Isolated Third, Fourth, and Sixth Cranial Nerve Palsies from Presumed Microvascular versus Other Causes

A Prospective Study

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Purpose: To estimate the proportion of patients presenting with isolated third, fourth, or sixth cranial nerve palsy of presumed microvascular origin versus other causes.

Design: Prospective, multicenter, observational case series.

Participants: A total of 109 patients aged 50 years or older with acute isolated ocular motor nerve palsy.

Testing: Magnetic resonance imaging (MRI) of the brain.

Main Outcome Measures: Causes of acute isolated ocular motor nerve palsy (presumed microvascular or other) as determined with early MRI and clinical assessment.

Results: Among 109 patients enrolled in the study, 22 had cranial nerve III palsy, 25 had cranial nerve IV palsy, and 62 had cranial nerve VI palsy. A cause other than presumed microvascular ischemia was identified in 18 patients (16.5%; 95% confidence interval, 10.7−24.6). The presence of 1 or more vasculopathic risk factors (diabetes, hypertension, hypercholesterolemia, coronary artery disease, myocardial infarction, stroke, and smoking) was significantly associated with a presumed microvascular cause ($P = 0.003$, Fisher exact test). Vasculopathic risk factors were also present in 61% of patients (11/18) with other causes. In the group of patients who had vasculopathic risk factors only, with no other significant medical condition, 10% of patients (8/80) were found to have other causes, including midbrain infarction, neoplasms, inflammation, pituitary apoplexy, and giant cell arteritis (GCA). By excluding patients with third cranial nerve palsies and those with GCA, the incidence of other causes for isolated fourth and sixth cranial nerve palsies was 4.7% (3/64).

Conclusions: In our series of patients with acute isolated ocular motor nerve palsies, a substantial proportion of patients had other causes, including neoplasm, GCA, and brain stem infarction. Brain MRI and laboratory workup have a role in the initial evaluation of older patients with isolated acute ocular motor nerve palsies regardless of whether vascular risk factors are present.

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Isolated third, fourth, and sixth cranial nerve palsies in adults frequently occur from presumed microvascular ischemia to the nerve in the setting of atherosclerotic risk factors, such as older age, diabetes mellitus, hypertension, and hyperlipidemia.[1−3] Since the development of magnetic resonance imaging (MRI), less benign and potentially treatable causes for acute ocular motor mononeuropathies have been documented, including intracranial neoplasm, aneurysm, inflammation, infection, and brain stem infarction.[3−30] In prior prospective studies, the percentage of patients with identifiable non-microvascular causes of acute ocular motor mononeuropathy has ranged from 1% to 15%.[3,27−29] On the basis of these findings, some authors recommend that early neuroimaging with MRI be performed during the initial evaluation of adults presenting with acute ocular motor mononeuropathies,[3,27,28,30] whereas other studies have advocated observation without neuroimaging unless spontaneous resolution has not occurred by 3 to 6 months.[29,31−35] We thus conducted a multicenter prospective study to assess whether early neuroimaging is warranted in the evaluation of acute isolated ocular motor nerve palsy.

Methods

Patients aged 50 years or older presenting with neurologically isolated third, fourth, or sixth cranial nerve palsies within 30 days of onset were prospectively evaluated by neuro-ophthalmologists at 10 centers from June 2010 to December 2011. Patients with a history of strabismus, orbital disease, head trauma, neurosurgical

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intervention, or lumbar puncture, or those for whom an MRI could not be obtained were excluded from the study.

Neurologically isolated palsy was defined as the absence of other signs and symptoms, with the exception of headache or periorbital pain, within 1 month of the onset of diplopia and during follow-up until enrollment. A standardized protocol was used to document the time course of diplopia symptoms, the presence of headache or pain, and a history of vasculopathic risk factors other than older age (i.e., diabetes mellitus, hypertension, hypercholesterolemia, stroke, myocardial infarction, coronary artery disease, and tobacco use). The presence or absence of a history of neurologic disease, ocular motor palsy, or cancer or any other pertinent history was assessed by the examining neuro-ophthalmologist. Magnetic resonance imaging of the brain with and without gadolinium was obtained for all patients who presented with no prior neuroimaging or computed tomography (CT) scan only, performed for this acute event. All patients were followed until the resolution of diplopia or until a definitive diagnosis was established for their ocular motor palsy. Results of diagnostic testing (e.g., erythrocyte sedimentation rate, C-reactive protein, acetylcholine receptor antibody test, temporal artery biopsy, and lumbar puncture) were recorded when obtained. At the end of follow-up, the patients were determined to have had an ocular motor palsy due to presumed microvascular ischemia versus another cause. A presumed microvascular cause was assigned in those patients for whom the MRI scan and clinical testing did not reveal an alternative cause, other neurologic signs remained absent, and the ophthalmoparesis resolved spontaneously.[36]

