Paracentral Acute Middle Maculopathy and Risk of Cardiovascular Disease, Stroke, and Death: A Longitudinal Study

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• PURPOSE: To evaluate the risk of acute cardiovascular events (CVE), including cardiovascular diseases, cerebrovascular diseases, and all-cause mortality in patients with paracentral acute middle maculopathy (PAMM).

• DESIGN: Retrospective cohort study.

• METHODS: We studied 43 individuals with optical coherence tomography-documented PAMM attending Moorfields Eye Hospital between January 2014 and June 2021. We excluded patients with preceding (<2 years) major adverse cardiac events. We stratified patients by age (<50 and ≥50 years) and whether associated with retinal vascular diseases (RVD) or isolated (iPAMM). We assessed risk factors, clinical characteristics, and visual prognosis of the patients. CVE risk was estimated using Kaplan–Meier curves, the log-rank test, and Cox proportional hazards regression.

• RESULTS: In young patients with iPAMM patients ($n = 12$), underlying predisposing factors included six (50%) sickle cell disease and five (41.6%) others, including breakthrough bleeding in pregnancy, migraine, genetic cardiomyopathy, amphetamine use; among those with PAMM + RVD ($n = 12$) one (9%) had a vascular disorder, and four (44.4%) oral contraceptive use. In the older group of 20 patients, 15 (75%) had at least one coronary risk factor. During a median follow-up of 14 months (range 12-54), older subjects with iPAMM had a higher risk of developing CVE than those with PAMM + RVD ($P < .001$). Notably, iPAMM displayed a significantly earlier peak in peri-PAMM CVE risk compared to PAMM + RVD (median: one month, range 1-40 months vs 36 months, range 12-54 months). Relative to those with PAMM + RVD, risk of CVE was significantly higher in patients with iPAMM, adjusted for age and sex (hazard ratio: 6.37, 95% confidence interval 1.68-24.14, $P = .017$). No young patients experienced adverse CVE. At baseline, older iPAMM patients mean best corrected visual acuity of 0.7 (0-1.8) logarithm of the minimum angle resolution, which improved significantly to 0.2 (0-1.30) logarithm of the minimum angle resolution at the latest visit ($P = .033$).

• CONCLUSIONS: Young individuals with iPAMM have a higher prevalence of predisposing factors compared to those presenting with combined PAMM + RVD. Older patients with iPAMM had a higher risk of CVE than those with PAMM + RVD, especially in the peri-onset timeframe. This suggests the need for a prompt cardiovascular assessment to rule out systemic etiologies and optimize cardiovascular risk factors, in addition to ongoing ophthalmology input.

INTRODUCTION

Paracentral acute middle maculopathy (PAMM) describes a hyperreflective band observed at the level of the inner nuclear layer (INL) on optical coherence tomography (OCT) imaging in individuals experiencing an acute painless paracentral scotoma.[1,2] This lesion is attributed to transient macular hypoperfusion and consequent acute ischemia of middle retina tissue intermediate (ICP) and deep retinal capillary plexus.[1,2] As a legacy of PAMM, retinal ischemic perivascular lesion (RIPLs) represents focal irregularity in the middle retina due to INL thinning and outer nuclear layer hyporeflectivity on OCT.[3]

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Given its pathogenesis, an association between PAMM and retinal vascular diseases (RVD), specifically retinal vein occlusion (RVO) and artery occlusion (RAO), has been proposed.[2,4] Additionally, PAMM has been associated with systemic conditions such as hypertension, diabetes mellitus, autoimmune diseases, medication use, viral infections and vaccinations, intraocular surgeries, and cardiovascular procedures.[2] Furthermore, real-world evidence suggests that RIPLs could be a prognostic biomarker for subclinical cardiovascular disease (CVD).[3,5-7]

In our previous study,[8] we found a higher prevalence of CVD in individuals with isolated PAMM (iPAMM) compared to those with combined PAMM and RVD, emphasizing the need for thorough systemic evaluation as part of PAMM management. Recently, there have been several case reports in the literature documenting that PAMM, especially when observed as an isolated OCT finding, can be a possible presenting sign of giant cell arteritis (GCA) or carotid occlusive disease.[9-12] Thus, PAMM may manifest as the only clinical sign of ocular and systemic emergency that requires immediate systemic investigation.[9-12] Yet, limited information exists regarding the risk of developing cardiovascular events (CVE) in patients with PAMM, which would be important to reduce mortality and morbidity. Moreover, there is a lack of robust outcome data specifying the optimal CVD risk management, including ideal timing, in patients with PAMM, especially when the etiology is not readily apparent.

