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INVITED REVIEW

Third nerve palsy – surgical or medical?

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Abstract

Ischaemic oculomotor nerve palsies (IONP) usually are pupil-sparing. Diabetes, hypertension, and atherosclerosis are commonly associated with IONP. Vasculopathic third nerve mononeuropathies are caused by extra-axial infarcts of the core of the third nerve, which derives its blood supply from the vasa nervorum. The pupillomotor fibers are spared because of their more peripheral location and blood supply from the pial vessels. The superficial location of the pupillomotor fibers renders them more susceptible to damage from compressive lesions, most commonly posterior communicating artery aneurysms. The rule of the pupil states that an isolated, atraumatic third nerve palsy with complete external ophthalmoplegia and a normal pupil has a greater than 90% probability of being due to microvascular ischaemia. However, there are exceptions and more importantly misinterpretation of the rule can lead to unnecessary investigations and complications. This review is an attempt to clarify what a pupil sparing oculomotor palsy is and when to investigate further for a compressive lesion such as an aneurysm.

KEYWORDS

Oculomotor nerve palsy, third nerve palsy, rule of the pupil, posterior communicating artery aneurysm

INTRODUCTION

Clinical Vignette

A 53-year-old with a history of hypertension presents with a one day history of a droopy right upper eyelid accompanied by double vision. On examination, there is partial right upper lid ptosis with impaired levator function and 10% adduction, 0% elevation, and 20% depression on eye movement testing. Pupils are equal in size, reactive, with no relative afferent pupillary defect.

When assessing a patient with a third nerve palsy (TNP), the main concern is whether it is due to a surgical cause such as an aneurysm or tumour. If an aneurysm is likely, then the patient needs urgent neuroimaging because ruptured aneurysms causing subarachnoid haemorrhage have mortality rates over 25%.

The 'Rule of the pupil'

The rule states that an isolated, atraumatic TNP with complete external ophthalmoplegia and a normal pupil has a greater than 90% probability of being due to microvascular ischaemia, usually in a background history of age, diabetes, or hypertension, and is almost never due to compression by an aneurysm. Management then would be: if the pupil is spared, presume there is an infarct and observe; if the pupil is involved, presume there is an aneurysm and perform imaging.

This rule was first proposed in an era where computed tomography angiography (CTA) and magnetic resonance angiography (MRA) were not available and direct angiography had a risk of stroke in elderly vasculopathic patients. Trobe in an editorial in 1988 suggests some constraints to the above rule.[1]

1. This rule may not be valid for young patients (40-50 years) without vascular risk factors. In this group even if the pupil is spared, the chance of an aneurysm is relatively high. Below 20 years of age aneurysms are very rare and imaging may not be necessary.
2. This rule is not valid if the extraocular muscle palsy is not complete. In them, even if the pupil is spared an aneurysm is possible. Frequent observation of these patients is needed to identify development of pupil involvement.

If the oculomotor palsy is sudden and isolated, it should be categorized into three clinical patterns:

1. Complete external ophthalmoplegia with normal pupil,
2. Incomplete external ophthalmoplegia with normal pupil, and
3. Complete or partial external ophthalmoplegia with dilated pupil.

When evaluating a patient with a TNP, it is important to establish whether it is isolated or whether other cranial nerves are involved, and whether there are any other neurological symptoms/signs not attributable to a TNP such as hemiparesis, ataxia, tremor, and gait disturbance. Oculomotor dysfunction may result from many causes including microvascular ischaemia, aneurysm, head trauma amongst others.