A panel of neuro-ophthalmologists (S.L.G., G.T.L., and M.A.T.) reviewed all the patient data and classified the patients into 2 groups on the basis of the presence of relevant medical history. Group I included patients for whom the history and clinical examination suggested a different cause for the third, fourth, or sixth cranial nerve palsy (e.g., history of neurologic symptoms, worsening eye pain or headache, progression of diplopia, history of cancer, history of immunosuppression). Group 2 included patients who presented with isolated third, fourth, or sixth cranial nerve palsy with vasculopathic risk factors alone. These groups were further divided into subgroups: patients with no prior neuroimaging versus patients who presented to the study examiner with a prior CT or MRI of the brain that had been performed for the inclusion event. Study data were collected using a Microsoft Access database (Microsoft Corp, Redmond, WA) and transferred into SAS version 9.2 (SAS Inc., Cary, NC) for statistical analysis. Mean, standard deviation (SD), median, and range were used to summarize the continuous variables; proportions and 95% confidence intervals (CIs) were calculated for the categoric 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 exact test was used to compare the proportions between groups.

Institutional review board approval was obtained at each of the study sites. Patient enrollment and informed consent were all handled according to local institutional review board approval obtained at each site and in accordance with Health Insurance Portability and Accountability Act regulations. The research adhered to the tenets of the Declaration of Helsinki.

Results

Of the 109 patients enrolled in the study (Table 1), the mean (±SD) age of the cohort was 65.6±9.3 years (median, 64 years; range, 50−90 years). There were 76 Caucasian patients (69.7%), 22 African American patients (20.2%), 2 Asian patients (1.8%), and 9 patients (8.3%) of other or unknown race. The mean (±SD) duration of diplopia was 14±7.8 days (median, 14 days; range, 1−30 days). Sixty percent of the cohort (n=65) experienced pain or headache in association with double vision, and the presence or absence of pain was not predictive of the cause of the palsy. There were 22 patients with a cranial nerve III palsy (18 were partial and 4 were complete with pupillary sparing), 25 patients with a cranial nerve IV palsy, and 62 patients with a cranial nerve VI palsy. Seventy-one patients presented with neuroimaging (CT or MRI scan) before presentation, while a prospective MRI was obtained in 39 patients (36%). A total of 103 patients (95%) were reexamined during follow-up at 8 to 12 weeks, whereas in 6 patients, follow-up was obtained via telephone contact.

Table 1. Distribution of the 109 Enrolled Patients across Centers

Center	No.
University of Pennsylvania	31
Brigham and Women's Hospital	20
Emory University	19
Wilmer Eye Institute	13
Michigan State University	6
University of Minnesota	6
University of Illinois	4
University of California at Los Angeles	4
University of Colorado	3
University of Maryland	3

Of the 109 subjects, neuroimaging and other studies identified a nonmicrovascular cause in 18 patients (16.5%; 95% CI, 10.7−24.6), while 91 patients (83.5%; 95% CI, 75.4−89.3) were diagnosed with a presumed microvascular palsy. The comparisons of patient characteristics between the presumed microvascular ischemia group and the other causes are shown in Table 2. Distribution of age and sex was similar between the 2 groups. The percentage of patients with 1 or more vasculopathic risk factors (diabetes, hypertension, hypercholesterolemia, coronary artery disease, myocardial infarction, stroke, and smoking) was significantly higher in patients with presumed microvascular ischemia than in those with other causes (91.2% vs. 61.1%; $P = 0.003$, Fisher exact test). In univariate analysis, the association of diabetes with presumed microvascular palsy was most frequent, although this did not reach significance ($P = 0.06$). Vasculopathic risk factors also were present in 11 of the 18 patients (61%) with other causes. The sixth cranial nerve was the most commonly involved and had the highest incidence of other causes.

