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## Pain in Ischemic Ocular Motor Cranial Nerve Palsies

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### Abstract

**Background**—Pain is a common feature of microvascular ischemic ocular motor cranial nerve palsies (MP). The natural history of pain in this condition has not been studied. The purpose of this report is to define the spectrum of pain in isolated MP, with special reference to diabetics versus nondiabetics.

**Design and methods**—Retrospective and prospective chart review was performed on 87 patients with acute onset MP of a single cranial nerve (CN III = oculomotor, CN IV = trochlear, or CN VI = abducens) that progressively improved or resolved over 6 months.

**Results**—Five of the 87 patients had two events, making the total number events 92. There were 48 (52.2%) CN VI palsies, 39 (42.4%) CN III palsies, and 5 (5.4%) CN IV palsies. Thirty-six (41%) patients had diabetes. Pain was present in 57 (62%) events. The majority of diabetics and non-diabetics had pain. Pain preceded diplopia by 5.8 days ( $\pm 5.5$ ) in one third of events. There was a trend towards greater pain with CN III palsies but this was not statistically significant. Patients who experienced severe pain tended to have pain for a longer duration of time ( $26.4 \pm 21.7$  days compared to  $10.8 \pm 8.3$  and  $9.5 \pm 9$  days for mild and moderate pain, respectively). There was no correlation between having diabetes and experiencing pain.

**Conclusions**—The majority of MP are painful, regardless of the presence or absence of diabetes. Pain may occur prior to or concurrent with the onset of diplopia. Nondiabetics and diabetics presented with similar pain characteristics, contrary to the belief that diabetics have more pain associated with MP.

### Keywords

Microvascular; cranial nerve; pain

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## Introduction

Pain is a common feature of ocular motor cranial nerve palsies from presumed microvascular ischemia; however, the natural history of pain in this condition has not been studied. The purpose of this report is to define the temporal profile and severity of pain in isolated microvascular ocular motor cranial nerve palsies (MP), with special reference to diabetics versus nondiabetics.

## Methods

A retrospective chart review was performed on 76 patients who presented with an isolated MP to the neuro-ophthalmology services of University Hospitals of Cleveland (36 patients) and Emory University (40 patients). Patients were selected via review of all patients evaluated for oculomotor (CN III), trochlear (CN IV), or abducens (CN VI) palsy from 2000 to 2005 (University Hospitals of Cleveland) and from 1989 to 2001 (Emory University). Only those patients with a final diagnosis of MP were included for data analysis. An additional 11 patients diagnosed at University Hospitals of Cleveland, each with at least 6 months of follow up, were identified prospectively from 2005 to 2006 by one author (RT), and then retrospectively reviewed by another author (SW). All patients with MP who presented during the period of 2005 to 2006 were considered for eligibility, were subject to the same inclusion and exclusion criteria, and were assessed utilizing the same data collection sheet as for the purely retrospective group. Statistical comparison of the retrospective and prospective groups revealed no significant differences, and therefore the results from both groups were combined to form the basis of this report. Institutional Review Board approval was obtained for this study.

**Inclusion criteria:** All patients underwent detailed neuro-ophthalmologic examination, including complete examination of cranial nerves. Ocular motor cranial nerve palsies from presumed non-arteritic microvascular ischemia were diagnosed by the acute onset of diplopia and ophthalmoplegia that resulted from involvement of a single ocular motor cranial nerve (CN III, CN IV or CN VI) that spontaneously progressively improved nearly to normal, defined as less than 3 prism diopters of residual misalignment on clinical exam or mild symptoms suggesting residual diplopia in the absence of measurable deficit, or completely resolved, defined as no measurable deficit on clinical exam or symptoms suggesting residual deficit, over the following 6 months. Improvement was usually within 2-3 months, without development of aberrant regeneration and not reasonably attributed to another etiology. All patients had either complete spontaneous resolution or nearly complete resolution accompanied by brain MRI to exclude an alternative diagnosis.

**Exclusion criteria:** Charts were excluded if the initial presentation was consistent with MP but the patient was lost to follow-up before improvement or resolution was confirmed. One patient followed a course similar to MP but was excluded because he was 8 years old, and to our knowledge, this syndrome has not been previously described in a patient this young.

**Data collection:** Data collected included patient age, gender, side and type of cranial nerve involvement, presence or absence of pain, and presence or absence of diabetes. Presence of and characteristics of pain were obtained by the examining physician in both groups. If pain was reported, the following pain characteristics were recorded: description, location, intensity, time of onset relative to diplopia onset and duration. Intensity of pain was graded as mild, moderate or severe. In the 11 patients studied prospectively, a rating of pain based on a scale of one to ten (ten being the worst pain of their life and one being hardly noticeable) was obtained. One to three was considered mild, four to seven considered

moderate and eight to ten considered severe. Duration of pain was determined at follow-up visits.

