Objective: To derive a reliable estimate of the frequency of pupil involvement in patients with diabetes-associated oculomotor nerve palsy.

Patients and Methods: In this prospective study, standardized enrollment criteria were employed to identify 26 consecutive patients with diabetes-associated oculomotor nerve palsy who were evaluated in a referral-based, outpatient neuro-ophthalmology practice. A pupil ruler accurate to within 0.5 mm was used to measure pupil diameters using a standardized procedure. The degree of anisocoria, if present, was recorded at each office visit until the ophthalmoplegia had resolved. Descriptive statistics were used to identify the frequency and characteristics of pupil involvement.

Results: Internal ophthalmoplegia occurred in 10 (38%) of 26 patients. The size of the anisocoria was 1 mm or less in most patients. None of the patients had a fully dilated unreactive pupil.

Conclusions: Pupil involvement in patients with diabetes-associated oculomotor nerve palsy occurs more often than has been previously recognized, although the degree of anisocoria in any 1 patient is usually only 1 mm or less. Some characteristics of the internal ophthalmoplegia may help to distinguish diabetic ophthalmoplegia from injury of the oculomotor nerve caused by aneurysmal compression.


The size and reactivity of the ipsilateral pupil is generally considered a useful guide to help clinicians distinguish oculomotor nerve injury caused by aneurysmal compression from peripheral nerve infarction. The pupil is usually dilated and reacts poorly to light when an aneurysm compresses the oculomotor nerve, whereas the iris sphincter is usually unaffected by ischemic injury. Diabetes mellitus is the most commonly identified risk factor associated with ischemic oculomotor nerve injury. The anatomical basis for the "Rule of the Pupil" is the superomedial concentration of the pupillomotor fibers along the subarachnoid segment of the oculomotor nerve trunk. In this location, these fibers are particularly susceptible to injury if an aneurysm, such as one arising at the junction of the internal carotid and posterior communicating arteries, compresses the oculomotor nerve. On the other hand, the pupillomotor fibers are relatively spared from ischemic injury when the core of the extra-axial segment of the oculomotor nerve is infarcted in patients with diabetes mellitus.

While pupil involvement associated with oculomotor nerve palsy is a sensitive predictor of aneurysmal compression, the specificity of this sign remains less clear in regard to diabetes-associated infarction. The reported frequency of pupil involvement in several series that included up to 25 patients with diabetes-associated oculomotor nerve palsy ranges from 14% to 32%.

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These frequencies can only be considered estimates, however, since they were derived using retrospective analyses. The absence of a standardized approach to defining diabetic ophthalmoplegia, recording pupil signs, and defining pupil involvement further contributes to the unreliability of published estimates of pupil involvement in this condition. Furthermore, it is possible that some of the patients included in older series had compressive or infiltrative lesions unrelated to diabetes. The current study was designed to overcome these limitations to derive a more reliable estimate of the frequency of pupil involvement in patients with diabetes-associated ophthalmoplegia.
PATIENTS AND METHODS

I prospectively measured the pupil diameter and light reaction of consecutive outpatients with diabetes-associated ophthalmoplegia who had been evaluated in my referral-based neuro-ophthalmology practice from July 1, 1987, through August 31, 1997. Patients included for analysis were required to fulfill enrollment criteria to establish that they had either diabetes or glucose intolerance as well as clinical characteristics consistent with ischemic oculomotor nerve palsy. Patients already receiving treatment for diabetes were considered to have established diabetes. Those patients initially diagnosed as having ischemic oculomotor nerve palsy who did not have established diabetes underwent an assay of fasting serum glucose and, in many cases, a 2-hour postprandial serum glucose test as part of their general medical evaluation of risk factors. Those patients with abnormal results were considered to have newly diagnosed diabetes or glucose intolerance, defined using criteria established by the National Diabetes Data Group.

A predetermined set of enrollment criteria established the presence of ischemic oculomotor nerve palsy. The inclusion criteria required that an affected patient have paresis of only those muscles innervated by the oculomotor nerve at the initial evaluation and at all follow-up evaluations, no other neurologic symptoms or signs other than head or eye pain, negative results of forced duction testing of their ophthalmoplegia, and spontaneous recovery of eye movement without signs of aberrant regeneration within 6 months of the onset of symptoms. Patients were excluded if they had strabismus during childhood; head trauma within 3 months of onset of symptoms; prodromal symptoms suggestive of a viral illness; known or suspected cancer without having undergone either computed tomography or magnetic resonance imaging to exclude a metastatic lesion compressing their oculomotor nerve; established or suspected multiple sclerosis or myasthenia gravis; or clinical or laboratory evidence consistent with Lyme disease, syphilis, temporal arteritis, or other systemic vasculitis. In addition, patients were excluded if they had some other pupil disorder, such as Horner or Adie syndromes.