Among 29 patients who had a past significant medical condition (group 1), 10 (34.4%) had other causes responsible for the ocular motor palsy, which included neoplasms (n=6), and 1 patient each with idiopathic pachymeningitis, herpes zoster, pituitary apoplexy, and decompensated phoria (Table 3). Among 80 patients with presumed vasculopathic risk factors alone (group 2), 8 (10%) had other causes to explain their ocular motor palsy (Table 4), which included 3 patients with giant cell arteritis (GCA), 2 with neoplasms, and 1 each with midbrain infarction, inflammation, and pituitary apoplexy.

To assess the utility of early neuroimaging, analyses were performed on the subset of patients without third cranial nerve palsies (for which there is consensus regarding early imaging) and those without GCA in the subgroup of patients with no significant medical history (group 2). This revealed 3 of 64 subjects (4.7%) with a fourth or sixth cranial nerve palsy having a causative lesion on MRI. One was a 68-year-old man with multiple vasculopathic risk factors who presented with an isolated fourth cranial nerve palsy and was found to have an acute infarction of the dorsal midbrain. The second patient was a 58-year-old man with hypertension and hypercholesterolemia who presented with a 1-week

Table 2. Comparison of Characteristics of Patients with Acute Isolated Ocular Motor Palsy of Presumed Microvascular versus Other Causes

Characteristics	Presumed Microvascular Ischemia (n=91; 83.5%)	Other Causes (n=18; 16.5%)	P Value
Age (yrs), mean ± SD	65.6±9.5	63.4±7.9	0.27*
Median (range)	64 (50–90)	64 (50–80)	0.38†
Sex			
Female	35 (38.5)	8 (44.4)	0.79‡
Male	56 (61.5)	10 (55.6)	
Nerve involved (n)	91 (83.5)	18 (16.5)	
3 (22)	19 (21)	3 (17)	
4 (25)	22 (24)	3 (17)	
6 (62)	50 (55)	12 (67)	
History of vasculopathic risk factors			0.003‡
Yes	83 (91.2)	11 (61.1)	
No	8 (8.8)	7 (38.9)	

SD = standard deviation.
Values shown as n (%) unless otherwise indicated.
*P values from 2-sample t test.
†P value from Wilcoxon rank-sum test.
‡P value from Fisher exact test.

history of diplopia due to a right sixth cranial nerve palsy, and MRI revealed a sphenoid sinus mass infiltrating the cavernous sinus that was diagnosed as large B-cell lymphoma on biopsy. The third patient was a 53-year-old woman with a sixth cranial nerve palsy and a normal CT scan whose MRI revealed a petroclival meningioma that was subsequently treated with surgery.

There were 2 patients with a third cranial nerve palsy in the vasculopathic category: 1 patient had a normal initial MRI but then later developed pupillary involvement, and subsequent MRI of the orbits revealed enhancement of the third cranial nerve that was deemed idiopathic after further workup and resolved without treatment; the second patient had a pupil-sparing complete third cranial nerve palsy, and MRI showed an enlarged pituitary gland consistent with apoplexy. There were 3 patients (all with sixth cranial nerve palsies) who were diagnosed with GCA on the basis of high sedimentation rate, C-reactive protein, and positive temporal artery biopsies. These patients did not have any systemic symptoms of GCA apart from diplopia.

Discussion

Our results suggest that a substantial number of patients (16.5%) in our cohort were found to have an identifiable cause other than presumed microvascular ischemia. In the group without a significant medical history, we identified patients with ocular motor palsy in whom the management was modified by early discovery of an underlying cause other than presumed microvascular ischemia. By excluding patients with third cranial nerve palsies and GCA, there was an approximately 1 in 20 chance that a patient with vasculopathic risk factors alone had another cause found for the fourth and sixth cranial nerve palsy. In the past 2 decades, there have been major advances in the treatment of demyelinating disease, neoplasms, and other neurologic conditions, making early diagnosis important for those patients with isolated palsies not related to presumed microvascular ischemia.

Age and sex distributions were similar in patients with and without presumed microvascular palsies. The presence of at least 1 vasculopathic risk factor was significantly associated with presumed microvascular cause similar to findings in other studies.[28,29,36,37] Nonetheless, vasculopathic risk factors were also present in more than 60% of patients (11/18) with other causes. In a prospective study of isolated ocular motor palsies at a single institution, Chou et al[28] found that more than 50% of patients with nonmicrovascular palsies had vasculopathic risk factors, a finding not surprising given the inclusion only of patients aged 50 years or older.

