

# Neuroimaging and Acute Ocular Motor Mononeuropathies

## A Prospective Study

Ann P. Murchison, MD, MPH; Molly E. Gilbert, MD; Peter J. Savino, MD

**Objective:** To evaluate the necessity of neuroimaging in patients with acute, isolated ocular motor mononeuropathies.

**Methods:** A prospective case series evaluating diagnostic technology results in 93 patients older than 50 years with acute isolated mononeuropathies was performed. Patients were included in the study if they had new-onset diplopia with an isolated cranial neuropathy (cranial nerve III, IV, or VI palsy) and no other signs of neurologic dysfunction. All patients had gadolinium-enhanced magnetic resonance imaging (MRI). The number of patients with lesions noted on MRI and the overall cost of imaging the patients were determined. Cost analysis of the MRI was conducted using *Current Procedural Terminology* codes and Medicare costs in 2010 dollars. Cost utility was estimated using cost data as well as published utility values for adults with diplopia and sex-specific life tables for life expectancy in the United States.

**Results:** Four of 93 patients had lesions on MRI; however, only 1 of the 93 patients had a lesion related to the cranial mononeuropathy. The total modeled cost of imaging for these 93 patients was \$131 688 to determine an underlying cause in 1 patient with no change in treatment. The estimated cost utility for the patient with a causative lesion found by MRI was \$90.19 for diagnosis alone.

**Conclusions:** It may not be medically necessary to perform MRI scanning on every patient with an isolated cranial nerve III, IV, or VI palsy. In adults older than 50 years with an isolated mononeuropathy, physicians should carefully review the patients' history and findings to determine which patients to image at the initial evaluation.

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### Author Affiliations:

Oculoplastic and Orbital Surgery Service (Dr Murchison) and Neuro-Ophthalmology Service (Drs Gilbert and Savino), Wills Eye Institute, Thomas Jefferson University, Philadelphia, Pennsylvania. Dr Gilbert is currently with the Illinois Eye and Ear Infirmary, University of Illinois, Chicago. Dr Savino is currently with the Shiley Eye Center, University of California, San Diego, La Jolla.

**T**HE TRADITIONAL TEACHING in neuro-ophthalmology is that patients with isolated ocular motor mononeuropathies and risk factors for microvascular disease, with certain exceptions, may be safely followed clinically without neuroimaging. These exceptions include patients younger than 50 years, with other neurologic findings, with a progressive course of diplopia, or with a known history of cancer. This practice pattern is based on the results of natural history studies of the common causes of isolated mononeuropathies in various age groups.<sup>1-4</sup> In patients without the exceptions we have noted, the rate of finding an underlying cause for an acute mononeuropathy is low, with reports ranging up to 14%.<sup>1,5,6</sup>

This traditional teaching originated in the preimaging era, when investigative modalities including skull radiography, polytomography, pneumoencephalography, and catheter arteriography had potential

risks, were painful, or both. Since magnetic resonance imaging (MRI) has become widely available, several studies have suggested that MRI may identify lesions causing acute mononeuropathies that would not have been detectable in the preimaging era. Therefore, we performed a prospective study to determine the utility of neuroimaging in detecting causative lesions in patients with acute isolated cranial nerve (CN) III, IV, and VI palsies referred to a single neuro-ophthalmology practice over 15 months.

Although the risks of MRI are low compared with the risks of catheter arteriography or pneumoencephalography, the cost is relatively high compared with the alternative of outpatient observation. With the cost of health care reaching crisis levels, it is incumbent on physicians to carefully consider whether diagnostic testing, regardless of cost, is likely to change their treatment plan or patient outcome. With this in mind, we calculated the cost of imaging all acute isolated mononeu-

**Table 1. Microvascular Risk Factors by Sex**

Microvascular Risk Factor	No. (%)		
	Men	Women	Total
Diabetes	21 (31.8)	10 (37.0)	<b>31 (33.3)</b>
Hypertension	46 (69.7)	14 (51.9)	<b>60 (64.5)</b>
Elevated cholesterol level or abnormal lipid profile	45 (68.2)	16 (59.3)	<b>61 (65.6)</b>

ropathies against the likelihood of obtaining a positive scan result based on published data as well as our data. Additionally, we estimated the cost utility, sometimes termed *cost-effectiveness*, of this diagnostic testing.

