Expert Opinion

Transient Anisocoria in a Migraineur

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EVALUATING THE "PROBLEM PUPIL"

Clinical History.—A 43-year-old woman presented for evaluation of transient anisocoria. Eleven days previously on awakening in the morning, she noted that the right pupil was larger than the left and that she had trouble focusing. About 4 hours later, she saw an optometrist who found the right pupil to be 3 mm in bright light and 6 mm in dim light and the left pupil, 2 mm in bright light and 4 mm in dim light. The pupils were reactive to light. On testing the near response, the right pupil sluggishly constricted and the left was normal. There was no ptosis. Extraocular movements were full. Visual acuity with correction in the right eye was 20/25 and in the left eye, 20/20. Four and one half hours after the first examination, the optometrist repeated the examination and measured the right pupil as 2.5 mm in bright light and 4.5 mm in dim light and the left pupil, 2 mm in bright light and 4 mm in dim light. About 6 hours after she first noted the anisocoria, she developed a mild, nonthrobbing, tense feeling in the right temple without associated symptoms and lasting about 4 hours. Ten hours after her initial observation, she found her pupils to be the same size and she had no further visual complaints.

She reported a prior history of occasional migraine without aura lasting about 1 day and migraine aura (an enlarging flashing light in both eyes with a duration of less than 1 hour) without headache about once every 3 months. Neurologic examination was normal. In room light, the pupils were 4 mm, equal and reactive to light, and the palpebral fissures were both 10 mm. Extraocular movements were full. A magnetic resonance imaging (MRI) scan of the brain and magnetic resonance angiography (MRA) of the brain and neck were normal.

Questions.—What is the diagnosis? Was neuroimaging indicated?

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EXPERT COMMENTARY

This case exemplifies the difficulties of evaluating a patient with anisocoria. Which is the abnormal pupil, the larger or smaller one? When a patient is referred but the sign has resolved, the evaluation is even more problematic. One is forced to rely on the observations of the patient—notoriously unreliable—or those of the referring physician, often times surprisingly unreliable, as well.

Where does one start? The first step is to tease out which pupil is abnormal. If one pupil, regardless of its size, is poorly reactive or nonreactive to light or is oddly shaped, then it is likely to be the abnormal one. Possible etiologies for such a pupil include Adie tonic pupil, intentional or accidental pharmacological mydriasis (eg, atropine), or mechanical restriction (eg, synechiae). The diagnosis at that point is straightforward. For Adie pupil, look for a slow and tonic near response, slow redilation, light-near dissociation, and supersensitivity to dilute pilocarpine. To confirm suspected pharmacologic mydriasis induced by atropine, scopolamine, or a similar drug, apply pilocarpine 1% to both eyes and look for poor

constriction of the affected pupil. An ophthalmologist can help to establish these diagnoses, and to identify primary ocular causes of a poorly reactive pupil.

Next, carefully look for other neuro-ophthalmologic signs, such as ptosis, ophthalmoplegia, visual loss, or proptosis. If ptosis is present in the eye with a smaller pupil, then you should suspect Horner syndrome. If present in the eye with a larger pupil and subtle ophthalmoplegia, then third cranial nerve palsy should be suspected. Visual loss or orbital signs suggest an orbital apex lesion.

The usual dilemma, however, is a patient with isolated anisocoria. In that setting, the best way to determine which is the abnormal pupil is to compare the degree of anisocoria with added light and in darkness.[1] If anisocoria increases with added light and diminishes in darkness, then the larger pupil is most likely the abnormal one due to defective innervation of the iris sphincter muscle causing a constrictor (ie, parasympathetic) defect. Conversely, if anisocoria is minimized with added light but is exaggerated in darkness, then the smaller pupil is likely the abnormal one due to defective innervation of the iris dilator muscle causing a dilation (ie, sympathetic) defect.

The commonest isolated parasympathetic disorder causing an abnormally large pupil is Adie tonic pupil. "Isolated" implies the absence of ophthalmoplegia or other signs of orbital disease, and in that instance, ominous neurologic causes of third cranial nerve palsy (eg, aneurysmal compression) are essentially eliminated. Although the commonest cause of an apparent isolated sympathetic defect causing an abnormally small pupil is Horner syndrome, the ptosis associated with oculosympathetic denervation is mild and often overlooked. Recall that physiologic anisocoria varies in degree and, if exaggerated under certain generalized heightened sympathetic situations such as during pain or anxiety, will often behave similarly to Horner syndrome (ie, smaller in added light and greater in darkness). Reviewing old photographs to document the presence of the anisocoria can be quite reassuring if it is found to have been present for years in a patient with a seemingly acute presentation.

