Incidence, Associations, and Evaluation of Sixth Nerve Palsy Using a Population-Based Method

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Purpose: To determine the incidence of sixth nerve palsy in a population-based study, with particular emphasis on associated coexisting medical conditions and to use these data to develop a management algorithm.

Design: Retrospective, population-based case series.

Participants: All residents of Olmsted County, Minnesota, USA, diagnosed with sixth nerve palsy between January 1, 1978 and December 31, 1992.

Methods: All cases were identified by using the Rochester Epidemiology Project medical records linkage system, which captures all patient-physician encounters in Olmsted County. The entire medical record of each patient was reviewed to confirm the diagnosis, document county residency, and to determine associated medical conditions. We used stringent predetermined criteria to define diabetes mellitus and hypertension as associations. Incidence rates were adjusted to the age and gender distribution of the 1990 white population in the United States.

Main Outcome Measures: Etiology or systemic associations of the palsy.

Results: We identified 137 new cases of sixth nerve palsy over the 15-year period. The age- and gender-adjusted annual incidence of sixth nerve palsy was 11.3/100,000 (95% confidence interval, 9.3–13.2/100,000). Causes and associations were: undetermined (26%), hypertension alone (19%), coexistent hypertension and diabetes (12%), trauma (12%), multiple sclerosis (7%), neoplasm (5%), diabetes alone (4%), cerebrovascular accident (4%), postneurosurgery (3%), aneurysm (2%), and other (8%). When sixth nerve palsy was the presenting sign in cases of neoplasm (n = 1) and aneurysm (n = 3), history and examination revealed the presence of other neurologic symptoms or signs.

Conclusions: We provide population-based data on the incidence of sixth nerve palsy with a notably lower incidence of neoplasm and higher incidence of diabetes and hypertension than previous institution-based series. We suggest that patients with nontraumatic neurologically isolated sixth nerve palsy may undergo a focused medical evaluation followed by close observation, whereas non–neurologically isolated cases warrant a full neurologic evaluation, including prompt neuroimaging. Ophthalmology 2004;111:369–375 © 2004 by the American Academy of Ophthalmology.

The occurrence and etiology of sixth nerve palsy or paresis is well documented in several institution-based series,1–5 but these studies reflect referral bias to tertiary centers and provide little information on the true population-based incidence of sixth nerve palsy. Such population-based data would help guide the comprehensive ophthalmologist or neurologist in the diagnosis, evaluation and counseling of patients with sixth nerve palsy. In addition, systemic conditions such as diabetes mellitus and hypertension are frequently cited as risk factors or causative for sixth nerve palsy. Few studies, however, have used rigorous definitions of such systemic conditions when determining the etiology and associations of sixth nerve palsy.

In the present study, we combined a population-based approach with stringent definitions of coexisting medical conditions to determine the incidence and associations of sixth nerve palsy or paresis. Using our results, we propose a management algorithm for patients presenting with sixth nerve palsy.
Materials and Methods

We retrospectively identified the records of patients with sixth nerve palsy or paresis by using the resources of the Rochester Epidemiology Project (REP), a medical records linkage system designed to capture data on any patient-physician encounter in Olmsted County, Minnesota.6,7 The population of this semurban area, located in the upper Midwest of the United States, is relatively isolated from other urban areas, and virtually all medical care is provided to residents of the county by the Mayo Clinic or the Olmsted Medical Group and their affiliated hospitals. For brevity, we will refer to “palsy” whether or not the deficit was complete (palsy) or incomplete (paresis).

Institutional review board approval was obtained for this retrospective chart review study. All records of all patients who had the onset of sixth nerve palsy between January 1, 1978 and December 31, 1992 were reviewed by study ophthalmologists to confirm the diagnosis and determine the cause. Patients were identified by searching the REP databases for sixth nerve palsy (using hospital adaptation of the International Classification of Diseases 8 codes). These diagnoses are entered by trained personnel who review the entire medical record. In addition, billing records were searched for the International Classification of Diseases 9 code for sixth nerve palsy. We also searched both the REP databases and billing databases for cases of sixth nerve palsy that might have been coded alternatively, such as strabismus associated with neuromuscular disease and miscellaneous ophthalmoplegia and strabismus. Each occurrence of sixth nerve palsy, whether unilateral or simultaneous bilateral, was considered a separate incidence case. We reviewed additional records in which the diagnosis was made in the 2 years after December 31, 1992 to avoid missing cases with onset of palsy before this date. Trained residency checkers verified the patient’s county residency status at the time of onset by using information from city and county directories or medical records. All patients who were not residents of Olmsted County at the time of onset were excluded.