## METHODS

Consecutive patients seen at the Wills Eye Institute Neuro-Ophthalmology Service with a diagnosis of acute isolated mononeuropathy were enrolled in the study from July 1, 2005, through September 30, 2006. Inclusion criteria were being older than 50 years and having a new onset of CN III, IV, or VI palsy within 1 month of the initial evaluation without evidence of other neurologic findings on clinical examination. Other neurologic findings would include multiple neuropathies, ataxia, papilledema, weakness, vertigo or dizziness, and paresthesias.

Exclusion criteria included congenital strabismus, known medical conditions explaining diplopia (eg, cavernous sinus disease, orbital disease, sarcoidosis, recent lumbar puncture), known history of cancer, multiple CNs involved simultaneously, contraindication to undergoing MRI, other signs or symptoms of neurologic dysfunction, variability of diplopia suggestive of myasthenia, or recent head trauma. Patients who did not have follow-up until 3 months later or the resolution of their diplopia were excluded from the study. We did not exclude patients with pupil-involving or partial CN III palsies in order to have more comparative data and to encompass different practice patterns.

Investigative review board approval was obtained and the principles of the Declaration of Helsinki were observed.

Each patient underwent a neuro-ophthalmologic examination by one of us (P.J.S.). A gadolinium-enhanced MRI was obtained when not previously performed, and all MRIs were reviewed. We noted the date of onset of symptoms, time to imaging, and whether imaging was ordered by the Neuro-Ophthalmology Service or by the referring physicians. Patients were followed until resolution of their diplopia was noted either in a follow-up appointment or by telephone contact with one of us. Patients were reevaluated if their symptoms did not resolve after 4 months.

The cost of imaging was estimated by using the 2010 Medicare reimbursement for performing MRI of the brain (*Current Procedural Terminology* code 70553) and neck (*Current Procedural Terminology* code 70543) with and without contrast, \$587.63 each, combined with the hospital billing professional fee for interpretation, \$126.00 and \$114.74, respectively. This was a total cost of \$1416.00 for each study. Action threshold projections were used to compare the overall cost of imaging patients with mononeuropathies with the overall likelihood of finding an underlying disease process. Value calculations used the median utility value for adults with diplopia (0.93 using the time trade-off technique)<sup>7</sup> and Medicare dollars for all costs. Quality-adjusted life-years (QALYs) were determined based on this utility value and sex-specific life expectancy in the United States.<sup>8</sup> Cost utility, or cost-effectiveness, used the dollars ex-

pendent in imaging for the value (QALYs) gained. All value calculations were estimated because the utility value used was not from our cohort of patients.

## RESULTS

One hundred twenty-nine patients were evaluated for new-onset diplopia. Of these, 93 patients (72.1%) met inclusion criteria. Thirty-six patients were excluded: 18 for being younger than 50 years, 3 for multiple CN involvement, 7 with decompensation of a congenital heterophoria, 1 with known multiple sclerosis, 3 with recent head trauma, 3 with papilledema, and 1 with known prostate cancer.

Seventy-seven patients (82.8%) were examined in follow-up and 16 (17.2%) confirmed resolution of their diplopia via telephone contact. There were 14 cases of CN III palsy, 27 cases of CN IV palsy, and 52 cases of CN VI palsy. The majority of patients were male (66 men [71.0%]). The most frequent microvascular risk factor overall was hypercholesterolemia, followed closely by hypertension (**Table 1**).

Fifty-five patients (59.1%) had been imaged prior to our evaluation; we personally reviewed these studies. We ordered imaging for the remaining 38 patients (40.9%).

Four of the 93 patients (4.3%) had identifiable abnormalities on neuroimaging. These were considered to be incidental findings in 3 patients, including 2 whose MRI findings were on the side opposite their CN VI palsies (1 acoustic neuroma and 1 meningioma) and a third patient with an inverted papilloma in the maxillary sinus ipsilateral to his CN VI palsy without evidence of extrasinus extension on MRI and at the time of sinus surgery. The single remaining patient of the 93 (1.1%) had a CN VI palsy and a pontine hemorrhage demonstrated on MRI. Catheter angiography showed no arteriovenous malformation. He was observed and the CN VI palsy resolved.

