

Idiopathic Multifocal Choroiditis and Punctate Inner Choroidopathy – Evaluation of Risk Factors for Increased Relapse Rate: A 2-Year Prospective Observational Cohort Study

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Keywords

Punctate inner choroidopathy · Multifocal choroiditis · Immunomodulatory therapy

Abstract

Introduction: The aim of this study was to describe the course of disease in patients with idiopathic multifocal choroiditis (MFC) and punctate inner choroidopathy (PIC) and to identify risk factors associated with an increased relapse rate of disease activity. **Methods:** In this prospective observational cohort study, demographical and clinical data were collected concerning the relapses rate of disease activity, the conclusions of the multimodal imaging results, treatment, complications, and self-reported quality of life. Disease activity was defined as new inflammatory lesions or active inflammation in preexisting chorioretinal lesions either with or without active choroidal neovascularization (CNV). Linear regression analysis was performed to identify risk factors associated with an increased relapse rate. **Results:** In total, 122 eyes of 82 patients (93% females) were included with a median age (IQR) of 45 (37–54) years. A history of secondary CNV was present in 66% of the eyes. During follow-up, the best-corrected visual acuity remained stable despite a median relapse rate (IQR) of 1.0 (0.25–3). Cycles of oral corticosteroids were given in 59% of the patients, 72% were treated

at baseline or started treatment during follow-up with a disease-modifying antirheumatic drug (DMARD), and 35% with a biological agent in addition to the DMARD. Both a history of secondary CNV ($B = 1.2$, 95% CI: 0.7–1.7, $p = 3.6 \times 10^{-5}$) and high myopia (< -6 diopters) ($B = 0.6$, 95% CI: 0.1–1.1, $p = 0.02$) independently increased the relapse rate of disease activity. **Discussion/Conclusion:** A history of secondary CNV and high myopia were associated with an increased relapse rate of disease activity. Moreover, the results of this study emphasize the challenging character of treating patients with MFC/PIC.

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Published by S. Karger AG, Basel

Introduction

Central multifocal choroiditis (cMFC) is part of the spectrum of the white dot syndromes or more specifically of the group of primary inflammatory choriocapillaris [1]. cMFC is characterized by inflammation of the choriocapillaris resulting in the typical white dots in the fundus of the eye. cMFC comprises several subtypes including punctate inner choroidopathy (PIC), idiopathic multifocal choroiditis (MFC), serpiginous choroiditis, and relentless placoid chorioretinitis. cMFC has a chronic and relapsing character often resulting in the develop-

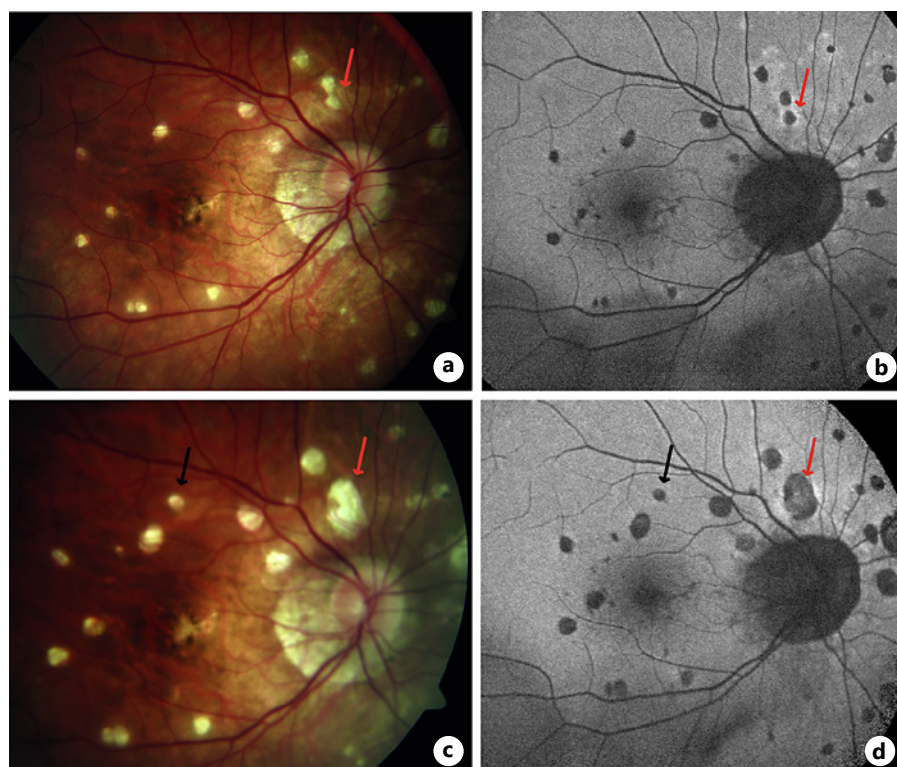


Fig. 1. Substantial growth of chorioretinal lesions in 24 months of follow-up (red arrows) and the development of a new chorioretinal lesion (black arrow). **a, b** Fundus picture (**a**) and fundus autofluorescence picture (**b**) taken at baseline. **c, d** Both the fundus picture (**c**) and the fundus autofluorescence picture (**d**) demonstrate growth of the chorioretinal lesions.

