Title: Stroke and Transient Ischemic Attack Incidence After Acute Microvascular Ocular Motor Palsies

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Abstract

Background: In the past, microvascular ocular motor palsies (OMPs) have been regarded as a benign vascular condition with excellent prognosis.

Purpose: To determine the incidence of subsequent stroke or transient ischemic attack (TIA) in acute isolated microvascular third, fourth and sixth cranial nerve palsies.

Methods: The medical records of 95 consecutive patients presenting with ocular motor palsies (OMPs) in the Emergency Department of Coimbra University Hospital Center between January 2007 and October 2012 were reviewed.

Results: Six out of 57 patients (10,5%) with presumed microvascular OMPs had subsequent stroke or TIA, 4 during the first year, 1 during the second year and 1 patient after this period. In comparison, only 1 out of 38 control subjects (2,5%) with non-microvascular OMPs developed subsequent stroke, albeit this difference has not reached statistical significance (P=0,149). Cumulative incidence of subsequent stroke or TIA was higher for the microvascular group, although not significantly (p=0,217). In the microvascular OMP group, age (p=0,633), gender (p=0,272), cranial nerve affected (p=0,256), the number of vascular risk factors (p=0,598), and the use of an antiplatelet agent before (p=0,313) or after the OMP (p=0,164), did not differed significantly between patients who had a subsequent stroke or TIA and those who did not.

Conclusions: A significant proportion of patients with presumed microvascular OMPs developed subsequent stroke, approaching stroke recurrence rates previously reported for other stroke types (e.g., lacunar stroke). This finding emphasizes the importance of initiating a focused secondary prevention strategy when managing patients with presumed microvascular OMPs.

Introduction

Eye movements are under the control of three ocular motor cranial nerves (CN): CN III (third nerve), CN IV (fourth nerve) and CN VI (sixth nerve). These innervate the six extra-ocular muscles responsible for ocular supraduction, infraduction and adduction (the superior rectus and the inferior oblique, the inferior rectus, and the medial rectus, respectively; CN III); infraduction (the superior oblique; CN IV); and abduction (the lateral rectus; CN VI). The CN III also innervates the lid elevator muscle, the ciliary muscle and the sphincter muscle of the iris [1].

Isolated neurological dysfunction of the ocular motor cranial nerves (ocular motor palsies; OMP) may arise from any disease process which affects them at any point along their anatomical pathways. In large adult population-based studies, the most common cause of OMP is presumed microvascular ischemia due to atherosclerotic risk factors and accounts for about 20% of the cases [2]. The abducens nerve is the most commonly affected nerve, followed by the oculomotor and trochlear nerves, respectively [3]. Other causes of isolated OMP include neoplasms and aneurysms, head trauma, congenital, infection, brain stem infarction, sinus thrombosis and multiple sclerosis [2, 3]. Importantly, in about 30% of patients, the cause remains undetermined [2]. As expected, microvascular OMPs are commonly associated with diabetes, hypertension, hyperlipidemia, and also with left ventricular hypertrophy, high haematocrit, coronary artery disease, myocardial infarction, stroke and smoking [2-6]. Clinically, microvascular OMPs are characterized by the onset of acute diplopia, short-lived ipsilateral pain, showing no other neurological findings, and resolving in most cases within a few months [7].

Since microvascular OMPs seem to share the same pathological mechanism (arteriosclerosis) of lacunar strokes, one could argue that the presence of vascular risk factors

and stroke recurrence rate should therefore be similar in both conditions. While this seems to hold true for some vascular risk factors, stroke recurrence after an episode of microvascular OMPs is largely unknown, when compared to previous data on lacunar stroke patients reporting a 5-8% stroke recurrence at 1 year [8, 9]. In a recent nationwide cohort study, Hoi et al. showed a 2.74-fold increased risk of ischemic stroke in patients with OMPs when compared with matched controls [10]. Indeed, if it is consistently demonstrated that microvascular OMP constitutes an independent risk factor for ischemic stroke, then clearly a more focused secondary prevention strategy will be needed for managing these patients.

