Pupil Involvement in Patients With Diabetes-Associated Oculomotor Nerve Palsy

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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.1 The pupil is usually dilated and reacts poorly to light when an aneurysm compresses the oculomotor nerve,2,3 whereas the iris sphincter is usually unaffected by ischemic injury.4 Diabetes mellitus is the most commonly identified risk factor associated with ischemic oculomotor nerve injury.5

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.6 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.7 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.8,9

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%.4,10-13 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.

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PATIENTS AND METHODS

I prospectively measured the pupil diameter and light re-
action 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 clin-
cal characteristics consistent with ischemic oculomotor
nerve palsy. Patients already receiving treatment for dia-
betes were considered to have established diabetes. Those
patients initially diagnosed as having ischemic oculomotor
nerve palsy who did not have established diabetes under-
went 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 pa-
tients with abnormal results were considered to have newly
diagnosed diabetes or glucose intolerance, defined using
criteria established by the National Diabetes Data Group.13

A predetermined set of enrollment criteria estab-
lished the presence of ischemic oculomotor nerve palsy.3
The inclusion criteria required that an affected patient have
paresis of only those muscles innervated by the oculomo-
tor nerve at the initial evaluation and at all follow-up evalu-
ations, 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 ex-
cluded 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 tomog-
raphy or magnetic resonance imaging to exclude a meta-
crion or suspected multiple sclerosis or myasthenia gravis; or
clinical or laboratory evidence consistent with Lyme
disease, syphilis, temporal arteritis, or other systemic vascu-
litis. 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 Labo-
ratory, Iowa City, Iowa) was used to estimate pupil diam-
eters 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 re-
corded. 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, me-
dial 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 ophthal-
moplegia grade was defined as the arithmetic mean of the
individual extraocular muscle scores, as previously out-
lined.13 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 classifi-
cation and years affected, hemoglobin A1c level (if per-
formed), whether pain was present, whether ophthalmople-
gia 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 com-
ercially available database and statistical software sys-
tem (Prism, Graphpad Software Inc, San Diego, Calif). De-
scriptive statistics were derived by tabulating variables
contained in the database and by reviewing the medical rec-
ords of the clinical course of individual patients. Fisher ex-
act 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 me-
dian of the study population, sex, whether diabetes was
established or newly diagnosed, duration of established dia-
betes shorter than or longer than the median duration of
the study population, presence or absence of pain, pres-
ence or absence of progression of ophthalmoplegia, and du-
ration of ophthalmoplegia shorter than or longer than the
median duration of the study population.

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 on-
set 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, mag-
netic 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 meas-
uring 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 anisoco-
ria in these patients remained similar whether observed
in room light or in dim light. The direct pupillary light
reaction was normal. These characteristics are consist-
ent with a simple anisocoria.10

Seven (27%) of the 26 patients had an anisocoria that
resolved completely during the course of their subse-

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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-
ing the frequency of pupillary involvement in patients with diabetes-associated oculomotor nerve palsy. The cohort was identified by applying predetermined enrollment criteria. The same examiner prospectively evaluated consecutive patients. A standard technique to measure pupil diameters was employed. The degree of pupillary involvement was quantified. It is unlikely that any patient was harboring a compressive lesion since almost all of them underwent unrevealing neuroimaging procedures and because spontaneous resolution was an enrollment criterion.

To investigate a homogeneous population, I only considered patients with established or newly diagnosed diabetes or glucose intolerance. Patients with otherwise similar clinical characteristics who do not have abnormal glucose metabolism, however, are commonly encountered. Hypertension and polycythemia are frequent additional risk factors in these patients. There is no reason to assume that the results of my reported cohort would not generally apply to patients with so-called ischemic or vasculopathic oculomotor nerve palsy.

I chose anisocoria, not pupil reactivity to direct light, as the primary end point for defining pupil involvement in this study for several reasons. When other variables that influence pupil size are controlled, the size of the pupil is directly related to the integrity of the efferent pupillomotor pathway. The degree of injury to the efferent pupillomotor pathway can be quantified if the size of the affected pupil is compared with the size of the fellow pupil, which serves as an internal control. In this study, the effect of certain variables that influence pupil size, such as degree of accommodation, intensity of ambient light, and level of alertness, were minimized by the examination procedure. Measuring and recording anisocoria is far more objective than making judgments of pupillary light reaction.

Some patients with diabetes develop a condition in which their pupils react poorly to light on the basis of 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, pupill 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 subsequent office visits was not uniform, the time course outlined in Figure 2 is artifactually 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.
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.