ment and growth of multiple chorioretinal lesions and frequently patients develop secondary choroidal neovascularization (CNV) (Fig. 1) [2, 3]. Interestingly, over 90% of the cases are reported in women and over 85% of the patients are myopic [4, 5]. The nature of the association between cMFC and myopia is not yet determined and requires further research. As mentioned, cMFC comprises different subtypes including the closely resembling subtypes PIC and idiopathic MFC. The literature is inconclusive if these subtypes should be considered as separate subtypes, or both subtypes represent an identical disease entity. Recently, several attempts have been made to create classification criteria for both PIC and MFC though most cases present with overlapping criteria [4–6]. As many others, the authors believe that these subtypes most likely belong to one disease entity. Future genetic and protein profiling studies exploring the pathophysiological mechanism are needed to provide more clear evidence on this matter. Even though the pathophysiological mechanism is still largely unknown, increasing evidence points toward a dysregulation of the immune system. Involvement of the immune system is supported by both small genetic studies [7, 8] and the efficacy of immunomodulatory therapy for this disease [7–11]. Nevertheless,

the severity of the course of disease and the demand for immunomodulatory therapy differ between patients. Subsequently, it is difficult to predict the course of disease in individual patients and practice personalized medicine. Moreover, the quality of life in these relatively young patients and the effect of treatment have not yet been evaluated. In this study, we aim to describe the clinical course of disease and self-reported quality of life during 24 months of follow-up in a large cohort of patients and to identify risk factors associated with an increased relapse rate.

Methods

Design and Study Population

This was a 2-year prospective observational cohort study in patients with idiopathic MFC and PIC, carried out between January 2019 and September 2021 in the outpatient clinic of the University Medical Centre (UMC) Utrecht, The Netherlands. Additionally, patients were asked to fill out questionnaires regarding the self-reported quality of life at the start and end of follow-up. This study is in adherence to the Declaration of Helsinki and its further amendments. All study participants provided written informed consent for using their medical data for research purpose and a subset of participants provided written informed consent for fill-

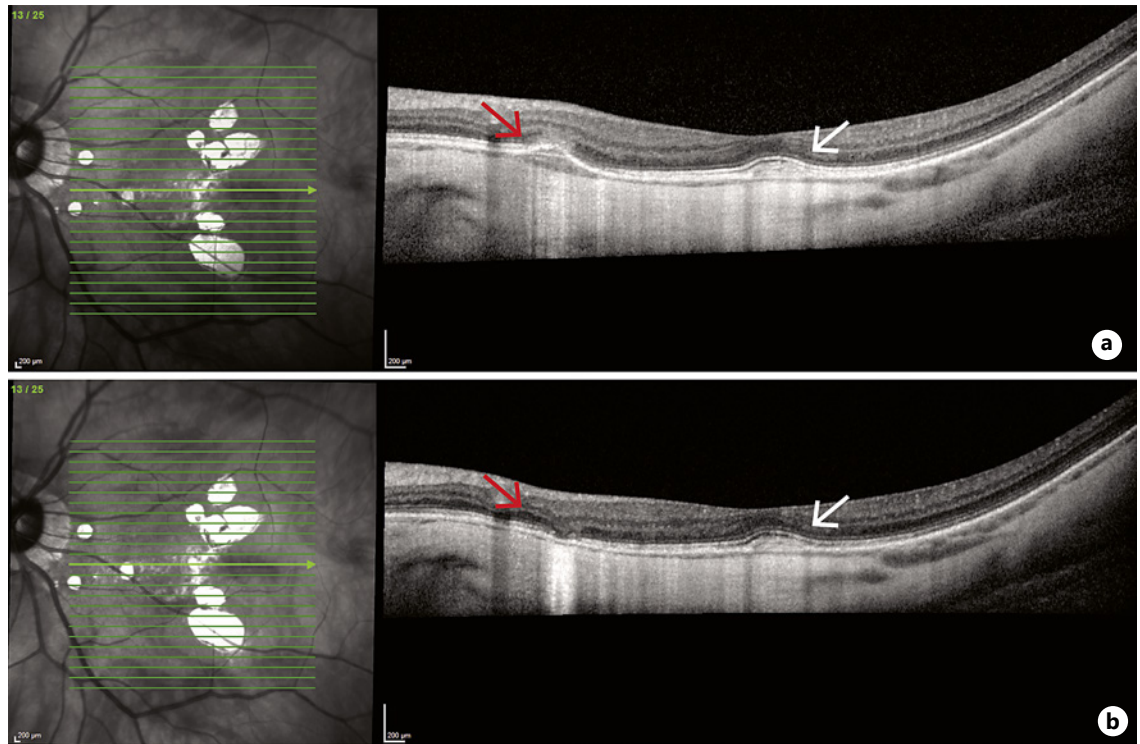


Fig. 2. Relapse of disease activity in one of the lesions visualized with the EDI SD-OCT. **a** Inflammatory activity in one of the lesions is observed (red arrow) and is characterized by an increased choroidal thickness beneath the lesion, focal elevation of the RPE with breakthrough of the underlying material into the retinal structures. The white arrow depicts an inactive preexistent CNV scar. **b** Six weeks after increasing the dose of the DMARD and ad-

ministering a periocular triamcinolone, the lesion does not show signs of inflammation (red arrow). The choroidal thickness normalized and the sub-RPE material disappeared. The CNV scar has remained inactive (white arrow). EDI SD-OCT, enhanced depth imaging spectral-domain optical coherence tomography; RPE, retinal pigment epithelium; CNV, choroidal neovascularization; DMARDs, disease-modifying antirheumatic drugs.

ing out the questionnaires. The Institutional Review Board of the University Medical Centre (UMC) of Utrecht approved this study (METC number 20-269). The UMC Utrecht is a tertiary referral center specialized in the care of patients with inflammatory ocular diseases. A standardized care protocol was developed within the expertise of the team of uveitis specialists outlining the diagnostics, treatment options, and follow-up regime for these patients (online suppl. Fig. 1a, b; see www.karger.com/doi/10.1159/000526663 for all online suppl. material).