We retrospectively reviewed the charts of patients with OMPs presenting in our Emergency Department between 2007 and 2012, focusing on stroke and transient ischemic attack recurrence in microvascular OMPs as our main outcome variable.

Materials and Methods

We conducted a retrospective cross-sectional study. The electronic medical records (EMR) of 618 consecutive patients >18 years old presenting with diplopia in the Emergency Department (ER) of Coimbra University Hospital Center over a five-year period from January 2007 to October 2012 were reviewed. Only those who were diagnosed by a neurologist, ophthalmologist and/or neurosurgeon with acute, third, fourth, or sixth cranial nerve palsies were included in the study. Thus, patients with monocular diplopia, decompensated phoria, multiple OMPs, orbital disease, myasthenia gravis, internuclear ophtalmoplegia, gaze palsy, vergence disorders, skew deviation, and previous history of diplopia and/or OMP diagnosis were excluded. Patients with incomplete records were also excluded.

A neuro-ophthalmologist (J.L.) reviewed all the patient data and classified the patients into two groups: microvascular and non-microvascular group. The latter group was further categorized into 8 etiologic subgroups: subarachnoid haemorrhage (SHA), neoplasm, giant cell arteritis (GCA), head trauma, brainstem stroke, hydrocephalus, multiple sclerosis (MS), and idiopathic group.

The microvascular group consisted of those demonstrating isolated OMP (defined as the absence of other neurological signs and symptoms at the time of initial examination, with the exception of concomitant headache and/or periorbital pain) who had one or more vascular risk factors including diabetes mellitus, hypertension, hypercholesterolemia, heart insufficiency (HI), ischemic heart disease (IHD), or previous ischemic event (i.e., stroke or transient ischemic attack (TIA)), with no history of trauma or evidence of neoplasm on imaging studies. Unlike other reports, we did not use strict age limit criteria for diagnosing microvascular OMP (e.g., above 50 years old). Indeed, due to the increasing prevalence of vascular risk factors including hypertension, IHD, HI and stroke, in young- and middle-aged

adults (around 40%), it should come as no surprise if the incidence of microvascular OMPs starts rising among younger age groups [11].

Results of diagnostic testing performed for the acute event (i.e., blood erythrocyte sedimentation rate, C-reactive protein, cholesterol, blood glucose and glycated hemoglobin; blood pressure level; head computed tomography (CT) scan; head magnetic resonance imaging (MRI)) and pertinent demographic (i.e., age; gender) and clinical data (i.e., cranial nerve and side affected; presenting symptom; diplopia duration; presence of headache and/or periorbital pain; presence of other neurological signs; past history of hypertension, diabetes, stroke or TIA, IHD, HI and hypercholesterolemia; previous use of an antiplatelet drug; subsequent treatment with an antiplatelet drug; history of subsequent stroke or TIA; follow-up duration) were recorded when available. In the case of third nerve OMP, due to the incompleteness of the EMR in what regards to pupil involvement in these cases, pupil status was withdrawn from the analysis.

A diagnosis of subsequent stroke or TIA was accepted by review of our own institutional EMR or outside primary care physician's EMR if a 5-day minimum time interval was present between index event (OMP) and subsequent stroke or TIA. We defined follow-up duration as the time from the date of ER visiting to death or last outpatient department follow-up. We made telephone calls to all patients not returning to the follow-up visit to determine whether patient status or condition had changed, particularly inquiring if a neurological vascular event had subsequently occurred or whether any new or changed diagnosis relevant to the OMP had been made.

University of Coimbra review board approval was obtained for this retrospective chart review study. The research adhered to the tenets of the Declaration of Helsinki.

Mean and standard deviation (SD), were used to summarize the continuous variables; proportions were calculated for the categorical outcomes. Two-sample t-tests were used to compare means of normally distributed variables, and Wilcoxon rank sum tests were used if distribution of data did not follow normal distribution. The Fisher's exact test was used to compare the proportions between groups. Kaplan Meyer curves and Log Rank test were used to compare survival curves between groups. Statistical analyses were conducted using Statistical Package for the Social Sciences version 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

In the 6-year period from January 2007 to October 2012, 95 cases of OMPs meeting our criteria were identified. The mean age of the cohort was 62,57 +/- 15,6 years ((range 22-85). Fifty six (58,9%) were male. The mean follow-up period was 43,65 +/- 27 months (range 0-95).