I used a standardized method to measure pupil size and to quantify the degree of ophthalmoplegia. Patients were instructed to look at a distant fixation target under room light conditions (960 lux). A pupil measurement device (Iowa Pupil Gauge, Hansen Ophthalmic Development Laboratory, Iowa City, Iowa) was used to estimate pupil diameters to the nearest 0.5 mm. I conversed with the patients while I measured their pupil diameters to ensure that they were alert. The degree of anisocoria, if present, was recorded. The quality of the direct pupillary light reaction was also recorded. I estimated the degree of limitation of ocular duction of the superior rectus, inferior rectus, medial rectus, and inferior oblique muscles using a grading scale of 0 through 4, where 0 represented full duction; 4, complete absence of function; and 1, 2, and 3, 25%, 50%, and 75% impairment of duction, respectively. An ophthalmoplegia grade was defined as the arithmetic mean of the individual extraocular muscle scores, as previously outlined. Progression of ophthalmoplegia was defined as an increase in ophthalmoplegia grade of at least 1.0 between 2 successive visits.

The following data were abstracted from the medical records of patients in the study: age, sex, diabetic classification and years affected, hemoglobin A1c level (if performed), whether pain was present, whether ophthalmoplegia progressed, duration of ophthalmoplegia, and whether neuroimaging procedures had been performed and, if so, the type of studies obtained. The pupil and eye movement findings at each visit were also abstracted.

The abstracted information was entered into a commercially available database and statistical software system (Prism, Graphpad Software Inc, San Diego, Calif). Descriptive statistics were derived by tabulating variables contained in the database and by reviewing the medical records of the clinical course of individual patients. Fisher exact test (2 tailed) was used to identify whether significant differences existed between proportions of patients with pupil involvement and without pupil involvement for the following variables: age younger than or older than the median age of the study population, sex, whether diabetes was established or newly diagnosed, duration of established diabetes shorter than or longer than the median duration of the study population, presence or absence of pain, presence or absence of progression of ophthalmoplegia, and duration of ophthalmoplegia shorter than or longer than the median duration of the study population.

RESULTS

Twenty-six patients fulfilled the enrollment criteria and were included for analysis (Table 1). Twelve (46%) of 26 patients were first evaluated within 7 days of the onset of diplopia, 18 (69%) of 26 within 14 days, and 22 (84%) of 26 within 21 days. Four additional patients were first evaluated 24, 30, 32, and 36 days after the onset of diplopia. None of the patients had isolated weakness of extraocular muscles innervated by only the superior or inferior division of the oculomotor nerve. Twenty-four (92%) of 26 patients underwent 1 or more neuroimaging procedures, including computed tomography in 14 patients, magnetic resonance imaging in 11 patients, magnetic resonance angiography in 3 patients, and catheter angiography in 6 patients. These studies were unrevealing in all patients.

Some degree of anisocoria was measured in 14 (54%) of the 26 patients. None of these patients had a fully dilated, nonreactive pupil. After reviewing the course of the internal and external ophthalmoplegia of each patient, I identified 3 patterns of anisocoria that accounted for the pupillary signs in this population (Table 2).

In 4 (15%) of the 26 patients, an anisocoria measuring 0.5 mm was present at every visit, including the final one when resolution of external ophthalmoplegia was documented (Table 2). The degree of the anisocoria in these patients remained similar whether observed in room light or in dim light. The direct pupillary light reaction was normal. These characteristics are consistent with a simple anisocoria.