Patients were diagnosed with cMFC when they presented with chorioretinal lesions within the posterior pole without papillitis and retinal vasculitis. Other frequent causes of posterior uveitis were ruled out by obtaining the medical history, routine laboratory diagnostics, and chest X-ray. These alternate diagnoses consist of ocular tuberculosis, toxoplasmosis, sarcoidosis, uveitis associated with inflammatory bowel disease, Birdshot chorioretinopathy, lymphoma, and other viral and bacterial ocular infections. When indicated routine diagnostic workup was extended with a (positron emission tomography-) computed tomography or an anterior chamber tap with aqueous humor analysis. Patients with cMFC were included if they were diagnosed with the subtypes idiopathic MFC and PIC, visited the outpatient clinic between January 2019 and June 2019, and were ≥ 18 years old. Patients diagnosed

with other subtypes of cMFC such as serpiginous choroiditis and relentless placoid chorioretinitis were excluded from this study.

Data Collection

The start of follow-up was a visit in the outpatient clinic in the first 6 months of 2019 and the follow-up duration was 24 months with a maximum follow-up time deviation of 3 months. At each follow-up moment, patients underwent routine ophthalmological examination including Snellen best-corrected visual acuity (BCVA), slit-lamp examination, fundus biomicroscopy, and indirect ophthalmoscopy. Routine retinal imaging consisted of enhanced depth imaging scans on the spectral-domain optical coherence tomography (SD-OCT) including the TruTrack Active Eye Tracking technology and 30° near-infrared imaging of the fundus (Spectralis HRA-OCT; Heidelberg Engineering, Heidelberg, Germany/FF 450 plus; Carl Zeiss Meditec, Jena, Germany). When indicated retinal imaging was extended with fluorescein and indocyanine green angiography, 55° fundus auto fluorescence (FAF) images (Spectralis HRA-OCT; Heidelberg Engineering), color fundus images (FF 450 plus; Carl Zeiss Meditec), and OCT angiography (SD-OCT Angioplex Cirrus HD-OCT 5000; Carl Zeiss Meditec). The affected area of the posterior pole was measured with the Region Finder software (Spectralis HRA-OCT; Heidel-

Table 1. Patient characteristics at baseline of patients with idiopathic multifocal choroiditis and punctate inner choroidopathy

	<i>n</i> = 82 patients/ <i>n</i> = 122 eyes
Median age start follow-up [IQR]	45 [37–54]
Median age first complaints [IQR]	37 [28–45]
Female, <i>n</i> (%) of all patients	76 (93)
Bilateral disease, <i>n</i> (%) of all patients	40 (49)
History of CNV, <i>n</i> (%) of affected eyes	81 (66)
Median BCVA (in logMAR) [IQR] of affected eyes	0.034 [–0.06 to 0.26]
BCVA <20/50, <i>n</i> (%) of affected eyes	20 (16)
BCVA <20/200, <i>n</i> (%) of affected eyes	13 (11)
Median refractive error [IQR] of affected eyes	–5.50 [–8.3 to –2.9]
History of anterior uveitis, ^a <i>n</i> (%) of affected eyes	10 (8)
History of vitritis, ^a <i>n</i> (%) of affected eyes	10 (8)
History of EpiMEWDS, <i>n</i> (%) of affected eyes	4 (3)
Median lesion number in the posterior pole ^b [IQR] of affected eyes	6 [3–13]
Lesions limited to the posterior pole, <i>n</i> (%) of affected eyes	60 (49)
Median affected area in the posterior pole ^b , mm ² [IQR]	4.1 [1.4–11.0]
Treatment with oral prednisolone, <i>n</i> (%) of all patients	30 (37)
Steroid-sparing immunomodulatory therapy, <i>n</i> (%) of all patients	
None	34 (41)
DMARD ^c	41 (50)
Biologicals ^d + DMARD	7 (9)

IQR, interquartile range; CNV, choroidal neovascularization; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; EpiMEWDS, Epiphenomenon of a secondary Multiple Evanescent White Dot Syndrome reaction; DMARDs, disease-modifying antirheumatic drugs. ^a Vitritis was defined as more than 1+ cells in the vitreous, and anterior uveitis was defined as more than ½+ cells in the anterior chamber. ^b Affected area and lesion number in the posterior pole were measured on the first available 55° fundus autofluorescence imaging during follow-up. Data were missing for 7 patients. ^c Mycophenolate mofetil (*n* = 20), ciclosporin (*n* = 7), methotrexate (*n* = 4), azathioprine (*n* = 4), ciclosporin + mycophenolate mofetil (*n* = 5), and tacrolimus (*n* = 1). ^d All patients treated with a biological were treated with adalimumab.

berg Engineering). This software allows semiautomatic identification and quantification of atrophic areas on FAF images.