Microvascular OMPs comprised 60% (57/95) of the cohort, and was the most common aetiology seen in our series. There were 38 (40%) non-microvascular cases which comprised the following aetiologies: subarachnoid haemorrhage (n=10; 10,5%); brainstem stroke (n=5; 13,1%); head trauma (n=4; 4,2%); multiple sclerosis (n=4; 4,2%); neoplasm (n=2; 2,1%); giant cell arteritis (n=2; 2,1%); 5,3%); hydrocephalus (n=2; 2,1%); idiopathic (n=9; 9,5%).

There were 44 (46,3%) patients with a CN VI OMP, 27 patients (28,4%) with a CN III OMP and 24 patients (25,3%) with a CN IV OMP. The left eye was more commonly affected in CN VI OMP (n=32; 72,7%) while the right eye was more commonly affected in CN III OMP (n=16; 59,3%) and CN IV OMP (n=15; 62,5%).

Diplopia was the presenting symptom in 78 patients (82,1%), either in isolation (n=48; 61,5%) or accompanied by other symptoms (n=30; 38,5%), including headache, periorbital pain, vertigo, imbalance, vomiting, slurred speech, ptosis and vision loss. Patients in whom diplopia was not the first symptom (n=17; 17,8%), initially presented with facial asymmetry (n=1; 5,8%), headache (n=14; 82,3%), confusion (n=1; 5,8%), vomiting (n=4; 23,5%), vertigo (n=1; 5,8%), imbalance (n=3; 17,6%) and syncope (n=1; 5,8%). Mean diplopia duration was 13,2 +/- 43,5 days, ranging from 30 minutes to 1 year. Forty eight patients (50,5%) complained of headache (n=40; 83,3%), periorbital pain (ipsilateral to OMP) (n=3; 6%) or both (n=5; 10,4%) during the OMP.

Vascular risk factors were present in the majority of patients (n=80; 84,2%). Specifically, hypertension (n=69; 72,6%) and hyperlipidemia (n=38; 40%) were the two most common risk factors present in our cohort, followed by the presence of diabetes (n=27; 28,4%), IHD (n=13; 13,7%), stroke or TIA (n=9; 9,5%), and HI (n=5; 5,3%). Twenty nine patients (30,5%) were on an antiplatelet drug.

In the exam, only 13 (34,2%) of the non-microvascular OMP patients showed additional neurological signs, including gait ataxia (n=1; 7,6%), clonus (n=1; 7,6%), central nystagmus (n=2; 15,3%), focal weakness (n=3; 23%), nuchal rigidity (n=4; 30,7%), somnolence (n=1; 7,6%), facial palsy (n=2; 15,3%), aphasia (n=1; 7,6%). Thus, 2 out of 10 SAH patients, 2 tumor patients, 2 GCA patients, 4 head trauma patients, 2 hydrocephalus patients, 2 out of 5 brainstem stroke patients, 1 out of 3 MS patients, and 9 idiopathic patients presented with an isolated OMP, showing no additional neurological sings at presentation.

Eighty seven patients performed head CT scan in the ER, which was unrevealing in the majority of cases (n=71; 81,6%). Head MRI on the other hand was only performed in a minority of OMP cases (n=23; 24,2%) and yielded significant findings in 7 cases (30,4%) (Table 1). Laboratory testing performed for the acute event revealed the following results: blood glucose, 135 +/- 63,6 mg / dL (73-375) (n=42); glycated hemoglobin A1C, 7,7 +/- 2,0 mmol / mol (5,6-12,2) (n=9); blood cholesterol, 207,5 +/- 55,6 mmol / L (121-325) (n=31); ESR, 14,0 +/- 15,3 mm / hr (0-52) (n=11); CRP, 0,87 +/- 1,46 mg / L (0-6,4) (n=33); systolic blood pressure, 159,4 +/- 28,1 mmHg (90-230) (n=43); and diastolic blood pressure 90,5 +/- 14,8 mmHg (65-126) (n=42).