Statistical analysis: Statistical significance of comparisons was performed using Fisher exact tests for proportions (counts), ANOVA for continuous outcomes with more than two comparison groups, and the Kaplan-Meier model was employed for estimating the median time to an event with its 95% confidence interval. Statistical significance was set at 0.05.

## Results

Eighty-seven patients with a typical course for MP not attributable to another etiology were identified. Five patients (6%) had two separate events of single cranial nerve palsies, making the total number of events 92. There were 54 men and 33 women, with an average age of 66.9 years (range 42-91). There were 48 (52.2%) CN VI palsies, 39 (42.4%) CN III palsies, and 5 (5.4%) CN IV palsies. Thirty-six (41%) patients carried a diagnosis of diabetes at the time of MP onset. Of the 36 patients with diabetes, 19 (52.8%) had CN III palsies and 17 (47.2%) had CN VI palsies. There were no CN IV palsies in diabetic patients.

Pain was present in 57 (62%) of the 92 events and was most commonly located in the ipsilateral brow and eye (Table 1). Only 1 of the CN IV palsies was painful (moderate severity). The number of CN IV palsies in this series was too small for statistical comparison. CN III palsies were more frequently associated with pain when compared with CN VI palsies (77% versus 54%, Fisher exact test  $p-v=0.042$ ) (Table 1).

Pain intensity was available for 40 CN III and CN VI events. Patients with CN III-related pain presented with more severe pain and less mild pain compared with patients with CN VI-related pain, although the difference was not statistically significant (Fisher exact test  $p-v=0.10$ ). Of the CN III-related events with pain, pain was mild in 7 (33%), moderate in 5 (24%) and severe in 9 (43%). Of the CN VI-related events with pain, pain was mild in 12 (63%), moderate in 4 (21%), and severe in 3 (16%) (Table 2). Pain intensity data on a 1-10 scale was available for the 11 patients studied prospectively. The average pain intensity score was 2.1 (i.e., mild intensity;  $SD=0.89$ ) for CN III palsies and 1.5 (i.e., mild intensity,  $SD=0.77$ ) for CN VI palsies. Combined, the average pain intensity for both groups was 1.8 (i.e., mild intensity,  $SD=0.87$ ).

Pain began 5.8 days ( $\pm 5.5$ ) prior to the onset of diplopia in 20 (35%) of the 57 patients with pain. The remaining 37 of 57 (65%) patients with pain reported pain concurrent with the onset of diplopia. No patient in this series reported pain occurring after the onset of diplopia. Data for pain duration was available for 33 patients with pain. Duration of pain was longer in patients with severe pain, but there was wide variation (F-test 4.58,  $p-v=0.02$ ). The mean number of days for mild pain was  $10.8 \pm 8.3$ , for moderate pain  $9.5 \pm 9.0$  days, and for severe pain  $26.4 \pm 21.7$  days (Table 3). Patients with mild or moderate pain experienced pain for a similar length of time.

Thirty-six (39%) events occurred in patients with a diagnosis of diabetes at onset of the MP. Of those events that occurred in diabetics, 26 (72%) were painful compared with 10 events (28%) that were not painful. In patients without diabetes, 31 (55%) MP were painful compared with 25 (45%) that were not (Table 1). No statistically significant difference was found between diabetics and nondiabetics with regard to the presence of pain with the MP.

## Discussion

The association of pain with microvascular ocular motor cranial nerve palsies (MP) is well known, especially in diabetic patients, but the pain characteristics and natural history are not

well defined. Prior reports of pain in MP are largely single case reports or small case series. The largest reported series consists of 24 diabetic patients with “diabetic ophthalmoplegia” (1). As in our series of diabetic patients, CN III was affected most often (71% in their series versus 53% in ours), although our series found a higher percentage of CN VI palsies in diabetics (29% in their series versus 47% in ours). No CN IV palsies occurred in diabetics in either series. Pain was present in 62% of our patients, compared to 44% of the series of 24 patients (1). In a study assessing the relationship between retinopathy and diabetic ophthalmoplegia, 137 of 329 patients (42%) had pain, but this was not further characterized (2).