The entire medical record of each patient was carefully reviewed to determine the most likely etiology or association of the sixth nerve palsy. All presenting features of the documented histories and physical examinations (made by ophthalmologists, neurologists or internists) pertaining to the sixth nerve palsy were thoroughly reviewed to determine the presence of definite neurologic symptoms or signs in addition to the sixth nerve palsy. We noted ancillary tests performed and documented their results.

Rigorous criteria were applied to define coexisting associated medical conditions. Diabetes mellitus was defined as present if subjects were taking insulin, oral hypoglycemic agents, or using diet and/or exercise to control elevated plasma glucose, or if elevated plasma glucose was documented within 1 month of the time of nerve palsy diagnosis. Elevated plasma glucose was defined as either a fasting plasma glucose ≥126 mg/dl, symptoms of diabetes with a random plasma glucose ≥200 mg/dl, or plasma glucose ≥200 mg/dl at 2 hours into an oral glucose tolerance test.8 Hypertension was defined as present if subjects were taking antihypertensive medications, or if blood pressure was elevated within 1 month of diagnosis of nerve palsy. Elevated blood pressure was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on 2 occasions separated by at least 2 weeks.9 Cases of sixth nerve palsy associated with either hypertension or diabetes were classified into the hypertension alone or diabetes alone groups respectively, whereas cases associated with both hypertension and diabetes were classified into the coexistent hypertension and diabetes group. Cases associated with hypertension were further reviewed for the presence or absence of left ventricular hypertrophy (LVH), a marker of hypertensive end-organ damage.10,11 Left ventricular hypertrophy was defined as present if standard electrocardiographic voltage criteria for LVH were met, or if a cardiologist deemed LVH was present based on echocardiographic data. Multiple sclerosis was recorded as present if criteria were met for a clinically definite or laboratory-supported diagnosis based on well accepted published criteria.12 In cases associated with multiple sclerosis, neoplasm or aneurysm, the sequence of symptoms was reviewed to determine whether the sixth nerve palsy was the presenting sign or late sign in the course of the disease, or was related to neurosurgical treatment. Traumatic nerve palsy was defined as the onset of nerve palsy immediately after head trauma with or without loss of consciousness. Cases in which the recorded history, physical examination and ancillary testing revealed no cause or associated medical condition were classified as undetermined.

For further analysis we classified the etiology and associations of sixth nerve palsy as either traumatic or nontraumatic. The nontraumatic cases were further subclassified as either neurologically isolated or non–neurologically isolated. Neurologically isolated cases were defined as those in which the sixth nerve palsy was the only physical sign, whereas non–neurologically isolated cases were defined as those in which additional neurologic symptoms or signs were present—for example, other cranial nerve palsies (including bilateral sixth nerve palsies), severe headache, ataxia, or paresis.

The annual age- and gender-adjusted incidence rate was calculated by using the age-specific and gender-specific population figures for Olmsted County, Minnesota, from the 1990 United States census. Age-specific and gender-specific denominators for individual years were generated from linear interpolation of the 1970, 1980 and 1990 census figures and state demographer projections of the 1995 Olmsted County population.13 The 95% confidence interval was calculated for the rate with assumptions based on the Poisson distribution.

After identifying and reviewing all cases of sixth nerve palsy, we reviewed additional medical records of patients with selected associations of sixth nerve palsy to minimize missed cases. To ensure we detected all cases of myasthenia gravis that presented with lateral rectus palsy, we reviewed the medical records of all Olmsted County residents with newly diagnosed myasthenia gravis during the 15-year study period. We also reviewed 100 randomly selected medical records of Olmsted County residents with intracranial neoplasia during the 15-year study period specifically to determine if any presented with neurologically isolated cranial nerve palsy.