Collected data consisted of demographic and clinical data and included patient characteristics, relapses of disease activity of choroidal inflammation, reactivation of CNV, or the development of new CNV sites, treatment, and complications. Disease activity was defined as new inflammatory lesions or active inflammation in pre-existing chorioretinal lesions either with or without active CNV. Choroidal inflammation was scored based on imaging parameters including (1) focal increase of the choriocapillaris thickness below the lesion and/or (2) new focal elevation of the RPE with underlying material and increased penetration of light through the inner choroid with or without retinal infiltration and/or (3) new RPE/EZ disruption on the SD-OCT (Fig. 2). On the late-phase ICGA imaging (4) areas of hypofluorescence can be observed, which are not well circumscribed with vague edges and are greater in size compared to the FAF images. New or reactivation of a CNV was scored in case (1) new intraretinal or subretinal fluid developed in the neovascular complex visualized with SD-OCT (atrophic cysts in scars not included) and/or (2) when growth of the neovascular complex was observed with decreased penetration of light through the inner choroid on SD-OCT and/or (3) leakage on the fluorescein angiog-

raphy and/or (4) in case a new vascular network was observed on OCT angiography. When patients presented with residual activity or reactivation of CNV without an active choroidal inflammation, this was not scored as disease activity. Inactive stage of disease is defined as no disease activity for at least 3 months while treated with ≤7.5 mg oral prednisolone, or in case of ocular corticosteroid injections, the last injection was <3 months ago. A relapse of disease activity was defined as the observation of disease activity after reaching an inactive stage of disease.

Within the first 6 months of follow-up, all patients received an invitation to fill out a set of questionnaires concerning the self-reported quality of life. The set comprised two questionnaires: the Dutch translation of the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25), a standardized questionnaire reporting on the vision-related quality of life (VR-QoL), and the Dutch translation of the Short Form Health Survey 36-items (SF-36), a standardized questionnaire reporting on the quality of life in relation to the patients' general health (GH-QoL). The NEI-VFQ-25 reports on the VR-QoL within 12 domains and the SF-36 reports on the GH-QoL within 8 domains (for specification of the domains, see Table 3). The questionnaires were filled out again in the last 6 months of follow-up.

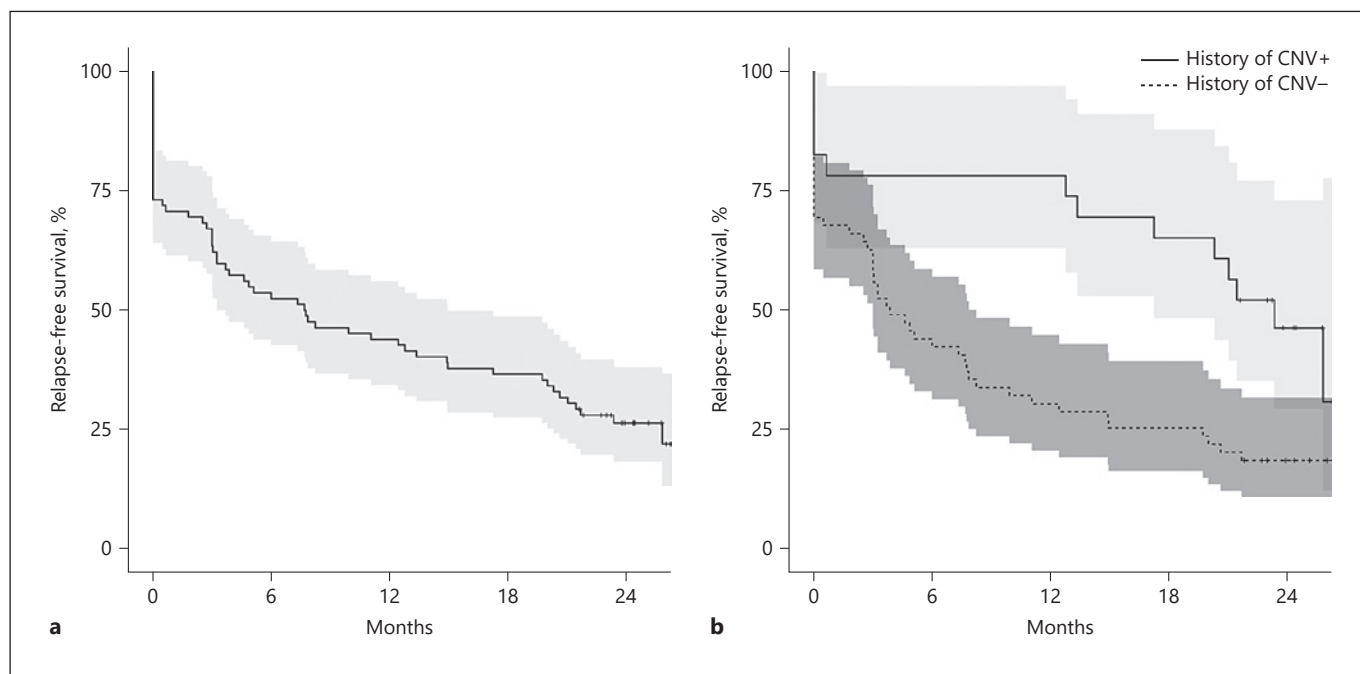


Fig. 3. Relapse-free survival visualized with Kaplan-Meier curves including 95% confidence intervals. **a** Relapse-free survival plot of all patients. **b** Relapse-free survival plot of the patients grouped by a history of secondary CNV. CNV, choroidal neovascularization.