The total cost of an MRI of the head and neck with and without contrast is \$1416, including technical and professional fees. Imaging our 93 patients cost \$131 688 total. The frequency of diagnosing an underlying cause by imaging all patients was 1.1% (1 of 93 patients), and that lesion did not require treatment (**Table 2**). Using a median utility value of 0.93, 15.7 QALYs were calculated for the study. The cost utility of performing an MRI for all patients in this study, based on MRI costs and calculated QALYs, was \$90.19. The single patient with a cause found for the mononeuropathy had 25.3 QALYs, with a cost utility of \$55.97 for the MRI. The single patient with an identified lesion had an overall cost utility of \$154.00, including angiography costs. This was determined using Medicare costs for the cerebral angiography (*Current Procedural Terminology* code 36217) professional fee, and adding technical charges gave a total estimated cost of \$2500 added to the MRI costs.<sup>9</sup>

## COMMENT

Since the availability of MRI became widespread, various causes for ocular motor mononeuropathies have been described in individual case reports or small series of pa-

**Table 2. Cost of Imaging at Various Proportions of Positive and Negative Scan Results for Acute Isolated Mononeuropathies**

Source	Scan Results, No. (%)		Total Cost of Imaging, \$ <sup>a</sup>	Cost/Positive Scan Result, \$
	Positive	Negative		
Chou et al, <sup>6</sup> 2004	4 (6.1)	62 (93.9)	93 456 <sup>b</sup>	23 364
Our study	1 (1.1)	92 (98.9)	131 688 <sup>c</sup>	131 688

<sup>a</sup>Costs based on magnetic resonance imaging.

<sup>b</sup>Based on percentage of causative lesions identified or isolated mononeuropathies, excluding pupil-involving cranial nerve III palsies (4 of 66 patients).<sup>6</sup>

<sup>c</sup>Based on the causative lesion identified in our data.

tients.<sup>5,6,10-13</sup> The accumulation of these studies and reports suggests that MRI may be underused in the investigation of acute mononeuropathies or that the traditional teaching may miss causes detected on MRI. The threshold approach to decision making in medicine suggests that if the pretest likelihood of disease is below a certain threshold level, the diagnostic test is not necessary. Conversely, if the pretest likelihood of disease is above a certain threshold level, diagnostic testing is warranted. Threshold levels combine information about the risk of disease, the sensitivity and specificity of the test, and the likelihood of the test affecting the physician's treatment plan. The currently published studies on using MRI in patients with acute ocular motor mononeuropathies frequently do not take into account information regarding the patient's age, medical history, other neurologic findings, or whether the lesion identified was truly causative of the diplopia. When deciding whether to perform an MRI, it is important to consider what imaging will add to the patient's care.

One case series identified 5 patients with skull base tumors, all of whom had a cranial mononeuropathy for 5 to 20 years.<sup>14</sup> These patients had a high pretest likelihood of underlying disease and would have been imaged according to the traditional teaching. Another report describes 2 patients, 1 with intracranial plasmacytoma and 1 with multiple myeloma who initially had isolated CN VI palsy before progressing to involvement of other CNs.<sup>13</sup> Although these patients may not have been imaged initially according to the traditional teaching, involvement of other CNs would have mandated imaging in these patients as well. A third case report describes an isolated CN IV palsy as a result of midbrain hemorrhage.<sup>12</sup>

A prospective study evaluated the use of MRI in 43 consecutive patients with acquired CN VI palsies,<sup>11</sup> and causative lesions were identified in 27 of 43 patients (62.8%). However, the median age of the patients with lesions on initial imaging was 43 years compared with 56 years in the patients with normal MRI results. Furthermore, although only neurologically isolated mononeuropathies were said to be included, no specifics were provided. Five of the patients (including 2 with a history consistent with microvascular disease) were found to have metastatic lesions. It is unclear whether the CN VI palsy was a manifesting sign of the underlying cancer or whether these patients had previously diagnosed cancers. Three other patients in the cohort were found to have inflammatory causes for the CN VI palsy; again, it is unclear whether any systemic or local inflammatory conditions or signs thereof had been previously diag-

nosed. The young patients in this study had a pretest probability of disease that would have caused them to be imaged according to the traditional rules. The patients with metastatic lesions and inflammatory lesions may have also had higher pretest probabilities, but their medical histories were not provided. Based on the information given in this report, the need for MRI of all CN VI palsies cannot be demonstrated.