Results

Overall Incidence

Over the 15-year period, 137 new cases of sixth nerve palsy or paresis were identified in our defined population. There were 69 male (50%) and 68 female (50%) incident cases. The age- and gender-adjusted annual incidence rate for sixth nerve palsy was 11.3/100 000 (95% confidence interval [CI], 9.3–13.2). The peak incidence of sixth nerve palsy was in the seventh decade of life (Fig 1). There were 4 cases (3%) of bilateral sixth nerve palsy, and 16 cases (12%) of sixth nerve palsy coexistent with third or fourth nerve palsies.

Cause and Association

In order of frequency, causes and associations of sixth nerve palsy were undetermined (26%), hypertension alone (19%), coexistent hypertension and diabetes (12%), trauma (12%), multiple sclerosis
(7%), neoplasm (5%), diabetes alone (4%), cerebrovascular accident (4%), postneurosurgery (3%), aneurysm (2%), and other (8%) (Fig 2). At the peak of incidence by age, the seventh decade of life, the most common associations were undetermined (31%), hypertension alone (20%), and coexistent hypertension and diabetes (17%).

A total of 51 cases of sixth nerve palsy met the criteria for a diagnosis of hypertension. Hypertension alone was present in 26 cases, and coexistent hypertension and diabetes was present in 16 cases. The remaining 9 cases were not included in either previous category because the sixth nerve palsy was attributed to an alternative cause (cerebrovascular accident, n = 3; aneurysm, n = 2; 1 case each for postneurosurgery, neoplasm, multiple sclerosis and Tolosa-Hunt syndrome). Data for LVH were available for 40 of 42 (95%) cases of hypertension, and LVH was present in 8 of 40 (20%) cases.

Traumatic versus Nontraumatic

Trauma accounted for 16 (12%) of the 137 cases of sixth nerve palsy. Of the 121 cases of nontraumatic sixth nerve palsy, 93 (77%) were neurologically isolated, whereas 28 (23%) were non-neurologically isolated. Both nontraumatic categories are considered in detail below.

![Figure 1. Frequency, cause, and associations of sixth nerve palsy by decade of life.](image1)

![Figure 2. Cause and associations of sixth nerve palsy (n = 137).](image2)

**Table 1. Causes and Associations of Nontraumatic, Neurologically Isolated Sixth Nerve Palsy**

<table>
<thead>
<tr>
<th>Cause and Association</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetermined</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>Hypertension alone</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Coexistent hypertension and diabetes</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Multiple sclerosis: known</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes alone</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Multiple sclerosis: presenting</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Intracranial neoplasm: known</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Congenital</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Neurosarcoïd</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>98*</td>
</tr>
</tbody>
</table>

*Percentages do not sum to 100% due to rounding.

**Nontraumatic, Neurologically Isolated**

Of the nontraumatic neurologically isolated palsies, 78 of 93 (84%) were either of undetermined etiology or were associated with hypertension or diabetes (Table 1). Undetermined cases occurred at any age, whereas diabetes and hypertension were not associated with sixth nerve palsy before the fifth and sixth decades of life respectively (Fig 1).

Of the 32 undetermined cases, 26 underwent neuroimaging (computed tomography [CT] alone, 20; magnetic resonance imaging [MRI] alone, 3; CT and MRI, 3), 28 were examined by a neurologist or internist or both, and 8 had a lumbar puncture for cerebrospinal fluid analysis. Two undetermined cases were not evaluated by a neurologist or internist, and did not undergo ancillary testing. The first was a 69-year-old male who underwent a negative evaluation for a previous left third nerve palsy which resolved 1 year before presenting with a right sixth nerve palsy; the latter was observed and resolved spontaneously. The second case was a 51-year-old female who did not return for further evaluation presumably because the palsy resolved quickly (the patient has 10 years of subsequent primary care follow-up without further mention of sixth nerve palsy or diplopia). Median follow-up after diagnosis of sixth nerve palsy for all 32 undetermined cases was 14 years, and was sufficient to document resolution of the palsy in 24 (75%) cases. Of the 8 undetermined cases for which documented resolution of the palsy could not be determined from the patient history, at the time of diagnosis of the palsy, 5 underwent neuroimaging and were examined by a neurologist, 1 underwent neuroimaging alone, and 2 were evaluated by an internist alone.