As often happens with patients whose episodic anisocoria has resolved by the time of neurologic evaluation, the reported case is filled with inconsistent observations that make it difficult to allow accurate localization or determination of etiology. For example, symptoms and signs of this patient's right eye included trouble focusing, sluggish pupillary constriction, and mild impairment of visual acuity, all features that could be explained on the basis of an ipsilateral and isolated parasympathetic defect (eg, Adie pupil). But, we are told that both pupils reacted (presumably normally) to light, and that the anisocoria was greater in dim light than in bright light. These signs speak against a parasympathetic defect of the larger pupil and are more suggestive of oculosympathetic denervation of the smaller pupil or exaggerated physiologic anisocoria.

By the time she was evaluated, the anisocoria had resolved and there were no neuro-ophthalmologic signs. The question at that point was whether or not further neurodiagnostic testing was needed. The answer depends, in part, on the comfort level of the patient and physician. Generally, however, no further workup is needed in this setting, when *isolated* anisocoria resolves without sequelae. If we were to assume that the larger pupil was the abnormal one, its presence in isolation (ie, no ophthalmoplegia or ptosis) essentially excludes third cranial nerve palsy; testing for an aneurysm or tumor would be fruitless. If we were to assume that the smaller pupil represented Horner syndrome, then ominous neurologic causes, such as acute internal carotid artery dissection, would not be likely to remit spontaneously in such a short time interval.

This patient had migraine, and there appears to be some association between primary headache disorders and anisocoria. Episodic anisocoria may occur in 2 established headache settings: transient mydriasis in migraine and transient miosis in cluster headaches.[2,3] In the former situation, mydriasis is usually ipsilateral to cephalgia, neurologically isolated, and lasts several hours. In the latter setting, anisocoria is due to Horner syndrome. It is transient at first, but may become persistent with repeated attacks. If transient and isolated anisocoria occurs in a patient with an established diagnosis of 1 of these 2 headache disorders, then no further evaluation is needed beyond careful clinical follow-up. In my experience,

however, transient mydriasis during migraine is uncommon and, if present, is usually due to exaggeration of physiologic anisocoria.

Do not fall into the trap of blithely diagnosing ophthalmoplegic migraine as the cause of isolated painful mydriasis. Ophthalmoplegic migraine generally begins in childhood and is associated with repeated attacks of external, in addition to internal, ophthalmoplegia that occurs at the peak of severe ipsilateral migraine pain. The ophthalmoplegia outlasts the headache and may persist for several weeks.

Finally, there is a heterogeneous group of conditions that fall under the rubric of benign episodic unilateral mydriasis that has been described in young (usually) women who frequently have migraines and experience recurrent episodes of isolated anisocoria that last several hours.[4] The episodes may occur during a migraine or independent of headache. During an episode, patients often report ipsilateral visual blurring, head or eye pain, and often photophobia and eye redness. When examined during an episode, some patients have impaired near visual acuity, impaired accommodation, and anisocoria that is greater in added light, features that implicate impaired parasympathetic innervation of the intraocular muscles. Reversible vasospasm or some other circulatory impairment of the ciliary ganglion is an attractive hypothesis to account for the phenomenology of this syndrome. Alternatively, exaggeration of physiologic anisocoria may account for the signs and symptoms in other affected patients. Regardless of the mechanism, the prognosis is excellent. As long as the episodes are neurologically isolated, no further neurodiagnostic evaluation is required.

So, what do I think was the cause of this patient's transient anisocoria? I suspect she had her first observed spell of benign episodic unilateral mydriasis or simply had exaggeration of physiologic anisocoria. When you work through the algorithms discussed above, neurogenic causes of anisocoria, such as third cranial nerve palsy or Horner syndrome, do not seem to fit. This case reminds us that there is more to the pupil than size alone, and that *isolated* and transient anisocoria is generally a benign sign.

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