In this longitudinal study, we aimed to identify the spectrum of systemic diseases found in conjunction with PAMM in an ethnically diverse cohort attending a tertiary ophthalmic hospital in London, United Kingdom. Secondly, we sought to determine the risk of CVE that is associated with PAMM and the temporal characteristics of these events.

METHODS

• **STUDY DESIGN AND PARTICIPANTS:** We conducted a single-center, retrospective cohort study based on the electronic healthcare database of Moorfields Eye Hospital (MEH). We reviewed electronic medical records (EMR) of patients presenting with PAMM from January 2014 to June 2021. The presence of PAMM lesions was defined as hyperreflective parafoveal bands of the INL in patients with sudden paracentral scotoma and confirmed by two senior retinal consultants. Patients with confirmed presence of PAMM on OCT scans were only included in the respective analysis if they had a follow-up period of at least 6 months after the onset of PAMM. Patients were excluded from the analysis if they had a history of major CVE, including stroke and acute myocardial infarction, in the 2 years prior to the PAMM event. Institutional review board approval was obtained for a retrospective chart review and the study was performed in accordance with the tenets of Declaration of Helsinki. We reviewed General Practitioner letters and hospital records recorded in EMRs from the MEH Accident and Emergency Department, neuro-ophthalmology, general ophthalmology, and glaucoma clinics.

We extracted from the EMR the demographic data, including age, gender, and ethnicity. We collected patients' comorbid disorders and medical conditions considered to be risk factors for CVD, including hypertension, dyslipidemia, diabetes mellitus, sickle cell disease (SCD), and oral contraceptive use. We also recorded best corrected visual acuity (BCVA) at the time of PAMM event and after its resolution. Patients were followed until an event occurred or until December 31, 2023.

Clinical records were longitudinally queried to adjudicate the occurrence of mortality or CVE at the onset or after PAMM. Study defines CVE as a composite of coronary heart disease (coronary insufficiency, acute myocardial infarction, revascularisation, angina), cerebrovascular events (ischemic stroke, hemorrhagic stroke, and transient ischemic attack), heart failure, and death potentially related to these conditions.[13] Other cardiovascular-related outcomes included carotid artery occlusion CAD), hypertensive crisis, and atrial fibrillation.

We a priori stratified patients into two relevant subgroups—firstly, by age: <50 and ≥ 50 years old. Secondly, patients were grouped by the presence of concomitant RVD at the time of PAMM event.

• **STATISTICAL ANALYSIS:** The Mann–Whitney *U* test was used to compare the continuous variables of age and BCVA between groups. The BCVA was measured in Snellen and converted to logarithm of the minimum angle resolution (logMAR) units for the statistical analyses.[14]

Descriptive statistical analyses using the Fisher exact test were done to compare the characteristics within the studied population in terms of demographics, medical comorbidities, and the frequency of CVE either at the onset of or after PAMM. Kaplan–Meier analysis was used to calculate the cumulative incidence of CVE between the two subgroups in the older cohort, and the log-rank test was used to analyze the differences between the survival curves. Hazard ratios for the association between PAMM and incident CVE were estimated using Cox proportional models, adjusting for age and sex. Statistical significance was set at $P < .05$. We used SPSS Statistics (IBM corporation, version 28) for all statistical analyses.