A prospective study by Chou et al<sup>6</sup> evaluating ocular motor cranial mononeuropathies included only patients older than 50 years and found that 9 of 66 patients (13.6%) had a cause other than a microvascular one for their mononeuropathies. However, this study included 9 patients with pupil-involving CN III palsies and 10 patients with partial CN III palsies. Patients with these types of palsies are routinely imaged regardless of the presence of microvascular risk factors, and 2 patients were found to have aneurysms. Therefore, the total number of patients with another cause who would not have been imaged using the traditional strategy was 7 of 66 patients (10.6%). Furthermore, the most frequent imaging finding was meningioma (3 of the 7 patients); however, no mention was made of the location of the meningioma, whether it was the cause of the diplopia, or whether treatment was instituted. Traditionally, patients with mononeuropathies that do not resolve in the expected time undergo imaging.<sup>15</sup> Therefore, these 3 patients most likely would have been imaged 3 months after their initial evaluation if their mononeuropathy persisted. Since meningiomas are almost always slow-growing benign lesions, this treatment delay would be unlikely to affect the patients' outcomes.<sup>16</sup> Excluding these patients, only 4 of 66 patients (6.1%) had causes that would have been overlooked had the patients not been imaged at their initial evaluation. This number is more representative of the number of patients who could arguably have benefited from prompt neuroimaging despite having microvascular risk factors.

Four of 66 patients (6.1%) with potentially treatable causes is considerably higher than in our study (1.1%). One explanation may be that their patients had highly unusual clinical manifestations. One patient in the study by Chou and colleagues was found to have pituitary apoplexy that manifested as an isolated CN VI palsy, which is uncommon enough to warrant a case report in the literature. Likewise in this situation, the CN VI palsy does not remain isolated.<sup>17</sup> Additionally, 2 patients, 1 with an isolated CN III palsy and 1 with a CN VI palsy, were found to have brainstem infarctions. Although these manifestations of brainstem infarction have been described, they

**Table 3. Guidelines for Performing Magnetic Resonance Imaging in Patients With Cranial Nerve III, IV, and VI Palsies**

Criterion
Aged <50 y
History of cancer of any type at any time
Other neurologic signs or symptoms
Pupil-involving or partial cranial nerve III palsy
No resolution 3 mo after initial visit

are also very uncommon.<sup>10,18</sup> The 66 patients included in the study by Chou and colleagues were gathered over a 5-year period as opposed to the 93 patients gathered over 15 months in our study. Therefore, it is possible that our referral base reflects the general population of patients with isolated mononeuropathies as opposed to being a tertiary referral site for primarily complicated mononeuropathies.

We believe that our study is the largest prospective study to evaluate the use of modern imaging in truly isolated acute ocular motor mononeuropathies. Our study included only patients in the vasculopathic age range who had no medical history or other signs or symptoms that would place them in a high-pretest-probability category. We found a very low prevalence (1.1%) of causative lesions in our series of patients with a low pretest probability. Our data corroborate the traditional teaching regarding the natural history of acquired mononeuropathies and the low incidence of nonvasculopathic causes in patients older than 50 years with isolated mononeuropathies.<sup>3</sup> Specifically, in patients older than 50 years, there is a very low rate of finding a causative lesion on imaging. Only 1 of our 93 patients had a potentially causative lesion on MRI. In his case, subsequent angiography did not locate an underlying arteriovenous malformation. Both his hemorrhage and CN VI palsy resolved without further treatment. Three additional patients older than 50 years were found to have lesions unrelated to the diplopia: 1 meningioma, 1 acoustic neuroma (both contralateral to the CN VI palsy), and 1 inverted papilloma without extrasinus extension. Additionally, in 3 of 4 patients with lesions detected on MRI, the lesions were not causative of the mononeuropathy and did not require treatment.

Action thresholds describe the number of positive scans that a physician believes outweighs the costs of imaging all patients with a low pretest probability. Table 2 delineates 2 action thresholds, or costs of negative scan results to find 1 positive scan result, based on both our study and the prospective study by Chou et al<sup>6</sup> of imaging isolated mononeuropathies. While the overall cost per positive imaging study was fairly low, \$131 688 in our study and \$23 364 in the study by Chou et al, in our study there were no treatable lesions identified. Thus, the cost per treatable lesion identified in our study was not found but must be greater than \$131 688.