After the OMP, 28 (29,5%) patients were kept on an antiplatelet agent, 16 (16,8%) patients started treatment and 1 (1,1%) patient stopped treatment. Fifty (52,6%) patients remained without an antiplatelet regimen.

When comparing microvascular with non-microvascular OMP group, older age, the presence of hypertension and the obvious lack of additional neurological signs were significantly different between groups. On the other hand, gender, presenting symptom (diplopia vs. other), diplopia duration, cranial nerve affected, and the presence of the remaining vascular risk factors were similar between groups (Table 2). Diagnostic testing results could not separate between groups either. An important exception was imaging. Indeed, performing head CT and MRI scan yielded positive results in 42,1% and 53,8% of the non-microvascular OMP patients, respectively (Table 3).

Seven (7,4%) patients had subsequent stroke or TIA, 4 during the first year, 2 during the second year and 1 patient after this period. Although the majority of patents had microvascular OMP (n=6) and only 1 patient had non-microvascular OMP, this difference did not reach significance between groups (Table 4). Although cumulative incidence of subsequent stroke or TIA was higher in the microvascular group, log rank test showed no significant difference between groups (p=0,217) (Figure 1).

Within microvascular OMP group, age (p=0,633), gender (p=0,272), cranial nerve affected (p=0,256), number of vascular risk factors (p=0,598), and use of an antiplatelet agent before (p=0,313) or after the OMP (p=0,164) were not significantly associated with the risk of subsequent stroke or TIA. Of note, after OMP, 25 (43,9%) patients remained without antiplatelet agents, while 32 (66,1%) were started or kept on an antiplatelet drug.

Table 1. Significant Findings in Head CT and MRI Scans in Non-Microvascular OMPs.

CT
Subarachnoid Haemorrhage (10)
Haemorrhagic Foci (1)
Brainstem Stroke (1)
Brainstem Glioma (1)
Hydrocephalus (2)
Multiple Sclerosis (1)
MRI
Brainstem Stroke (1)
Multiple Sclerosis (4)
Cavernous Meningioma (1)
Brainstem Glioma (1)

The number in parentheses is the number of cases.

OMP, Ocular Motor Palsy; CT, Computed Tomography; MRI, Magnetic Resonance Imaging

Table 2. Clinical Characteristics of OMP Patients.

		Microvascular	Non-Microvascular	P-value[§]
Age		66,6 +/- 13,4	55,5 +/- 16,4	**0,003**
(years)	<50	4 (7,0%)	14 (36,8%)	**0,0004**
	>50	53 (93,0%)	24 (63,2%)	
Gender				
	Male	36 (63,2%)	20 (52,6%)	0,395
	Female	21 (36,8%)	18 (47,4%)	
Presenting Symptom				
	Diplopia	48 (84,2%)	30 (78,9%)	0,348
	Other	9 (15,8%)	8 (21,1%)	
Diplopia Duration		19,3 +/- 55,4	4,2 +/- 5,6	0,046
(days)				
Cranial Nerve				
	III	15 (26,3%)	12 (31,6%)	0,711
	IV	16 (28,1%)	8 (21,1%)	
	VI	26 (45,6%)	18 (47,4%)	
Vascular Risk Factors				
	No	0 (0%)	15 (39,5%)	**<0, 0000001**
	Yes	57 (100%)	23 (60,5%)	
	No Diabetes	42 (73,7%)	26 (68,4%)	0,370
	Diabetes	15 (26,3%)	12 (31,6%)	
	No HBP	6 (10,5%)	20 (52,6%)	**0,000009**
	HBP	51 (89,5%)	18 (47,4%)	
	No HL	28 (49,1%)	29 (76,3%)	0,007
	HL	29 (50,9%)	9 (23,7%)	
	No Stroke*	51 (89,5%)	35 (92,1%)	0,480
	Stroke	6 (10,5%)	3 (7,9%)	
	No HI	53 (93,0%)	37 (97,4%)	0,331
	HI	47 (0%)	1 (2,6%)	

	No IHD	46 (80,7%)	36 (94,7%)	0,046
	IHD	11 (19,3%)	2 (5,3%)	
Other Neurological Findings				
	No	57 (100,0%)	25 (65,8%)	**0,000002**
	Yes	0 (0%)	13 (34,2%)	
Follow-up Duration (months)		45 +/- 25,4	41,5 +/- 29,5	0,540

[§]After Bonferroni correction; P-value was considered significant if < 0.0035.