RESULTS

A flowchart of cohort selection is provided in Figure 1. A total of 43 patients were included in the study, of which 23 were included in the younger group and 20 in the older

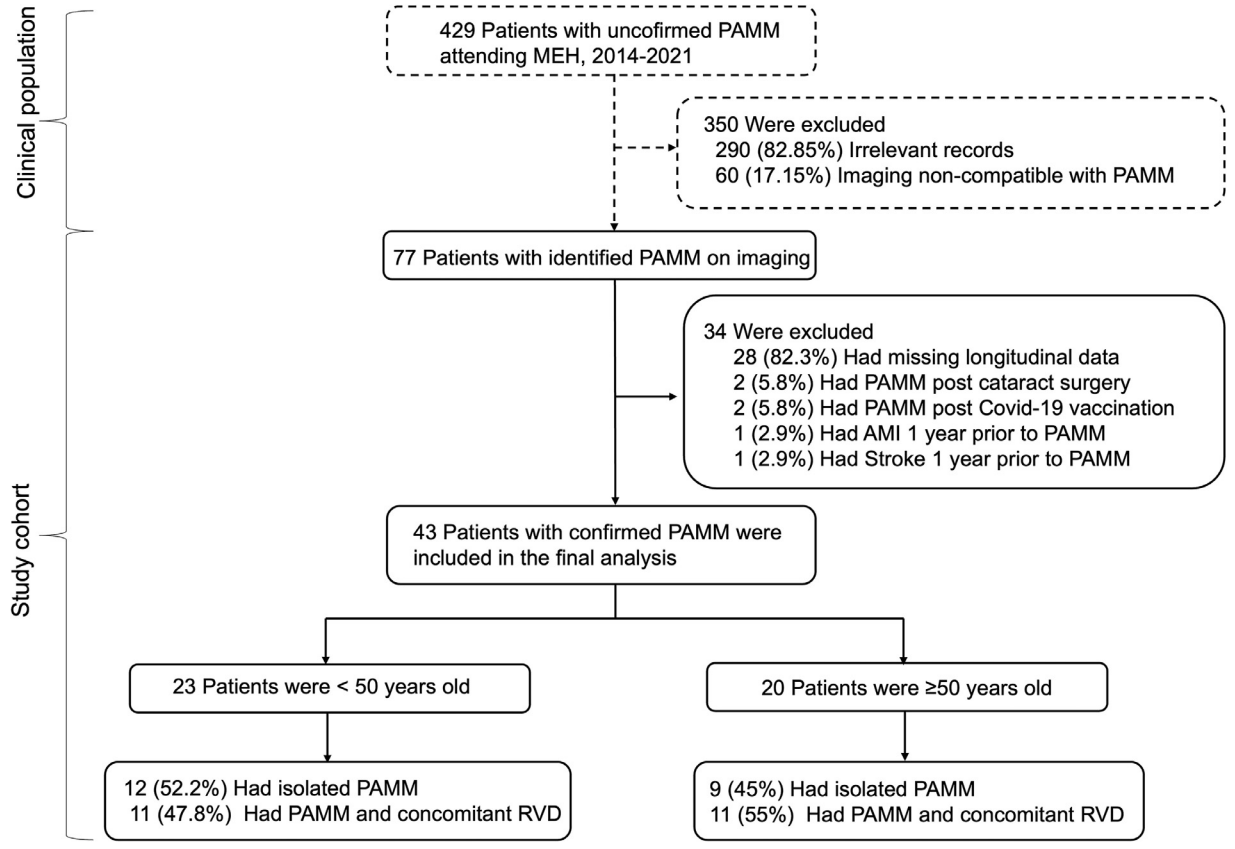

FIGURE 1. Study cohort. The workflow of patient data collection and stratification by age and concomitant retinal vascular disease. Patients with a provisional diagnosis of PAMM were extracted using structured query language from the MEH Accident and Emergency Department, Medical Retina, Neuro-ophthalmology, General Ophthalmology, and Glaucoma clinics. The data set was manually cleaned to exclude irrelevant records, such as words that contained the letters "PAM." AMI = acute myocardial infarction; PAMM = paracentral acute middle maculopathy; RVD = retinal vascular disease.

one. The demographic and health characteristics of each subgroup are provided in Table.