Magnetic resonance imaging is a more sensitive modality for identifying intracranial pathology compared with CT scan. In our study, 1 patient with a sixth cranial nerve palsy

Table 4. Other Causes for Patients in the Group with Vasculopathic Risk Factors Only (Group 2)

Vasculopathic Risk Factors Only (Group 2) (n=8)	Cranial Nerve Affected	Cause
No previous imaging (n=2)	Fourth	Infarct dorsal midbrain
	Sixth	Cavernous sinus B-cell lymphoma
Previous CT/MRI (n=6)	Sixth	Petroclival meningioma*
	Third	Enhancement of third nerve†
	Third	Pituitary apoplexy
	Sixth	GCA‡

CT = computed tomography; GCA = giant cell arteritis; MRI = magnetic resonance imaging.
*Presented with normal CT scan; MRI revealed a meningioma.
†The MRI of the brain was normal; MRI of the orbits revealed enhancement of the third nerve.
‡Three patients had GCA.

Table 3. Proportion of Patients with Presumed Microvascular Ischemia versus Other Causes of Acute Isolated Ocular Motor Nerve Palsy

Groups	Subgroups	Presumed Microvascular Cause (n=91, 83.5%; 95% CI, 75.4–89.3)	Other Causes (n=18, 16.5%; 95% CI, 10.7–24.6)
Significant medical history (n=29)	No prior imaging (n=10)	8 (8.8%)	2 (11.1%)
	Prior imaging (n=19)	11 (12.1%)	8 (44.4%)
Vasculopathic risk factors only (n=80)	No prior imaging (n=28)	26 (28.6%)	2 (11.1%)
	Prior imaging (n=52)	46 (50.6%)	6 (33.3%)

CI = confidence interval.

who had a normal CT scan and was referred to the neuro-ophthalmology service with the diagnosis of presumed vasculopathic palsy was found to have a clival meningioma with brain stem compression seen on MRI scan (Table 4). With increasing use of MRI over the past 20 years, there have been several published reports of other causes of acute isolated ocular motor palsies, including demyelinating disease, brain stem infarction/hemorrhage, and pituitary apoplexy.[3–30] In our study, we had 1 patient with isolated fourth cranial nerve palsy due to midbrain infarction. Prompt initiation of antiplatelet therapy or anticoagulation for brain stem infarction and immediate evaluation and control of blood pressure in the setting of hypertensive brain stem hemorrhage represent interventions that are often instituted after neuroimaging identifies such lesions. Some patients with brain stem infarction and isolated third cranial nerve palsies[16] or others with isolated or minimal neurologic deficits[37,38] have demonstrated cardiac sources of emboli or large-vessel thromboembolic disease. Therefore, although small vessel occlusion is a potential cause for a brain stem infarction, the causes of such infarction and their subsequent management may be heterogeneous and different from management of presumed microvascular cranial mononeuropathies. Finally, isolated ocular motor palsies may be a manifestation of multiple sclerosis, and the early initiation of immunomodulatory therapy should be strongly considered in patients with lesions distinct from the presenting lesion.