The location of pain in our patients was most commonly in the ipsilateral brow and eye. This is compatible with other case reports and series, in which pain is most commonly located in or around the ipsilateral eye or characterized by an ipsilateral frontal headache, suggesting involvement of the ophthalmic division of the fifth nerve (CN V) (1). Two diabetic patients with MP and ophthalmoplegia that cleared within three months had evidence of hypalgesia in the first and second divisions of CN V ipsilateral to the MP, leading to the speculation that the location of the lesion was in the cavernous sinus (3). Three pathologic studies are available (4-6), each reporting one patient and all involving CN III. In two, the site of the lesion was in the cavernous sinus, and in the third the subarachnoid portion of CN III was involved. Ischemic demyelination with axonal sparing, associated with microvascular arteriosclerotic changes in vasa nervorum, were the common findings. Pain was explained by involvement of branches of the first division of CN V that course along the epineural sheath of the CN III in the cavernous sinus (6). More recent work in animals suggests that sensory fibers from the first division of the trigeminal nerve are interspersed within CN III and possibly CN VI, as well (7,8).

Pain intensity was variable, but tended to be more severe in our patients with CN III palsies. In past series, pain is generally described as “severe”, “extremely severe” and “intense” (3,9). Descriptions in the literature about the character of pain have varied. Our patients tended to use descriptors like “dull” and “achy”. In the largest series of 24 patients, as in our patients, CN III palsies were more commonly painful than involvement of CN VI (1). In that series, the pain tended to be of moderate intensity. The intensity of pain is generally not helpful in distinguishing MP from cranial nerve palsies due to other lesions. This feature was discussed in a paper comparing microvascular CN III palsy associated with diabetes and that caused by intracranial internal carotid aneurysms which were historically considered the classic cause of unilateral frontal headache and oculomotor palsy (10). The presence of pain in both MP and in ocular motor cranial nerve palsies due to compressive lesions underscores the importance of ensuring spontaneous resolution when the diagnosis of MP is made clinically and of neuroimaging to exclude underlying compressive etiologies in the absence of complete resolution of the presumed MP.

About one third of our patients had pain preceding the onset of visual symptoms (on average by one week), compared to 11% of the 24 patients in the largest prior series (1). One reported patient in the literature had pain onset preceding ophthalmoplegia by 5 weeks (10). The majority of our patients had pain concurrent with diplopia. None of the patients in our series had delayed pain but this has been previously reported (9).

Pain duration in our series ranged from a few days to greater than two months, but tended to be longer lasting in patients with more severe pain. Given the retrospective nature of the study in the majority of patients, pain duration was subject to recall bias. However, this is similar to durations ranging from a few days to several weeks in prior reports (1,9).

Lastly, we found no correlation between having diabetes and a higher prevalence of experiencing pain when compared to patients who do not have diabetes, despite a perception in the literature that this was, in fact, the case. Ascertainment bias is a possibility in this study, as patients who are already known to have diabetes with painful ophthalmoplegia may be referred to a tertiary center less readily compared with patients who are not known to have diabetes prior to the onset of painful ophthalmoplegia. This potential bias is difficult to assess. The risk of nondiabetic patients with MP going on to develop diabetes is not known, but certainly could be studied.

## Conclusion

The majority of MP are painful, regardless of the presence or absence of diabetes. Pain may occur prior to or concurrent with diplopia. Nondiabetics and diabetics presented with similar pain characteristics, contrary to the belief that diabetics have more pain associated with MP.

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Institutional review board approval was obtained from both University Hospitals of Cleveland and Emory University. Waiver of consent and waiver of HIPAA were obtained at University Hospitals of Cleveland. Waivers of consent for retrospective chart reviews are not necessary at Emory University.

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**Table 1**

Pain in microvascular ocular motor cranial nerve palsies.

MP events	Pain	No pain
All (n = 92)	57 (62%)	35 (38%)
CN VI (n = 48)	26 (54%)	22 (46%)
CN III (n = 39)	30 (77%)*	9 (23%)
CN IV (n = 5)	1 (20%)	4 (80%)
In diabetics (n = 36)	26 (72%)**	10 (28%)
In non-diabetics (n = 56)	31 (55%)	25 (45%)

Abbreviations: MP = microvascular ocular motor cranial nerve palsies

CN VI = abducens nerve

CN III = oculomotor nerve

CN IV = trochlear nerve

\* Pain in CN III palsies was significantly more common than in CN VI palsies (p-v =0.042)

\*\* No statistically significant difference was found for the presence or absence of pain between diabetics and nondiabetics

**Table 2**

Severity of pain in microvascular ocular motor cranial nerve palsies.

	CN III	CN IV	CN VI
Mild	7 (33%)	0 (0%)	12 (63%)
Moderate	5 (24%)	1 (100%)	4 (21%)
Severe	9 (43%)	0 (0%)	3 (16%)

**Table 3**

Duration of pain in microvascular ocular motor cranial nerve palsies.

	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
Mean $\pm$ std. dev.	10.8 $\pm$ 8.3	9.5 $\pm$ 9.0	26.4 $\pm$ 21.7*

\* Duration of pain was longer in patients with severe pain (p-v=0.02)