• **YOUNG COHORT:** A total of 23 patients (14 male and 9 female) were included in this cohort. The median age was 32 (interquartile range 25.5-41.5) years. Out of 23 young patients, 11 showed PAMM associated with RVD—three cases involved RAO, while eight had RVO. Twelve young patients showed iPAMM (Figure 1). Detailed information on each group is provided inTable. The mean BCVA was 0.15 (–0.10 to 2.30) LogMAR at baseline and 0.05 (–0.10 to 1.00) LogMAR at the latest visit.

Cardiovascular risk factors and events. A wide range of concomitant disease entities or predisposing risk factors were noted across the young cohort at the time of PAMM event. In comparison to individuals experiencing RVD accompanied by PAMM, patients with iPAMM exhibited a significantly higher prevalence of underlying medical conditions ($P = .03$).

Specifically, in the isolated iPAMM group, 11 out of 12 patients (91.6%) were found to have an underlying etiology. A broad spectrum of causes was associated with iPAMM, including chronic disorders like SCD ($n = 6$, 54.5%) and genetic cardiomyopathy. Additionally, acute medical conditions such as migraine, breakthrough bleeding during pregnancy, and amphetamine abuse have also been reported in timely association with PAMM.

Conversely, within the group presenting concomitant RVD, 11 out of 12 patients (91.6%) were generally healthy, except for one patient with vasculopathy (8.3%). A detailed history and systemic workup, including blood test, clotting profile, thrombophilia screening, cardiovascular assessment, and COVID-19 serology, were reported in those patients to exclude inflammatory, infectious, and haematologic conditions. Four patients in this group were associated with oral contraceptive use (Table). In a median follow-up of 20.5 months (range 6-94 months), no occurrences of CVE were observed in young patients.

• **OLDER COHORT:** Twenty patients, 15 male, and five female, with a median age of 68.5 (55.7-75) years were included in the older cohort. Eleven individuals (55%) exhibited PAMM in association with RVD—four of them (36.4%) had RAO while seven had RVO (63.4%). The re-

TABLE. Socio-Demographic and Clinical Characteristics of Patients With PAMM

	Age < 50 y (n = 23)			Age ≥ 50 y (n = 20)		
	Isolated PAMM (n = 12)	PAMM + RVD (n = 11)	P	Isolated PAMM (n = 9)	PAMM + RVD (n = 11)	P
Age, yrs; median (IQR)	31.5 (22;41.2)	32 (26;40)	.926	72 (56;78)	67 (56;74)	.542
Male; *n* (%)	5 (41.7)	4 (36.4)	1	7 (77.7)	7 (63.6)	1
Ethnicity; *n* (%)						
Caucasian South-Asian Afro-Caribbean	4 (33.3)	6 (54.5)		3 (33.3)	6 (54.5)	
Unknown	1 (8.3)	0		0	1 (9.1)	
	1 (8.3)	1 (9.1)		0	1 (9.1)	
	6 (50)	4 (36.4)		6 (66.6)	3 (27.3)	
OD, *n* (%)	4 (33.3)	8 (72.7)	.100	6 (66.6)	4 (36.4)	.177
Comorbidities						
Hypertension, *n* (%)	0	0		7	9	
Dyslipidemia, *n* (%)	0	0		4	3	
Diabetes Mellitus, *n* (%)	0	0		1	1	
History of Coronary artery disease, *n* (%)	0	1		3	2	
Sickle Cell Disease, *n* (%)	6	0		0	0	
Oral Contraceptive use, *n* (%)	0	4		0	0	
Other[a]	5	0		0	0	
Follow-up months, median (range)	31.2 (13 to 94)	21.3 (2 to 62)	.109	36 (12 to 54)	27 (12 to 40)	.105
BCVA LogMAR, baseline, mean (range)	0 (–0.1 to 0.2)	0.3 (–0.1 to 2.3)	.147	0.7 (0 to 1.8)	0.6 (–0.1 to 1.8)	.704
BCVA LogMAR, final, mean (range)	0 (–0.1 to 0.3)	0.1 (–0.1 to 1)	.129	0.3 (0 to 1.3)	0.3 (0 to 2.30)	1