Seven (27%) of the 26 patients had an anisocoria that resolved completely during the course of their subse-
quent follow-up visits (Table 2 and Figure 1). The direct pupillary light reaction was variably impaired in all of these patients. The size of this anisocoria was 0.5 mm in 5 patients. One of these patients had no anisocoria when seen 1 day after the onset of diplopia at a time when her ophthalmoplegia grade was 0.5; however, when seen on day 10, she had complete external ophthalmoplegia and an anisocoria of 0.5 mm. Another of these patients had no anisocoria when first evaluated on day 5 when her ophthalmoplegia grade was 1.7; however, when she was next seen on day 12, her ophthalmoplegia grade had progressed to 2.3 and she had an anisocoria of 0.5 mm. In the remaining 3 patients who had an anisocoria of 0.5 mm, it was present at their first visits, which were 2, 18, and 30 days after the onset of diplopia when their ophthalmoplegia grades were 2.5, 4, and 4, respectively. The anisocoria was greater than 0.5 mm in 2 patients. One of these patients had an anisocoria of 1.5 mm and an ophthalmoplegia grade of 3.5 when she was first evaluated 19 days after she first noted diplopia. The other patient had an anisocoria of 2.5 mm and an ophthalmoplegia grade of 3.8 when he was first evaluated 14 days after he first noted diplopia. The course of the anisocoria in these 7 patients is consistent with internal ophthalmoplegia associated with oculomotor nerve palsy.

Three (12%) of the 26 patients had an anisocoria that decreased in size, but never resolved completely, as their external ophthalmoplegia resolved (Table 2 and Figure 1). The affected pupil demonstrated variable impairment of the direct light reaction. The size of the anisocoria when the external ophthalmoplegia resolved was 0.5 mm in all 3 patients. The direct pupillary light reaction appeared normal at that time. One of these patients was first seen on day 14 with an ophthalmoplegia grade of 4 and an anisocoria of 1.0 mm. Another patient was first seen on day 3 with an ophthalmoplegia grade of 2.4 and an anisocoria of 0.5 mm; however, when he was next evaluated on day 12, his ophthalmoplegia grade had improved slightly to 1.8, but he then had an anisocoria of 1.0 mm. The third patient had an anisocoria of 0.5 mm and an ophthalmoplegia grade of 4 when she was first seen 7 days after she noted diplopia; when she was evaluated 1 week later, her ophthalmoplegia grade was still 4 and her anisocoria had increased to 1.0 mm. The course of the anisocoria of these 3 patients is consistent with simple anisocoria superimposed on internal ophthalmoplegia associated with oculomotor nerve palsy.

In my study population, therefore, 10 (38%) of 26 patients had internal ophthalmoplegia associated with their oculomotor nerve palsy, ranging in size from 0.5 to 2.5 mm (median size, 0.8 mm) (Figure 1). The degree of anisocoria was 1 mm or less in 8 (80%) of these 10 patients. The office visit during which the maximum anisocoria was first observed occurred within 14 days of the onset of diplopia in 7 (70%) of these patients (Figure 2).

I did not identify any significant difference in the proportion of patients with pupillary involvement and those without for the abstracted clinical variables. The number of patients in each group was small, however, so that the absence of identifying an association does not necessarily imply that none existed.

The design of this study overcomes many of the methodological problems inherent in previous series report-

Table 1. Demographic and Clinical Characteristics of 26 Patients With Diabetes-Associated Oculomotor Nerve Palsy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>68 (46-96)</td>
</tr>
<tr>
<td>Sex, No. (%) of patients</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>11 (42)</td>
</tr>
<tr>
<td>M</td>
<td>15 (58)</td>
</tr>
<tr>
<td>Median duration of diabetes in those with established disease, y (range)</td>
<td>17 (5-30)</td>
</tr>
<tr>
<td>Median duration of ophthalmoplegia, wk (range)</td>
<td>10 (5-20)</td>
</tr>
<tr>
<td>Established diabetes, No. (%) of patients</td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Type 2</td>
<td>15 (58)</td>
</tr>
<tr>
<td>With elevated hemoglobin A1c level*</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Newly diagnosed diabetes, No. (%) of patients</td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Type 2</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Newly diagnosed glucose intolerance, No. (%) of patients</td>
<td></td>
</tr>
<tr>
<td>Pain, No. (%) of patients</td>
<td>23 (88)</td>
</tr>
<tr>
<td>Progression of ophthalmoplegia, No. (%) of patients</td>
<td></td>
</tr>
</tbody>
</table>

* Hemoglobin A1c level was not obtained in 4 patients so that the results reflect 12 of 16 patients with established diabetes.