The need for immediate neuroimaging in older patients remains controversial, in part because of the presumed low yield, to save expense, and the belief that delay in neuroimaging does not necessarily lead to adverse outcomes. Three prior prospective studies have attempted to address the question of need for early neuroimaging in older adults presenting with isolated acute ocular motor mononeuropathies.[3,28,29] In 1 study, the yield of MRI in identifying other causes for sixth cranial nerve palsy was 15% (4 patients: 2 with metastasis, 1 with a meningioma, and 1 with aneurysm). The details of medical history were not provided, and the median age of the cohort in this study was 43 years, an age at which there is a higher likelihood of finding a specific cause.[3] A second study of patients aged more than 50 years by Chou et al[28] found a 13.6% (9/66) incidence of other identifiable causes in patients presenting with acute ocular motor mononeuropathies. Even excluding third cranial nerve palsies from this cohort (because the majority of patients with third cranial nerve palsy will undergo neuroimaging regardless of the presence of vasculopathic risk factors), the incidence of other causes for fourth and sixth cranial nerve palsies was 13.5% (5/37). The causes were neoplasm, brain stem infarction, demyelinating disease, and pituitary apoplexy. The authors concluded that early neuroimaging should be performed in all patients with an acute ocular motor cranial mononeuropathy. In contrast, a third study by Murchison et al[29] assessed the yield and cost utility of neuroimaging for acute isolated ocular motor mononeuropathies in adults older than 50 years and found a low prevalence of causative lesions on MRI (1.1%, 1/93 patients).[29] The 1 patient identified had a sixth cranial nerve palsy from a pontine hemorrhage that did not require intervention. The authors concluded that early neuroimaging was not cost-effective in older adults with the presence of vasculopathic risk factors. The 2 studies[28,29] discussed were single-center studies and excluded all patients with a history of cancer or neurologic and orbital disease, as well as head trauma. In contrast, our multicenter study encompasses a wider geographic distribution of patients and different practices and referral patterns, and therefore perhaps is more representative of the general population of patients with acute isolated ocular motor palsies, although it is also potentially biased by the inclusion of only patients referred to neuro-ophthalmology services. Our rationale in including those patients with a medical, neurologic, and cancer history was to get an overall sense of the yield of neuroimaging in isolated acute ocular motor nerve palsies among all older patients, which in turn may aid the nonspecialist in deciding whether to obtain neuroimaging, more so if the patient fails to report a cancer or systemic disease history, especially if they have been told that the disease is in remission, leading to a false sense of reassurance for the clinician. By dividing the cohort into those who had a significant medical history versus those who did not and further separating patients who presented with prior MRI and those who did not have prior neuroimaging helped to ascertain a true incidence of causes of ocular motor palsy among different groups and overcome a referral bias.

Given the higher incidence of other causes found in our cohort of patients, early neuroimaging is recommended as a general guideline in all patients presenting with acute isolated ocular motor palsies, especially when the patient presents to a nonspecialist who may fail to elucidate a thorough history and may lack the expertise of the neuro-ophthalmologist.

Cost-effectiveness of early MRI in our study compares favorably with such accepted practices in imaging patients with headaches and nonfocal neurologic examinations. For example, the diagnostic yield of neuroimaging in patients with headache has been estimated at 1.5%.[39,40] Although the overall yield of MRI scan in our cohort of patients was 16.5%, in patients with fourth and sixth nerve palsies who had vasculopathic risk factors alone, the yield from neuroimaging was significantly lower. In such patients the decision to perform an immediate MRI scan could be weighed against observation alone, especially in patients with no insurance coverage, and MRI should be obtained if there is nonresolution of the palsy. However, the decision to delay neuroimaging in such patients often depends on the expertise of the clinician in obtaining a thorough history and clinical examination and making an accurate diagnosis or the patient's ability to pay for the imaging study. It may also be argued that obtaining an MRI to evaluate the cause of the palsy has an intrinsic value to the patient that has not been acknowledged previously. A normal MRI obtained in patients who experience acute-onset diplopia from isolated ocular motor palsy may help to allay anxiety and fears of brain tumor or other serious diseases, which in turn may have significant social, psychologic, and even economic benefits in terms of productivity. However, this value is inherently subjective and difficult to measure.

Study Limitations

Since the source of patients in our study came from patients referred to neuro-ophthalmology clinics, it is possible that subtle clues from the history and physical examination led referring physicians to seek additional consultation, thereby increasing our proportion of patients with serious underlying pathologies. It is also possible that referring physicians have different referral patterns depending on whether they initially image the patients and discover an underlying lesion or refer patients without prior imaging to neuro-ophthalmology. In the former situation, it is possible that patients may not be referred to a neuro-ophthalmologist if an underlying lesion is identified, and may instead be sent to other providers, such as emergency department physicians, neurosurgeons, and oncologists, which may lead to underestimation of the true incidence of other causes. Finally, although all patients received MRI, not all patients underwent identical laboratory evaluations and other testing. Such systematic screening would have likely increased the proportion of alternative lesions identified.

In conclusion, the advances in the management of multiple sclerosis, stroke, and neoplasms make early diagnosis and treatment of these conditions more important than in the past. Although the presence of vasculopathic risk factors in patients aged at least 50 years is a significant predictor for a presumed microvascular cause for an isolated ocular motor mononeuropathy, a substantial proportion of our patients with other causes also harbored vasculopathic risk factors. Our results suggest that a contrast-enhanced brain MRI has an important role to play in the initial evaluation of patients who present with acute isolated ocular motor mononeuropathies, even in the population aged more than 50 years.

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