[a]Pregnancy, migraine, genetic cardiomyopathy, amphetamine use.The Mann–Whitney *U* test was used to compare groups. In cases of correlated data, Wilcoxon test was selected. Fisher's exact test was used for contingency analysis. P values<0.05 were considered statistically significant.BCVA, best corrected visual acuity; IQR, interquartile range; LogMAR, logarithm of the minimum angle of resolution; OD, right eye; PAMM, paracentral acute middle maculopathy; RVD, retinal vascular diseases.

maining nine patients (45%) displayed iPAMM. Notably, three of the latter had a documented history of cardiovascular problems, although none had experienced a CVE within the previous 2 years. The demographic and health characteristics of the two groups are reported in Table.

At baseline, iPAMM patients had a mean BCVA of 0.7 (0-1.80) LogMAR, which improved significantly to 0.2 (0-1.30) LogMAR at the latest visit (P = .033). Baseline BCVA in PAMM + RVD patients was 0.6 (–0.10 to 1.80) LogMAR, and final BCVA was 0.3 (–0.10 to 2.30) LogMAR, showing a not statistically significant improvement (P = .191). These outcomes are detailed in Table.

Cardiovascular risk factors and events. With regard to CV risk factors listed in Table, 77.7% of iPAMM patients (n = 7) and 72.7% of PAMM + RVD patients (n = 8) presented with pre-existing CV risk factors. Of note, a significant proportion of cases had inadequate control of blood pressure, as 70% (14 of 20) displayed systolic blood pressure ≥130 mm Hg at clinic visits.

In the PAMM + RVD group, CVE was newly diagnosed in 6 patients (54.5%) within a median period of 36 months (range 12-54 months). The reported CVE included one stroke, one case of coronary heart disease, one case of GCA, and three deaths. Each of these patients had one or more cardiovascular risk factors or past events in their medical history. The other five patients (45.4%) did not experience any CVE; among them, three (27.2%) had one or more cardiovascular risk factors or events in their history, while two (18.2%) were otherwise healthy.

In contrast, in the iPAMM group, CVE was newly diagnosed in all nine patients (100%) over a median observation period of one month (ranging from one to 40 months). CVE included two strokes, two cases of coronary heart disease, two deaths, three cases of CAD, two hypertensive crises, and one case of atrial fibrillation. Seven of these patients (77.7%) had one or more CV risk factors or historical events, and two (22.3%) were otherwise healthy.

There was a significant group difference in CVE risk, particularly at the time of PAMM onset (log-rank test P < .001) (Figure 2). Individuals with iPAMM displayed a significantly increased risk of CVE compared to those with PAMM + RVD (adjusted hazard ratios 6.37, 95% confidence interval 1.68-24.14, P = .017).

DISCUSSION

In this retrospective, longitudinal study, we examined 43 patients with PAMM extracted from the EMR database of MEH to assess the prevalence of pre-existing vasculopathic disorders and the risk of CVE that is associated