Eight of 93 (8%) nontraumatic neurologically isolated palsies were associated with multiple sclerosis, and 5 of these cases had known multiple sclerosis at the time of onset of the palsy. All 8 cases were examined by a neurologist at the onset of sixth nerve palsy. The 3 cases in which the sixth nerve palsy was the presenting sign of multiple sclerosis occurred in 2 patients. The first patient was a 33-year-old male who presented with a right sixth nerve palsy that resolved, but then developed a left sixth nerve palsy 3 years later, which also resolved. At first presentation, MRI and cerebrospinal fluid analysis were negative, and a neurologist’s evaluation did not reveal any additional signs or symptoms, but 1 year after the second sixth nerve palsy, the patient was re-evaluated for paresthesias and a cerebrospinal fluid analysis supported a diagnosis of multiple sclerosis. The second patient with multiple sclerosis who presented with a sixth nerve palsy was a 37-year-old male who subsequently developed retrobulbar optic neuritis, followed by paresthesias; this patient had no additional signs or
symptoms on full neurologic evaluation at the time of first presentation. Only 2 of 93 (2%) of the nontraumatic neurologically isolated sixth nerve palsies were caused by neoplasia, and in both of these cases, a history of neoplasia had been established before onset of the palsy. No new cases of neoplasm or aneurysm presented with a sixth nerve palsy in the absence of other symptoms or signs.

There were 2 cases of nontraumatic neurologically isolated sixth nerve palsy associated with upper respiratory tract infection, and both occurred in children (ages 4 and 5 years). The single case of congenital sixth nerve palsy was in a 2-week-old infant with complete limitation of abduction that resolved spontaneously by age 4 months. An additional case initially diagnosed as sixth nerve palsy was actually lateral rectus weakness caused by myasthenia gravis. This was the presenting sign in an 84-year-old female, and the palsy resolved spontaneously. Eleven months later the patient presented with bilateral sixth nerve palsies and unilateral fourth nerve palsy. The single case of isolated sixth nerve palsy caused by neurosarcoid occurred in a 50-year-old male who had a history of pulmonary sarcoid. Neurologic examination was completely negative, but cerebrospinal fluid analysis was consistent with an inflammatory response; the patient was treated with corticosteroids with subsequent resolution of the sixth nerve palsy.

Nontraumatic, Non–Neurologically Isolated

Of the 28 sixth nerve palsies that presented with other neurologic symptoms and signs, 18 (64%) were caused by cerebrovascular accidents (all involving the pons), neoplasm, or aneurysm (all involving the internal carotid artery at the cavernous sinus), or occurred after neurosurgery (Table 2). When sixth nerve palsy was the presenting sign of aneurysm (n = 3) or neoplasm (n = 1), additional neurologic symptoms and signs were always present.

Three cases of nontraumatic sixth nerve palsy presenting with other neurologic symptoms and signs were classified as undetermined. The first case was a 61-year-old male who had abnormal facial sensations for 3 years before presentation with a sixth nerve palsy. At the time of presentation, the patient also had ipsilateral reduction of the corneal blink reflex and ipsilateral reduction of facial sensation in the trigeminal distribution. Electromyography demonstrated bilateral trigeminal neuropathy but subsequent evaluation was negative, and the sixth nerve palsy spontaneously resolved. The second case was a 34-year-old male who presented with bilateral sixth nerve palsy and unilateral fourth nerve palsy. Medical evaluation revealed increased oligoclonal bands in the cerebrospinal fluid, elevated serum angiotensin-converting enzyme level, lymphoplasmacytic infiltration on conjunctival biopsy, and the presence of yeasts consistent with histoplasmosis on biopsy of an enlarged paratracheal lymph node. The ocular nerve palsies resolved within 2 years of onset without any treatment. The third case was a 37-year-old male who presented with ipsilateral third and sixth nerve palsies. The patient underwent a transsphenoidal hypophysectomy and pituitary irradiation for acromegaly 14 years before presentation. No evidence of tumor recurrence was found and the ocular palsies spontaneously resolved within a year.