Data Analysis

To determine clinical characteristics associated with the relapse rate during the 24 months of follow-up, data of the most active eye were used in case of bilateral disease. We compared the affected area in the posterior pole on 55° FAF imaging exclusively for patients with available date at baseline (± 3 months) and at the 24 months of follow-up (± 3 months). The Snellen BCVA was converted to the logarithm of the minimum angle of resolution equivalent for analysis. The answers from the NEI-VFQ-25 and SF-36 questionnaires were converted to a 0–100 points scale where 0 corresponds with the worst and 100 with the best QoL-related outcome. The scores of the domains of the NEI-VFQ-25 questionnaires were compared to a reference group within the working population [12], and the scores of the domains of the SF-36 questionnaires were compared to a Dutch reference group [13].

Statistical Approach

Data analyses were performed in RStudio version 1.2.5001 (RStudio Team, Boston, USA) and R version 3.6.1 (R Foundation for Statistical Computing, Austria). Between-group differences for continuous variables were compared with the Student's *t* test and for categorical variables with the χ^2 test with false discovery rate correction at 5% to correct for multiple testing. For longitudinal analysis the paired sample *t* test was used. Normality of the data was tested using the Shapiro-Wilk's method, and in case of non-normal distributed data, the nonparametric variant of the statistical tests was performed. To evaluate the survival time until a relapse of disease activity, we used Kaplan-Meier curves of the survival R package [14]. Multivariate linear regression analysis was

performed to evaluate the effect of clinical characteristics on the quality of life scores of the different domains of the NEI-VFQ-25 and SF-36 questionnaires. Relapse rate, treatment with IMT, treatment with prednisolone, age, and gender were incorporated in these models, and false discovery rate correction at 5% was applied as indicated. To identify the clinical factors associated with the relapse rate, univariate linear regression analyses were performed and significant parameters resulting from the univariate analyses were used for a multivariate linear regression analysis. Multicollinearity was checked with the variance inflation factor. A *p* value of <0.05 was accepted as indicating statistical significance.

Results

Study Population

A total of 91 patients with PIC and idiopathic MFC were included in this study. Nine patients were lost to follow-up with several reasons including referral back to the initial ophthalmologist ($n = 3$) or no follow-up visit at 24 ± 3 months ($n = 6$); thus, the study group consisted of 82 patients. The median age was 45 years (interquartile range [IQR] 37–54) and 76 (93%) patients were female. The baseline characteristics of the patients are demonstrated in Table 1.

Table 2. Treatment and complications during follow-up in patients with idiopathic multifocal choroiditis and punctate inner choroidopathy

	<i>n</i> = 82 patients/ <i>n</i> = 122 eyes
Systemic corticosteroids, <i>n</i> (%) of all patients	
1 cycle of oral prednisolone	31 (38)
≥2 cycles of oral prednisolone	17 (21)
Systemic DMARDs, <i>n</i> (%) of all patients	
Start DMARD ^a	17 (21)
Switch DMARD	34 (42)
Reason for switch, <i>n</i> (%) of all switches (<i>n</i> = 46)	
No disease control	30 (65)
Side effects	15 (33)
Pregnancy	1 (2)
Stop DMARD	
Side effects	6 (7)
Disease control	2 (2)
Systemic biological therapy, <i>n</i> (%) of all patients	
Start biological ^b	21 (26)
Corticosteroid injections, <i>n</i> (%) of all eyes	
Periocular triamcinolone	20 (16)
Parabulbar betamethasone	20 (16)
Intravitreal triamcinolone	5 (4)
Dexamethasone implant	1 (1)
Anti-VEGF therapy, <i>n</i> (%) of all eyes	48 (39)
Median [IQR] number of injections of all eyes with at least 1 injection	7 [4–12]
Complications, <i>n</i> (%) of all eyes	
Steroid-induced ocular hypertension	7 (6)
Ocular hypotony	1 (1)
Cataract extraction	3 (2)
Reversible ptosis	4 (3)

DMARDs, disease-modifying antirheumatic drugs; VEGF, vascular endothelial growth factor; IQR, interquartile range. ^a Mycophenolate mofetil (*n* = 8), ciclosporin (*n* = 3), methotrexate (*n* = 3), and azathioprine (*n* = 3). ^b All patients started treatment with adalimumab.

Longitudinal Analysis

In total, 135 relapses of active choroiditis occurred in 61 patients with a median (IQR) number of relapses of 1.0 (0.25–3) per patient. In 25% of the relapses the patient experienced symptoms at the time the relapse was diagnosed. In 41% of the relapses, the active choroiditis was accompanied by active secondary CNV (of which in 10% of the relapses a new CNV site developed, and 31% of the relapses the CNV reactivated). Figure 3a visualizes the relapse-free survival time in all patients and Figure 3b displays the survival curves for the patients grouped by whether the patients had a history of secondary CNV.