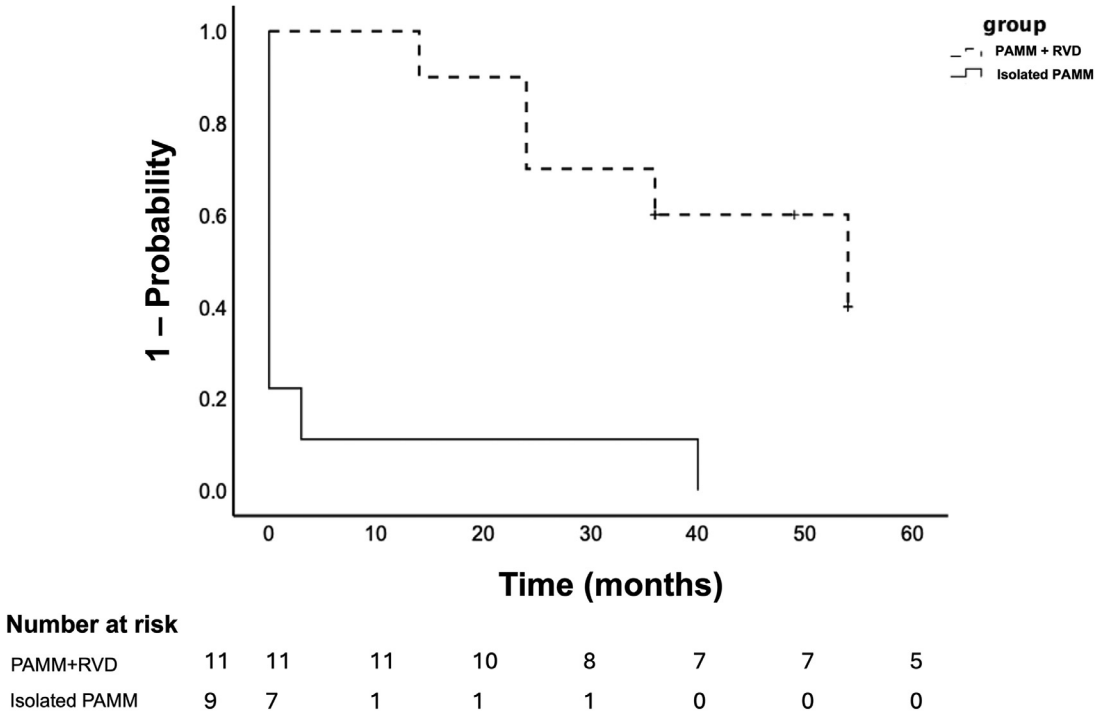

FIGURE 2. Results of Kaplan–Meier survival analysis to compare the differences in CVE development between iPAMM and PAMM + RVD groups ≥50 years old.

with PAMM. Our major findings are that: (1) across the whole cohort, individuals with PAMM exhibited a diverse spectrum of concurrent medical conditions, primarily RVD; (2a) older individuals with PAMM as an isolated ocular finding had a significantly higher risk for CVE development over a median 14-month follow-up period (range 12-54), compared to subjects presenting with both PAMM and RVD, despite sharing similar cardiovascular risk factors, (2b) and the incidence of CVE was particularly increased in the peri-onset timeframe; (3) PAMM is associated with favorable visual outcomes, with good final visual acuity. These results highlight that PAMM not only could have a prognostic impact on visual outcomes but could act as a sentinel vascular event for serious CVE with known attendant significant morbidity and mortality.

Including a series of consecutive patients ensured our findings were not influenced by selection bias. In our cohort, a broad spectrum of concomitant disease entities was noted in the young adults (<50 years old). In 91.5% (11 out of 12) of iPAMM patients, we reported an underlying systemic disorder or triggering factor in association with the development of PAMM, including SCD, hypercoagulable state, migraine, and vasoactive systemic medication use. Conversely, in individuals diagnosed with both PAMM + RVD, we did not observe any underlying medical disorders, as RVD itself predominantly contributed to the onset of PAMM in this group.

Among the older, 75% (15 out of 20) showed pre-existing cardiovascular risk factors, headed by systemic hypertension. It follows that PAMM, even if isolated or seen in a person with apparently good health, is an important clinical sign the etiology of which should be determined. These findings support the existing literature that shows the presence of a wide range of etiologies causing PAMM[2,3] led by RVD as the most common etiology.[4]

One of the main aims of our study was to examine if individuals presenting with PAMM are at risk of CVE, including CAD, GCA, and death, and to evaluate the temporal characteristics of that risk. In the longitudinal outcomes assessment of the older cohort (≥50 years old), we found that all patients with iPAMM developed CVE, which occurred significantly more frequently than in PAMM + RVD patients (54.5%), based on a median 14-month follow-up. Furthermore, we showed that they also exhibited a higher risk for CVE development after adjusting for possible confounding effects, such as age and sex, compared to patients with PAMM and concomitant RVD. In particular, patients with iPAMM are at a short-term, but significantly increased peri-PAMM incidence of CVE (median 1 month, range 1-40), compared to PAMM + RVD (36 months, range 12-54).

These findings provide novel insights into PAMM, primarily when occurring independently of any other RVD, and its increased short-term risk of vascular disease affecting vital organs such as the brain and heart.