Table 2. Patterns of Anisocoria in 26 Patients With Diabetes-Associated Oculomotor Nerve Palsy

<table>
<thead>
<tr>
<th>Pattern of Anisocoria</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Simple</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Completely resolved</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Incompletely resolved</td>
<td>3 (12)</td>
</tr>
</tbody>
</table>

Figure 1. Frequency profile of the maximum degree of anisocoria in 10 patients with diabetes-associated oculomotor nerve palsy who had pupillary involvement. Seven patients had relapsing and then completely remitting anisocoria while 3 patients had incompletely resolved anisocoria.
An autonomic neuropathy. As the neuropathy usually affects both pupils, this variable would not influence the anisocoria that develops as a result of oculomotor nerve injury in most patients. It is possible, however, that some of the patients in this series had unilateral or asymmetric pupillary autonomic neuropathy and were included in the subgroups that I classified as simple anisocoria or incompletely resolved anisocoria. Since all patients had a normal-appearing direct pupillary light reaction as their ophthalmoplegia resolved, it is unlikely that misclassification contributed substantially, if at all, to the overall results of this investigation. In fact, patients with tonic pupils were specifically excluded. In clinical practice, signs that a poorly reactive or larger pupil might be the result of long-standing diabetic neuropathy, not the result of acute oculomotor nerve injury from aneurysmal compression, include light-near dissociation and segmental paresis of the iris sphincter observed during slitlamp biomicroscopy.

After accounting for those patients with simple anisocoria, pupil involvement occurred in almost 40% of patients in my series. Methodologic differences can explain why the frequency of pupillary involvement identified in my series is higher than those estimates reported in previous series. The proportion of patients with pupillary involvement depends on how one defines the end point that distinguishes a normal pupil from an abnormal one. In this study, I prospectively measured and recorded pupil sizes to the nearest 0.5 mm in all patients. This level of scrutiny may have resulted in detection of many patients with an anisocoria of 0.5 mm. An anisocoria of such small size might have been undetected, considered insignificant, or assumed to be related to simple anisocoria by previous investigators.

In most of the patients in my series with pupillary involvement, the maximum anisocoria developed within the first 2 weeks after the onset of diplopia. Similar to a previous observation on progression of external ophthalmoplegia, the degree of anisocoria subsequently progressed in some of the patients who were first evaluated early in that 2-week period. However, since the interval between onset of symptoms and first and subsequent office visits was not uniform, the time course outlined in Figure 2 is artifically prolonged. Had all patients been seen on a daily basis, for example, the interval from onset of symptoms to maximum anisocoria would first have been detected at a much earlier stage.

The 1- to 2-week period during which anisocoria progressed in some of the patients in this series is similar to the time frame during which the pupil may become maximally dilated in patients harboring aneurysms compressing the oculomotor nerve. A fully dilated, unreactive pupil occurs in roughly 53% to 71% of patients with aneurysmal compression of the oculomotor nerve. In contrast, the pupil was incompletely involved and remained reactive in all patients in my series who had internal ophthalmoplegia. Additionally, most patients in my series with pupillary involvement had only minimal internal ophthalmoplegia, as evidenced by anisocoria of 1 mm or less in most of those affected. These pupil characteristics may help to distinguish diabetic (ischemic) from aneurysmal (compressive) injury of the oculomotor nerve.

**Figure 2.** Early time course of the size of the anisocoria in 10 patients with diabetes-associated oculomotor nerve palsy who had pupillary involvement. Each curve indicates the amount of anisocoria measured during office visits for an individual patient. Time 0 refers to the onset of diplopia. The last data point plotted for each patient represents the maximum anisocoria recorded at any office visit. Most patients demonstrated maximum anisocoria within the first 2 weeks (dotted line). Although data points are connected by straight lines, it is unlikely that anisocoria progressed in that manner.
REFERENCES


Announcement

American Academy of Ophthalmology Cautions Viagra Users

Physicians at the American Academy of Ophthalmology warned users about the potential side effects that may affect vision of patients who use the newly approved anti-impotence drug, Viagra.

Michael F. Marmor, MD, professor of Ophthalmology at Stanford University in Palo Alto, Calif, and spokesperson for the Academy, said that a moderate percentage of people taking Viagra have experienced problems with their vision. “FDA [Food and Drug Administration] clinical trials show that taking the medication, especially at higher doses, can cause some retinal dysfunction and affect the way we see for a number of hours.” Patients reported visual disturbances described as bluish color tinge and light sensitivity. Dr Marmor said a clinical study showed that electrical measures of retinal function dropped by 30% to 50% and lasted for at least 5 hours after taking a high dose of Viagra.

It is not known whether the drug causes any permanent changes in vision. Studies about the long-term effects of taking Viagra are needed. In the meantime, Dr Marmor urged those with retinal eye conditions such as macular degeneration or retinitis pigmentosa to use the drug with caution and to stay at the lowest dose level possible. According to the FDA, the recommended dose level for most patients is 50 mg.