Review of Additional Medical Records

We identified 25 patients with a new diagnosis of myasthenia gravis during the 15-year study period. Only the previously identified case presented with lateral rectus weakness. None of the 24 other cases presented with lateral rectus weakness.

Of the 100 randomly selected medical records of patients with intracranial neoplasia, none presented with neurologically isolated cranial nerve palsy (95% CI, 0–3.6%).

Discussion

Our study provides data on the incidence and etiology of sixth nerve palsy in a geographically defined population. We found the age-adjusted incidence to be 11.3/100 000 (95% CI, 9.3–13.2/100 000). The 4 most common associations were undetermined, hypertension alone, coexistent hypertension and diabetes, and trauma. The peak incidence of sixth nerve palsy was the seventh decade of life. There was a striking difference between associations of neurologically isolated and non–neurologically isolated cases; the former group was predominantly associated with vascular (diabetes and hypertension) or undetermined disorders, whereas the latter group was largely associated with more serious medical and neurologic disorders.

There are notable differences between our population-based data and the data from tertiary referral-based series.1–5 In the present study, we found 72% of sixth nerve palsies in the general population were of undetermined etiology, traumatic, or vascular (hypertension or diabetes mellitus), whereas only 4% were associated with neoplasm. In the largest referral-based series by Richards et al,2 21% of sixth nerve palsies were associated with neoplasm, and only 12% were of vascular etiology. Such overrepresentation of neoplasm as an etiology of sixth nerve palsy in referral-based series may have previously prompted many physicians to advocate a complete evaluation, including neuroimaging and cerebrospinal fluid analysis, for any sixth nerve palsy. Our data suggests that a careful history and neurologic examination will help distinguish those patients who need extensive workup from those who can be observed.

Our review of presenting histories and physical findings in the nontraumatic cases of sixth nerve palsy provides valuable data for the evaluation of patients with sixth nerve palsy. When sixth nerve palsy was the only physical sign

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Table 2. Causes and Associations of Nontraumatic, Non–Neurologically Isolated Sixth Nerve Palsy

<table>
<thead>
<tr>
<th>Cause and Association</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular accident</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Intracranial neoplasm: known</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Intracranial neoplasm: presenting</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>After neurosurgery: neoplasm</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>After neurosurgery: aneurysm</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Undetermined</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Multiple sclerosis: known</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Parasellar abscess</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Tolosa–Hunt syndrome</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Sinus disease or mucocele</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Pituitary apoplexy</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Brainstem arteriovenous malformation</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>103*</td>
</tr>
</tbody>
</table>

*Percentages do not sum to 100% due to rounding.
present (nontraumatic neurologically isolated), 83% of cases were undetermined or associated with diabetes or hypertension. The remaining cases were caused by, in order of frequency, multiple sclerosis, neoplasm and upper respiratory tract infection, with single additional cases of myasthenia gravis, congenital and neurosarcoid.

Although hypertension was a frequent associated condition in the present study, left ventricular hypertrophy, which represents end-organ damage from sustained hypertension, was present in only 8 of 40 (20%) cases of neurologically isolated sixth nerve palsy. In Jacobson’s case–control study of cranial nerve palsies affecting ocular motility, a higher proportion of hypertensives with left ventricular hypertrophy (15/43, 35%) was reported, and hypertension was found to be a risk factor for nerve palsy only if associated with LVH. Although we had electrocardiographic or echocardiographic data available for 95% of subjects with hypertension in our study, it is still possible that we did not detect all cases of LVH because the standard electrocardiographic voltage criteria for LVH are specific but not sensitive, and echocardiographic diagnoses of mild cases of LVH are often subjective.