Over the past decade, increasing attention has been paid to PAMM and RIPLs as possible first clinical signs of underlying or impending serious CVE and GCA.[5,9-12] Recently, Bousquet et al[9] demonstrated that the presence of PAMM might suggest an incomplete central RAO or be the only ocular sign of carotid artery disease and GCA. GCA is the most common of the systemic vasculitis of older adults,[15] and potentially blinding disease[10,11,16]; therefore, early recognition of its ocular symptoms is crucial to prevent blindness.[17]

In our previous study, we showed a higher prevalence of CVD in individuals with iPAMM.[8] In this study, our data continues to corroborate the underlying ischemic origin of PAMM, regarded as a manifestation of the retinal ischemic cascade[6,18,19] and supports that PAMM is a clinical finding of various vascular diseases affecting retinal microcirculation.

Given the observed earlier peak in peri-PAMM CVE incidence in patients with iPAMM older than 50 years compared to those presenting with PAMM + RVD, optimal management of PAMM would require addressing systemic atherosclerotic risk factors and conducting a prompt comprehensive risk assessment for CVD. Measuring blood pressure is essential given the association between PAMM and uncontrolled hypertension. Early evaluation and implementation of preventive treatments should be conducted in these high-risk patients, regardless of age and sex, to potentially reduce CVE-related mortality and morbidity.

Finally, we found that PAMM is associated with good final visual acuity (≤0.15 LogMAR), although permanent vision loss (≥1 LogMAR) was found in 3 (6.82%) of the 44 patients. Of note, in the older cohort, VA improved ≥0.4 LogMAR, with a relatively greater improvement in the iPAMM group. In line with our results, it has been reported that PAMM is a self-limited disorder with a good visual prognosis.[2] However, permanent, paracentral scotoma can result, depending on the extent of ischemic injury to the retina.

Our study has several limitations. First, the small sample size and inherent limitations of the retrospective study design limit the findings. Second, documentation of all CVE may not have been reported, and the chronological sequence between the PAMM occurrence and the onset of CVE may not have been precise; this might have affected the observed associations in this study, which used information only from medical records. Third, the risk for CVE in PAMM cases may have been inflated due to the selection bias of patients followed longitudinally, who may have been more vulnerable or more inclined to seek medical care. Moreover, although our findings showed an increased risk of CVE in patients with PAMM, the study could not determine the absolute risk of CVE compared with the normal population. Finally, we could not assess the effect of systemic work-up and subsequent interventions in patients with PAMM and CVE.

Notwithstanding these limitations, this is the first study to report the occurrence of peri-PAMM stroke and the largest longitudinal study documenting cardio- and cerebrovascular acute adverse events and all-cause mortality associated with PAMM to date.

Our findings hold significant implications for both primary and secondary prevention of vascular diseases in risk-stratified patients with PAMM. These data underscore the importance of iPAMM as a harbinger of life-threatening CVE and suggest the need for a prompt cardiovascular assessment to rule out systemic etiologies and optimize CV risk factors, in addition to ongoing ophthalmology input.

Further research is needed to ascertain the appropriate investigation, optimal timing, and ideal settings for systemic evaluation as well as the effectiveness of interventions aimed at preventing CVE in patients experiencing incident PAMM. A thorough understanding of PAMM development and pathophysiological mechanisms underlying PAMM-associated CV risk is essential to its effective management.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Celeste Limoli: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Laxmi D. Raja:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Siegfried Karl Wagner:** Writing – review & editing, Validation, Supervision, Methodology, Data curation. **Praveen J. Patel:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration. **Luke Nicholson:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration. **Matthias Bolz:** Visualization, Validation, Supervision. **Stela Vujosevic:** Writing – review & editing, Visualization, Validation, Supervision. **Paolo Nucci:** Visualization, Validation, Supervision, Project administration. **Pearse A. Keane:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Conceptualization. **Hagar Khalid:** Visualization, Validation, Supervision, Resources, Project administration, Formal analysis, Data curation, Conceptualization. **Josef Huemer:** Visualization, Validation, Supervision, Resources, Project administration, Formal analysis, Data curation, Conceptualization.

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