Statistically significant comparisons are marked in bold.

* Or transient ischemic attack

OMP, Ocular Motor Palsy; HBP, High Blood Pressure; HL, Hyperlipidemia; HI, Heart Insufficiency; IHD, Ischemic Heart Disease

Table 3. Diagnostic Testing in OMP Patients.

		Microvascular	Non-Microvascular	P-value[§]
Blood Pressure				
(mmHg)	Systolic	158,5 +/- 19,6 (n=25)	160,6 +/- 37,4 (n=18)	0,826
	Diastolic	92,4 +/- 14,5 (n=25)	87,7 +/- 15,3 (n=18)	0,319
Glycated Hemoglobin (mmol / mol)		7,0 +/- 1,4 (n=5)	8,5+/- 2,5 (n=4)	0,312
Blood Glucose (mg / dL)		115,1 +/- 47,1 (n=21)	155,7 +/- 72,2 (n=21)	0,038
Blood Cholesterol (mmol / L)		218,6 +/- 49,6 (n=18)	192,1 +/- 61,6 (n=13)	0,195
ESR (mm / hr)		10,3 +/- 10,6 (n=6)	18,6 +/- 19,9 (n=5)	0,401
CRP (mg / L)		0,43 +/- 0,54 (n=19)	1,48 +/- 2,04 (n=14)	0,040
Head CT Scan				
	Negative	49 (100%)	22 (57,9%)	**<0,0000001**
	Positive	0 (0%)	16 (42,1%)	
Head MRI Scan				
	Negative	10 (100%)	6 (46,2%)	0,007
	Positive	0 (0%)	7 (53,8%)	

[§]After Bonferroni correction; P-value was considered significant if < 0.005.

Statistically significant comparisons are marked in bold.

OMP, Ocular Motor Palsy; ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; CT, Computed Tomography; MRI, Magnetic Resonance Imaging

Table 4. Subsequent Stroke or TIA in OMP Patients.

		Microvascular	Non-Microvascular	P-value
Stroke or TIA				
	No	51 (89,5%)	37 (97,4%)	0,149
	Yes	6 (10,5%)	1 (2,6%)	
	1st Year			
	No	53 (93,0%)	38 (100%)	0,124
	Yes	4 (7,0%)	0 (0%)	
	2nd Year			
	No	56 (98,2%)	37 (97,4%)	0,643
	Yes	1 (1,8%)	1 (2,6%)	
	After 2 Years			
	No	56 (98,2%)	38 (100%)	0,600
	Yes	1 (1,8%)	0 (0%)	