For 24 patients (36 eyes) fundus autofluorescence imaging was available both at baseline and at 24 months of follow-up. In these patients, there was a significant increase of the median (IQR) affected area between baseline (5.5 [1.5–13.6] mm²) and after 24 months of follow-up (6.0 [2.7–15.9] mm²) ($p_{\text{Wilcoxon signed-rank test}} = 2.0 \times 10^{-5}$)

(Fig. 1b, d). This corresponds with a total median (IQR) growth of the affected area of 0.8 (0.2–2.0) mm² during follow-up. In eyes of patients with (*n* = 19) and without (*n* = 17) treatment with disease-modifying antirheumatic drugs (DMARDs) or biologicals at baseline, the median growth was 0.4 (0.1–2.3) mm² and 0.9 (0.4–1.7) mm², respectively ($p_{\text{Wilcoxon rank sum test}} = 0.51$). The median (IQR) percentage increase was 13.4% (5.8–18.4%) versus 22.5% (12.7–51.7) in eyes of patients with treatment with DMARDs or biologicals at baseline versus patients without treatment ($p_{\text{Wilcoxon rank sum test}} = 0.03$).

The median BCVA (IQR) in logarithm of the minimum angle of resolution at baseline and after 24 months of follow-up was 0.034 (0.061–0.26) and 0.018 (–0.061 to 0.21), respectively ($p_{\text{Wilcoxon signed-rank test}} = 0.20$). Table 2 demonstrates the treatment initiated during follow-up and complications that occurred during follow-up. In summary, 59% of the patients were treated with oral cy-

Table 3. The results of the quality of life-related questionnaires of patients with idiopathic multifocal choroiditis and punctate inner choroidopathy compared to healthy control subjects

	Scale	Idiopathic MFC/PIC				Ref ^a		<i>p</i> _{adj} value ^b
		median	(range)	mean	(SD)	mean	(SD)	
<i>NEI-VFQ-25 baseline</i>		<i>n</i> = 46				<i>n</i> = 511		
General health	0–100	65	(25–100)	62	(15)	80	(17)	4.2×10 ⁻¹⁰
General vision	0–100	74	(40–85)	70	(12)	79	(16)	7.4×10 ⁻⁶
Ocular pain	0–100	88	(38–100)	81	(17)	88	(15)	0.02
Near vision activities	0–100	83	(33–100)	80	(16)	92	(13)	7.4×10 ⁻⁶
Distance vision (<i>n</i> = 45)	0–100	83	(42–100)	80	(16)	92	(11)	7.4×10 ⁻⁶
Social functioning	0–100	100	(33–100)	95	(14)	98	(8)	0.14
Mental health	0–100	75	(20–95)	75	(17)	88	(10)	5.2×10 ⁻⁶
Role difficulties	0–100	75	(19–100)	75	(20)	93	(13)	5.3×10 ⁻⁷
Dependency	0–100	100	(50–100)	94	(12)	99	(6)	0.03
Driving (<i>n</i> = 41)	0–100	75	(33–100)	70	(17)	89	(11)	1.6×10 ⁻⁷
Color vision	0–100	100	(50–100)	98	(9)	98	(9)	0.94
Peripheral vision	0–100	100	(25–100)	84	(21)	93	(15)	7.8×10 ⁻³
Composite score (<i>n</i> = 40)	0–100	86	(51–96)	83	(11)	91	(7)	2.9×10 ⁻⁶
<i>SF-36 baseline</i>		<i>n</i> = 46				<i>n</i> = 1,742		
Physical functioning	0–100	95	(35–100)	90	(15)	83	(23)	6.6×10 ⁻³
Role limitations – physical	0–100	100	(0–100)	74	(40)	76	(36)	0.78
Bodily pain	0–100	82	(21–100)	78	(21)	75	(23)	0.36
General health	0–100	60	(20–100)	58	(21)	71	(21)	1.8×10 ⁻⁴
Vitality/energy	0–100	63	(15–100)	60	(20)	69	(19)	5.4×10 ⁻³
Social functioning	0–100	89	(0–100)	81	(23)	84	(22)	0.50
Mental health	0–100	78	(40–100)	76	(14)	77	(17)	0.84
Role limitations – emotional	0–100	100	(0–100)	82	(36)	82	(33)	0.94

NEI-VFQ-25, National Eye Institute Visual Function Questionnaire 25; SF-36, Short Form Health Survey 36-items. ^a Reference group for NEI-VFQ-25: Hirneiß et al. [12]; reference group for SF-36: Aaronson et al. [13]. ^b Student's *t* test after 5% false discovery rate correction for multiple testing.

cles of prednisolone during follow-up, 21% of the patients started treatment with a DMARD, and 26% of the patients started treatment with a biological agent in addition to a DMARD. Complications occurred in 13% of the eyes and for the majority consisted of a temporary steroid-induced ocular hypertension.

Self-Reported Quality of Life

From the 82 study participants, 46 (56%) filled out the questionnaires concerning the quality of life at baseline. The results are demonstrated in Table 3. The study population scored significantly lower on almost all domains of the NEI-VFQ-25 compared to the reference group except for the domains “Social functioning” and “Color vision.” On the contrary, on the domains of the SF-36, the study population only scored significantly lower for the domains “General health” and “Vitality/Energy” and scored significantly higher on the domain “Physical function-

ing.” Forty-one of the 46 patients filled out the questionnaires once more at 24 months of follow-up. Multivariate linear regression analysis revealed that treatment with IMT (DMARD or DMARD + biological) significantly decreased the quality of life scores of the domains of “Distance vision” and “Driving” though after correction for multiple testing none remained significant. The relapse rate during follow-up and treatment with prednisolone did not influence the self-reported quality of life (online suppl. Table 1).