Multiple sclerosis was associated with 8.6% of isolated sixth nerve palsies in our series, similar to previous reports of 4% to 9%. In our series, 3.2% (n = 3) of neurologically isolated sixth nerve palsies were subsequently attributed as the presenting sign of multiple sclerosis. These 3 cases were initially deemed undetermined by the treating physician. Our rate of isolated sixth nerve palsy as the presenting sign of multiple sclerosis is higher than the 0.8% reported in another study by Barr et al. and may reflect differing lengths of follow-up.

Although myasthenia gravis is not a cause of sixth nerve palsy, we included the single case of lateral rectus palsy caused by myasthenia gravis in our series because it initially presented as lateral rectus weakness that resolved. The evaluation of acute sixth nerve palsy does not routinely include tests for myasthenia gravis unless the history is suggestive. The diagnosis in our case was not suspected and was confirmed only when new signs developed 11 months after initial presentation. Our review of the additional medical records of Olmsted County residents presenting with myasthenia gravis showed that lateral rectus palsy is an uncommon presentation.

Regarding neoplasia and neurologically isolated sixth nerve palsy, we had only 2 such cases associated with neoplasm. In both cases the neoplasm had been diagnosed before onset of the nerve palsy. Our review of 100 additional medical records of patients with intracranial neoplasia found no cases that presented with neurologically isolated cranial nerve palsy (95% CI, 0–3.6%). Although the absence of intracranial neoplasia in cases of neurologically isolated sixth nerve palsy may not reflect the experience of many neuro-ophthalmologists, this finding can reasonably be attributed to our population-based study design.

In contrast to the neurologically isolated cases, most of the etiologies of the non–neurologically isolated cases required significant medical or surgical intervention (Table 2). Neoplasm accounted for 18% of cases in this group, but the diagnosis of a neoplasm had been made before presenting with the sixth nerve palsy in 4 of 5 cases. The additional case of neoplasm was our only case in which the sixth nerve palsy was the presenting sign of an intracranial neoplasm, but on review of the presenting history and physical examination, other symptoms and signs were present, including papilledema and ataxia.

Our population-based data will enable comprehensive ophthalmologists and neurologists to focus their evaluation of sixth nerve palsy, depending on findings in the medical history and clinical examination, resulting in more efficient use of ancillary tests. The data highlight the need to take a thorough presenting history, past medical history and to perform a comprehensive neurologic examination in all patients. Such patients should be asked about previous neurologic symptoms and signs in addition to concurrent symptoms and signs because of the relapsing and remitting nature of some associated conditions.

Using our population-based data, we have devised a management algorithm for sixth nerve palsy (Fig 3). Each case of sixth nerve palsy can be classified as traumatic or nontraumatic, and nontraumatic can be subclassified as neurologically isolated or non–neurologically isolated. Traumatic sixth nerve palsies recover in almost all cases if partial, and in at least one third of cases if complete, and thus may be treated conservatively with prisms for at least 6 months. We recommend that cases of sixth nerve palsy associated with other neurologic symptoms and signs undergo a complete neurologic and medical evaluation including prompt neuroimaging and cerebrospinal fluid analysis. Neurologically isolated sixth nerve palsies in the presence of medical conditions such as diabetes and hypertension may be observed without extensive evaluation unless the palsy progresses or fails to resolve, or new neurologic signs or symptoms develop. Close follow-up is therefore essential, in addition to appropriate management of the existing medical conditions. Certain cases of neurologically isolated sixth nerve palsy may require more extensive evaluation when the medical history is suggestive of a cause, as in the single case of neurosarcoid or the 2 cases with prior history of a neoplasm. When sixth nerve palsy is neurologically isolated and the medical history does not suggest an etiol-
ogy, our data suggest that the most likely diagnosis will be undetermined. With median follow-up of 14 years for undetermined cases in our study, we found that 75% of undetermined sixth nerve palsies resolved spontaneously. We recommend that such patients be observed carefully without neuroimaging, assuming careful follow-up can be provided. If any new neurologic symptoms or signs appear, or if the sixth nerve palsy is progressive, further evaluation including neuroimaging is warranted. Although progression of sixth nerve palsy associated with diabetes within the first few days of onset is not unusual, progression after 2 weeks mandates further evaluation.