TIA, Transient Ischemic Attack; OMP, Ocular Motor Palsy

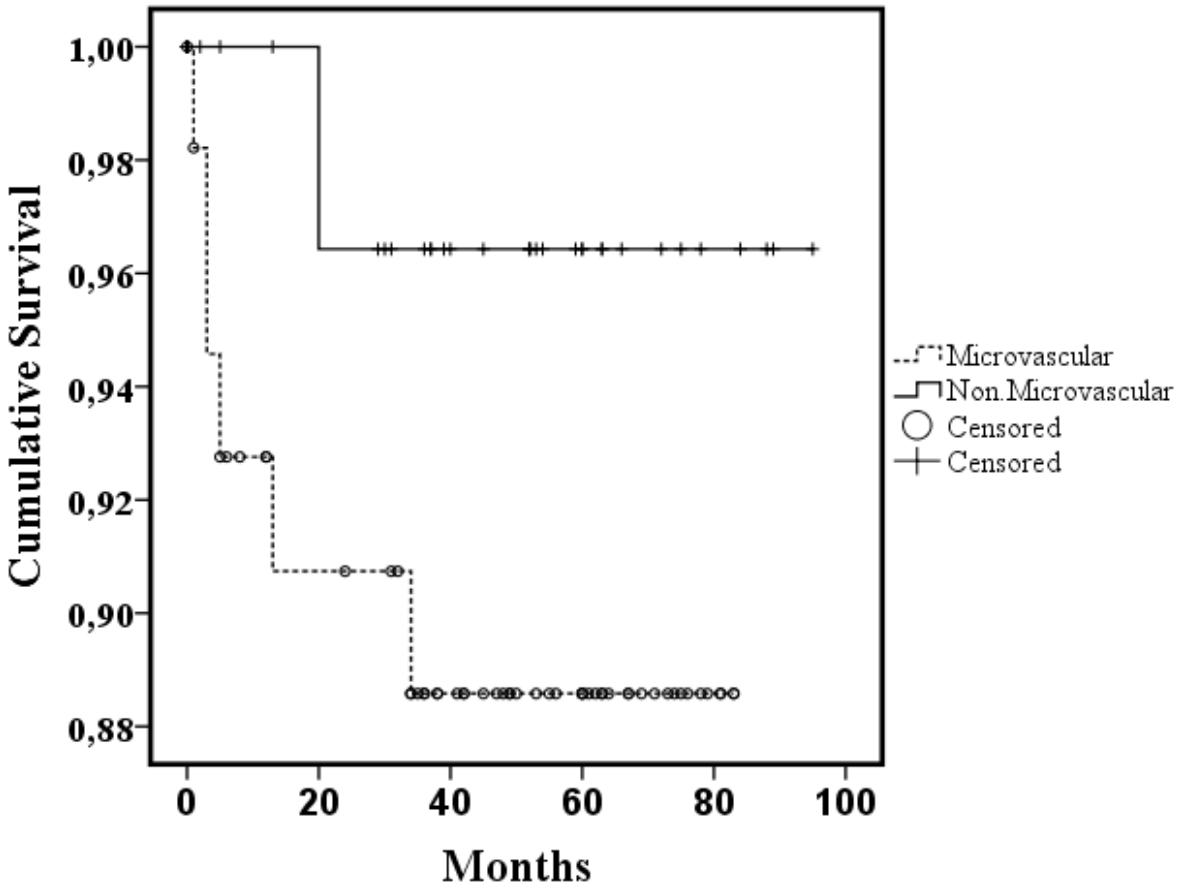

Figure 1. Kaplan Meyer Analysis of Subsequent Stroke or TIA in patients with OMPs. mV, Microvascular; non-mV, Non Microvascular; TIA, transient ischemic attack; OMP, Ocular Motor Palsy

Discussion

In this study involving 57 patients diagnosed with presumed microvascular ocular motor palsies, subsequent stroke was found in about 10% of patients, during a mean follow-up period of 43 months. Importantly, 4 patients (7%) had subsequent stroke within the first year. The risk of subsequent stroke in OMPs has only been addressed recently in one study. Hoi et al., in a large nationwide retrospective cohort study involving 657 patients with isolated OMPs, showed that patients had roughly a three times higher risk of developing ischemic stroke, when compared with matched control subjects, particularly for CNIII OMPs [10]. Unfortunately, the proportion of *microvascular* OMPs within the isolated OMPs cases was not detailed and a clear definition of microvascular OMP was not provided either. Since non-microvascular idiopathic isolated OMP can represent up to 50% of cases in some series, one cannot firmly draw conclusions about the true risk of stroke in isolated microvascular OMPs from Hoi et al.'s study [2, 3, 10]. In contrast, in our series, we calculated the incidence of subsequent stroke, separately for microvascular and non-microvascular OMP groups, providing first time evidence for the real incidence of subsequent stroke in microvascular OMPs. Interestingly, in a contemporary systematic review it was shown that in another type of ischemic event (i.e., lacunar stroke), the risk of stroke recurrence during the first year ranged from 5-8%, which roughly parallels our results [8]. One possible reason that may explain a similar risk of subsequent stroke in microvascular OMP and lacunar stroke is that both entities share common arteriosclerotic causes which can not only result in ischemia of nutrient arteries of ocular motor nerves (OMP) and deep penetrating arteries (lacunar stroke), but also contribute to the occurrence of subsequent ischemic stroke [12, 13]. One additional reason is that traditional vascular risk factors, including hypertension, diabetes, IHD, and HI seem to commonly affect patients with lacunar stroke and microvascular OMPs. Microvascular OMP patients however, seem to have a lower number of risk factors, including