Clinical Characteristics Associated with Relapse Rate

We evaluated whether clinical characteristics could be identified that were associated with the number of relapses of disease activity during the 24 months of follow-up (Table 4). These analyses revealed that both a history of secondary CNV and high myopia significantly increased the relapse rate of patients during follow-up. High myo-

Table 4. Clinical characteristics associated with relapse rate of disease activity during follow-up in patients with idiopathic multifocal choroiditis and punctate inner choroidopathy

	Univariate			Multivariate		
	B	95% CI	<i>p</i> value	B	95% CI	<i>p</i> value
Age start follow-up	-0.012	-0.036 to 0.012	0.34			
Age start of symptoms	0.007	-0.015 to 0.029	0.54			
Female gender	-0.233	-1.31 to 0.85	0.67			
Bilateral disease	-0.149	-0.71 to 0.42	0.60			
History of CNV	1.167	0.31–1.72	7.5×10^{-5}	1.192	0.65–1.73	3.6×10^{-5}
High myopia ^a	0.557	0.0025–1.11	0.049	0.599	0.10–1.10	0.02
History of anterior uveitis	-0.806	-1.80 to 0.19	0.11			
History of vitritis	0.600	-0.40 to 1.60	0.24			
History of EpiMEWDS	0.314	-1.00 to 1.62	0.64			
Affected area in the posterior pole ^b	-0.020	-0.04 to 0.002	0.07			
Lesion number in the posterior pole ^{b, c}						
2–5	-0.537	-1.63 to 0.56	0.33			
>5	-0.397	-1.43 to 0.64	0.45			
Lesions limited to the posterior pole	-0.246	-0.81 to 0.32	0.39			
Therapy at baseline ^c						
DMARD	-0.178	-0.77 to 0.41	0.55			
DMARD + biological	-0.749	-1.81 to 0.31	0.16			

B, beta; CI, confidence interval; CNV, choroidal neovascularization; EpiMEWDS, Epiphenomenon of a secondary Multiple Evanescent White Dot Syndrome reaction; DMARD, disease-modifying antirheumatic drug. ^aHigh myopia was defined as a refractive error of more than or equal to -6 diopters. ^bAffected area and lesion number in the posterior pole were measured on the first available 55° fundus autofluorescence imaging during follow-up. Data were missing for 7 patients. ^cReference was set at: lesion number = 1, therapy at baseline = no DMARD or biological agent.

myopia was defined as a refractive error of more than -6 diopters. Multivariate linear regression analysis revealed that both a history of secondary CNV and high myopia independently significantly increased the relapse rate (Table 4). No multicollinearity was observed between myopia and a history of secondary CNV. A history of secondary CNV increased the relapse rate with 1.2 relapses (95% CI: 0.7–1.7, $p = 3.6 \times 10^{-5}$), and high myopia increased the relapse rate with 0.6 relapses (95% CI: 0.1–1.1, $p = 0.02$).

Discussion and Conclusion

In this study, we described the course of disease in the 24 months of follow-up in patients with idiopathic MFC and PIC. We discovered that the self-reported quality of life in these patients is substantially decreased compared to healthy controls. Moreover, we identified that a history of secondary CNV and high myopia both independently increased the relapse rate of disease activity.

Previously, it was suggested that the development of secondary CNV is the result of a chronic and severe inflammatory process in the choriocapillaris [15, 16]. This inflammation results in hypoperfusion of the choriocapillaris visualized as hypofluorescent areas on indocyanine green angiography. These areas of hypoperfusion are often larger and more widespread than one would expect based on color fundus imaging and ophthalmological examination [17]. Probably both the inflammatory environment in the choriocapillaris and the subsequent hypoperfusion of the choriocapillaris contribute to the trigger for neoangiogenesis and the development of secondary CNV. In line with this hypothesis, only patients presenting with severe inflammation in the choriocapillaris and severe hypoperfusion will develop secondary CNV. This could possibly explain the observed association between a history of secondary CNV and the increased relapse rate of disease activity in these patients, though we must take into account that it can still be challenging to distinguish choroidal inflammation and secondary CNV activity on multimodal imaging especially in the absence of fluorescein and indocyanine green angiography [18, 19]. How-

ever, considering the extensive treatment of secondary CNV in these patients (online suppl. Fig. 1B), especially compared to the treatment of myopic CNV, it is highly unlikely that secondary CNV reactivates in the absence of choroidal inflammation [20]. In addition, we found that high myopia is associated with an increased relapse rate. As hypothesized by Herborg et al. [15], myopia causes structural changes to the choriocapillaris, Bruch's membrane, and the retinal pigment epithelium, resulting in an increased fragility of this complex. Due to this increased fragility, this complex is eminently prone to be targeted by inflammatory diseases. This could perhaps also explain why predominantly myopic patients are affected. However, due to the complex and multifactorial nature of both inflammatory processes and the process of myopia, it remains challenging to unravel all the aspects of this relationship. The risk factors of high myopia and the history of secondary CNV are probably also related to each other (no correlation was observed in this study) since the choriocapillaris of myopic eyes is more sensitive for hypoperfusion and ischemia. This could probably also explain why in idiopathic MFC and PIC the prevalence of secondary CNV is much higher than other forms of uveitis without an association with myopia [15]. In line with the results of this study, one could debate if a patient developed secondary CNV at the first presentation and has high myopia, immunosuppressive therapy with DMARDs and biologicals should be initiated more timely to decrease the number of relapses of disease activity, since the course of disease is expected to be more severe.