The median utility value, using the time trade-off technique, of adults with strabismus is 0.93 based on the study by Beauchamp et al.<sup>7</sup> This value gives an objective assessment of quality of life for these patients with diplo-

pia. Permanent normal health, or normal vision in this case, is given a utility of 1.0 by convention. When the utility is closer to 0.0, the quality of life associated with diplopia is worse. Utilities obtained from patients, as in the study by Beauchamp et al, are generally thought to be the most valuable.<sup>19</sup> The overall cost utility was \$90.19 for MRI in our set of patients with isolated mononeuropathies in the vasculopathic age group and \$154.00 for our single patient with an identified causative lesion. If this patient had instead had a treatable cause, the cost utility would have been significantly greater. Given the spectrum of treatable causes for mononeuropathies (tumor, hemorrhage, etc), there is a large range of possible treatments with associated treatment costs. The cost utility, quality of life, and societal costs of each of these permutations are beyond the scope of this article. However, based on cost utility alone, our cost utilities of less than \$155.00 are below the standard acceptable cost utility ratio of \$50 000/QALY.<sup>19</sup> Based on this information, in isolation it is acceptable to image every patient in our cohort. However, this does not take into account the fact that this cost utility is only an estimate as the utility values are pulled from another set of patients. Additionally, there is a risk to the diagnostic imaging with a low potential of diagnosing a treatable lesion, 0 of 93 in this study.

As noted, there were no lesions identified that needed treatment in our study. At a minimum, based on our data, 1 in 94 patients (1.1%) could be found to have a treatable cause, assuming the next patient evaluated could have had a treatable lesion. It is unlikely that any treatable lesion would have had a mononeuropathy that resolved during the follow-up period. Thus, we suspect that all patients with treatable lesions would still meet the guidelines we recommend in **Table 3** without undergoing initial imaging in all patients.

The importance of recognizing when to image patients and when to follow them clinically is greater in this age of escalating health care costs. Currently, there are no number-needed-to-treat data to guide physicians in the use of imaging studies for these patients. A prospective study with a control arm would be useful to determine these data and further refine the guidelines for patient evaluation. Using diagnostic expertise can help to determine how likely a patient is to have an underlying lesion and avoid imaging all patients with isolated mononeuropathies. It is understood, however, that different physicians will have different comfort levels when presented with data suggesting that any causative lesion may be found by imaging all acute isolated mononeuropathies.<sup>20</sup> This action threshold is the number of positive scan results a physician believes outweighs the costs of imaging all patients with a low pretest probability. Physicians must decide at which action threshold they are most comfortable while applying the traditional principles to stratify patients into high or low pretest probabilities. Our frequency of positive scan results was very low (1.1%), and this single positive result did not require treatment; therefore, we do not have data to support a change in initial diagnostic evaluation of these patients.

Our study supports the traditional guidelines for imaging patients with acute, new-onset mononeuropathies.<sup>21</sup> These

guidelines include imaging all patients younger than 50 years, with a history of any type of cancer,<sup>22</sup> and with multiple cranial neuropathies or evidence of additional neurologic dysfunction. Additionally, patients with incomplete or pupil-involving CN III palsies should be imaged immediately.<sup>23-25</sup> Lastly, imaging should be undertaken in any isolated mononeuropathy that progresses or has not resolved 3 months after the initial visit (Table 3). If any treatable causes of isolated mononeuropathy had been found in our study, one could argue that the testing should be revised. Until a number needed to treat is determined for this population, we cannot recommend a change in this guideline based on our results.

We believe that following these rules will identify the patients with a higher likelihood of having a nonvasculopathic cause for their mononeuropathy. Additionally, following these guidelines may avoid unnecessarily increasing the cost of health care, exposing patients to the risk associated with diagnostic testing, or negatively affecting patients' outcomes.

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**Correspondence:** Ann P. Murchison, MD, MPH, Oculoplastic and Orbital Surgery Service, Ste 910, Wills Eye Institute, 840 Walnut St, Philadelphia, PA 19107 (amurchison@willseye.org).

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