previous stroke [9, 14]. Interestingly in our study, within the microvascular OMP group, the number of vascular risk factors, age, gender, cranial nerve affected, and use of an antiplatelet agent before or after the OMP were not associated with the occurrence of subsequent stroke or TIA. This finding further highlights that there may be other mechanisms involved in the development of subsequent stroke or TIA in microvascular OMP patients that are independent of the common vascular risk factors or age-related vascular changes that have been associated with ischemic stroke, including inflammation, infectious processes and hypercoagulability [10, 15-18]. Indeed, in Hoi et al.'s study, isolated OMP was identified as an independent risk factor for subsequent stroke even after adjusting for patient age and the presence of common vascular risk factors such as hypertension and diabetes [10]. The role of aspirin in microvascular OMPs is still under discussion. Previous aspirin use, regardless of dose and/or duration, appears to be ineffective in preventing microvascular OMPs and OMP recurrences [9, 14]. In our study, the use of aspirin did not seem to prevent subsequent stroke either. Notably in our series, only about half of patients were kept on an antiplatelet agent after presumed diagnosis of microvascular OMP. Due to the retrospective nature of our study, it is possible however that some microvascular OMP patients could have inadvertently omitted the information about their intermittent or regular use of aspirin. Nevertheless, such omissions should have been equally prevalent among microvascular and non-microvascular OMP groups, since we included patients in a consecutive fashion. In our study, albeit microvascular OMP group demonstrated a higher stroke incidence than the non-microvascular OMP group, this difference has not reached significance, both in association and survival analysis. Caution is needed when interpreting these results however, since there was only one occurrence in the non-microvascular OMP group, which makes the lack of significance less conclusive.

In line with other reports, in our series, sixth nerve was the most commonly affected nerve in microvascular OMPs, followed by the third and the fourth cranial nerves, which may

reflect an exposure of the sixth nerve to a greater number of arteries along its pathway [3, 14, 19]. Patients with microvascular OMP were significantly older than non-microvascular OMP patients, a finding that was not surprising, since our non-microvascular OMP group comprised aetiologies that are classically known to affect young/mid adult individuals (e.g., multiple sclerosis) and may have further accentuated this difference. Hypertension and hyperlipidemia were significantly and near-significantly more frequent in the microvascular OMP group, respectively. Apart from previous evidence clearly showing that diabetes, hypertension, and hyperlipidemia are independent risk factors for ischemic third, fourth, or sixth cranial nerve palsy, the criteria used in this study for diagnosing microvascular OMP, which required at least the presence of one vascular risk factor, may have further biased the results [20]. Possibly due to the addiction of two vascular risk factors not commonly included in microvascular OMP criteria (i.e., hyperlipidemia and the occurrence of previous stroke or TIA), we may have increased microvascular OMP frequency in our series (~60%), which is usually around 30% [21]. Of note, 11 OMP patients (12,9%) presenting with no additional neurological signs harboured potentially visual and/or life-threatening conditions (e.g., SAH, hydrocephalus, brainstem glioma, giant cell arteritis) which were promptly diagnosed by either imaging (CT and/or MRI) or laboratory testing (ESR). Therefore we, like Tamhankar and colleagues, believe that early neuroimaging is recommended as a general guideline in all patients presenting with acute isolated OMPs, especially when the patient presents to a nonspecialist or may fail to give a thorough history [6].

The small size of our study population and its retrospective nature limit generalization of our results onto all patients with microvascular OMPs. However, our data suggests that the risk of future stroke in microvascular OMPs may parallel the risk of subsequent stroke in other ischemic events such as lacunar stroke, which reinforces the idea that a more intensive preventative focus may be necessary after the occurrence of vasculopathic OMPs and stresses

the possibility that microvascular OMP may be an unrecognized independent risk factor for stroke.

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