The results we report at baseline and during the 24 months of follow-up are relatively favorable in comparison to the literature. We report a better preserved BCVA, less patients had bilateral disease, and less complications occurred [2, 21–23]. Moreover, compared to the literature, the reported annual growth of chorioretinal lesions was fewer [24]. Several reasons could explain these positive outcomes. In this study, the patients were closely monitored with multimodal imaging and many relapses of disease activity were diagnosed even before the patient developed symptoms. In our opinion, an asymptomatic inflammatory process in the choriocapillaris should be treated to avoid the development of new chorioretinal lesions and substantial growth of existing lesions (more than expected as part of the natural history of lesions) and to avoid the development or reactivation of secondary CNV. Moreover, most of the patients in our study population did not demonstrate cells in the vitreous of anterior chamber and could therefore be classified as “multifocal choroiditis without panuveitis” a term introduced by Fung and col-

leagues [25]. Since vitritis and anterior uveitis are considered risk factors for the development of several complications including glaucoma, cystoid macular edema, and cataract [21], this could partly also explain our relatively positive outcomes. Even though the outcomes are relatively favorable, this study also confirms that the treatment of patients with idiopathic MFC and PIC can be challenging. In a considerable proportion of the patients, there was incomplete response to treatment with a DMARD and a biological was added to the treatment regime. Even though in the literature monotherapy with a DMARD is described as effective as steroid-sparing treatment [9, 10], this study shows that in more than one-third of the patients, DMARD monotherapy is insufficient to achieve long-term steroid-free remission. Treatment with biologicals seems to be very effective in this patient group though the literature is limited to small case series [26–28]. However, in this study, we did not observe an association between treatment with biologicals and a decrease in the relapse rate, probably due to the low number of cases.

Although the disease is considered to be eye-limited without an association with a systemic disease, the majority of the patients report a decreased quality of life on a wide variety of domains including the domain “General health.” This group of patients has a worse perception of their quality of life than one would expect based on the visual acuity and disease localization. Perhaps this is the result of the relatively young age of disease manifestation in combination with the recurrent and chronic character of the disease and the frequent necessity of systemic immunomodulatory therapy. Even though we did not find a clear association between the quality of life and relapse rate, treatment with oral prednisolone, and immunomodulatory therapy, this could possibly be attributed to the limited number of patients that filled out the questionnaires. Moreover, Pearlman et al. [29] described an increased prevalence of self-reported autoimmune diseases in patients with white dot syndromes and their families. Thus, another explanation could be that patients with idiopathic MFC and PIC are more likely to develop other autoimmune diseases affecting the general health of the patients [29]. We compared our results with a study carried out in the UMC Utrecht including patients with noninfectious uveitis (NIU) [30]. Patients with idiopathic MFC and PIC scored significantly higher on almost all domains of the NEI-VFQ compared to NIU patients (online suppl. Table 2). Thus, even though the vision-related quality of life is decreased in patients with idiopathic MFC and PIC, this patient group still scored higher than patients with NIU.

Strengths of this study are its prospective nature and the relatively high number of included patients considering the low prevalence of the disease. Diagnostics and treatment are standardized in our tertiary referral center for inflammatory eye disorders. To preserve homogeneity within the group of patients, only patients with the subtypes idiopathic MFC and PIC were included. This study was executed during the COVID-19 pandemic. Fortunately, for the majority of the follow-up time, limited restrictions were present for ophthalmological visitation and none of the patients structurally canceled their appointments during the COVID-19 pandemic. However at onset of the pandemic uveitis specialists were reluctant to start treatment with immunomodulatory therapy because of the unknown effect on COVID-19 progression and response to COVID-19 vaccines.

In summary, our data demonstrate that both a history of secondary CNV and high myopia are associated with an increased relapse rate in patients with PIC and idiopathic MFC. Moreover, the results of this study emphasize the challenging character of monitoring and treating patients with idiopathic MFC and PIC.

Statement of Ethics

This study is in adherence to the Declaration of Helsinki and its further amendments. All study participants provided written informed consent for using their medical data for research purpose and a subset of participants provided informed consent for filling out the questionnaires. This study protocol was reviewed by the Institutional Review Board of Utrecht and the need for ethics approval was waived.

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Conflict of Interest Statement

The authors have no conflict of interest to declare.

Funding Sources

Dr. F.P. Fischer Foundation: Achtersloot 212-C, 3401 NZ IJsselstein, The Netherlands. Foundation Beheer het Schild: Wolfhezerweg 101, 6874 AD Wolfheze, The Netherlands. Landelijke Stichting voor Blinden en Slechtzienden (LSBS): Galvanistraat 1, 6716 AE Ede, The Netherlands. Rotterdamse Stichting Blindenbelangen (RBS): Schiekade 77, 3033 BE Rotterdam, The Netherlands. Stichting Louise Rottinghuis Fonds: Ringenum 6, 9934 PM Delfzijl, The Netherlands. Oogfonds: Churchilllaan 11, 3527 GV Utrecht, The Netherlands.

Author Contributions

Evianne L. de Groot contributed to the design of the study, performed the analyses, and wrote the manuscript. Jeannette Ossewaarde-van Norel and Joke H. de Boer contributed to the design of the study, contributed to the interpretation of results and discussion of the manuscript, and reviewed the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

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