Our recommendation not to undertake neuroimaging at the time of diagnosis of isolated sixth nerve palsy could be considered controversial. Bendzsus et al recommend that magnetic resonance imaging should routinely be performed in patients presenting with acute isolated sixth nerve palsy, but others disagree. Miller et al suggest that nonvasculopathic isolated sixth nerve palsies should undergo neuroimaging. In contrast, they recommended sixth nerve palsies attributed to vascular etiologies could be observed without neuroimaging for 2 to 3 months. Using our population-based data, we suggest expanding Miller’s recommendations to delay neuroimaging, and we believe that if sixth nerve palsy is not accompanied by other neurologic signs (excluded by a comprehensive neurologic examination), and no historical features suggest an etiology, it is reasonable to defer imaging while continuing to observe the patient monthly. Such an approach would reduce patient medical expenses and eliminate the small risks associated with sedation or anesthesia when these are required for imaging.

We predict that the major objection to not performing neuroimaging in cases of isolated sixth nerve palsy would be the risk of failing to diagnose an intracranial neoplasm. We had no cases of neoplasm that were unknown at the time of diagnosis of neurologically isolated sixth nerve palsy (0 of 93 cases; 95% CI, 0–3.9%) in our population-based study. We believe, in the rare case of intracranial neoplasm in which isolated sixth nerve palsy was the presenting sign, it is unlikely that this would be sufficiently altered by delaying the diagnosis for 2 to 3 months to allow observation for progression or resolution of the sixth nerve palsy. Thus, with appropriate counseling and provision of information at diagnosis of isolated sixth nerve palsy, and the ability to provide careful follow-up, we recommend the deferral of neuroimaging. We are not stating that neurologically isolated sixth nerve palsy cannot be associated with serious neurologic disease, but rather that using a population-based approach we find that such an association is rare. Given an era of limited health care resources, such data should be considered when ordering diagnostic tests and counseling patients.

Our study reports population-based incidence for sixth nerve palsy, but the study is not without limitations. Due to the predominantly white population of Olmsted County, our results can most reasonably be extrapolated to only the semiurban United States white population. Population-based data from Olmsted County are similar to data from other US communities, supporting extrapolation of population-based data from Olmsted County to a large proportion of the US population. In 1990, 80% of the total United States population was white, and so we believe that our results can be generalized to a large part of the United States population. This limitation is far outweighed by the fact that the study is “population based” rather than “tertiary referral center based.” Despite our retrospective design, we believe that nearly all cases of sixth nerve palsy would have been captured, because few patients would have been asymptomatic and not sought evaluation. Nevertheless, we acknowledge that the evaluation of patients presenting with sixth nerve palsy was not uniform because of the retrospective design of the study. Regarding possible overrepresentation of undetermined cases, we had 4 cases of sixth nerve palsy that were deemed undetermined at the time of diagnosis, but were actually associated with systemic conditions that manifested later (3 cases of multiple sclerosis and 1 case of myasthenia gravis as described above). It is unlikely that more undetermined cases were associated with systemic conditions because our study period allowed a minimum of 10 years of follow-up from the time of initial diagnosis to the time of review of medical histories in 2002 (for patients who continued to reside in Olmsted County, where 90% of the population is examined every 3 years). The median follow-up for all undetermined cases in the present study was 14 years. In addition, resolution was documented in 75% of these cases, and 6 of the 8 cases for which resolution could not be determined had a negative neuroimaging study at diagnosis. Therefore, we believe it is unlikely that any of the undetermined isolated sixth nerve palsies may have represented undetected cases of neoplasm.

In summary, we have presented population-based data on the incidence and etiology of sixth nerve palsy, and have described the frequency of association with diabetes and hypertension by using strict criteria. We have applied our data to devise a diagnostic algorithm suggesting that only non–neurologically isolated sixth nerve palsies need prompt neuroimaging and cerebrospinal fluid analysis, whereas neurologically isolated sixth nerve palsies may undergo a more focused evaluation and careful observation.

References

8. Report of the Expert Committee on the Diagnosis and Clas-


