towards the more severe end of the disease spectrum.

In conclusion, the clinical spectrum of MEWDS seems to be wider than reported and includes bilateral presentation and incomplete visual recovery. In our series, poor presenting VA and young age were independently associated with poor VA outcome. Further study is warranted to confirm these findings.

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