The fascicles of the third nerve exit the midbrain ventrally between the posterior cerebral artery superiorly and the superior cerebellar artery inferiorly, and travels in the subarachnoid space parallel and below the posterior communicating artery until it pierces the dura and enters the cavernous sinus. Parasympathetic fibers are located on the outer aspect of the nerve with somatic fibers traveling deeper within the nerve. The subarachnoid space is the most common anatomic location of injury to the third nerve. It is in this segment that it is vulnerable to compression, most commonly by an aneurysm arising from the junction of the internal carotid and posterior communicating arteries. Despite advances in neuroimaging and neurosurgery, patients with subarachnoid hemorrhage produced by a ruptured aneurysm have a very high morbidity and mortality rate: 15% die before reaching the hospital with an additional 40% dying in the hospital while a third of survivors experience major neurological disability.[2] Thus, an unruptured cerebral aneurysm producing compressive TNP constitutes a life-threatening emergency. Even though only a small portion (10% to 15%) of patients with TNP will harbor an underlying aneurysm,[3,4] because the cost of missing it is so high, investigation of all patients with TNPs is focused on detecting an aneurysmal compressive lesion.

One cannot reliably differentiate ischaemic and compressive TNP based on the historical/examination findings and, thus, it is now a reasonably well accepted standard that all patients with TNPs should undergo noninvasive neuroimaging, which if performed using modern imaging techniques and interpreted by a neuroradiologist experienced in vascular imaging, should result in almost 100% sensitivity of detecting unruptured aneurysms.[5,6] Most posterior communicating artery aneurysms must be at least 4 mm to cause TNP and CTA and/or MRA should detect all aneurysms that are 3 mm or larger in diameter.[5-7]

Jacobson and Trobe explored the risk of harbouring an aneurysm in the setting of a negative MRA.[8] In a review, they found that most well-documented posterior communicating artery aneurysms causing third nerve palsies were 5 mm or larger in diameter, than less than 5 mm in diameter (91.3% vs. 8.7%). Furthermore, when compared with catheter angiography, MRA was able to pick up nearly all aneurysms 5 mm or larger in diameter versus <5 mm in diameter (97% vs. 53.6%). A mathematical interpretation of the data suggested that a properly performed and interpreted MRA will overlook only 1.5% of aneurysms which cause TNP that will go on to rupture during the next 8 years, if untreated. Clinical follow-up can suggest an undetected enlarging aneurysm in patients who fail to recover or begin to develop signs of aberrant regeneration. The advent of CTA and higher resolution MRA techniques is likely to have resulted in greater sensitivity for detecting small aneurysms.

Pupil-sparing third nerve palsy

The term pupil-sparing should be reserved for situations in which there is normal pupillary function but *complete* loss of eyelid and ocular motor (somatic) functions of the third nerve. This is the typical finding of an ischaemic cranial neuropathy, often associated with pain, which improves (and usually fully resolves) within 3 months.

A complete TNP with sparing of the pupil is almost always benign and secondary to microvascular disease, often associated with diabetes, hypertension, and/or hyperlipidemia. It is not uncommon, however, for the pupil to react normally and for there to be only minimal impairment of levator palpebrae and extraocular function (a partial third nerve palsy). Although the pupil is normal in this scenario, it should not be considered in the same category as pupil-sparing with otherwise complete oculomotor paresis, given that many other fibres within the third cranial nerve are also “spared”. This distinction is crucial given that some proportion of partial TNP with normal pupillary function are related to compressive lesions and may later progress to involve the pupil. Management of a partial third nerve palsy without pupillary involvement must be individualized based on the demographics, presence of vascular risk factors, and the availability of accurate non-invasive imaging modalities. Some clinicians favour non-invasive imaging; others advocate close, frequent observation for 7-10 days. An aneurysm should be suspected even with a seemingly benign pupil-sparing TNP if the patient is within the high-risk age for developing an aneurysm (between 20 and 50 years) and does not have diabetes mellitus or other vascular risk factors (Box 1).

Box 1. Neuroimaging is recommended

- If aged less than 50 years
- If the pupil is involved
- Pupil sparing partial third nerve palsy
- History of any cancer at any time
- Any other associated signs or symptoms
- If not started to improve after 1 month
- If not resolved fully after 3 months

Conversely, a patient who presents only with efferent pupillary dysfunction (i.e. the pupil is dilated and responds poorly to light) and who has normal eyelid and extraocular muscle function, almost always has a benign disorder. Such isolated pupillary involvement is not due to a third nerve palsy but rather a tonic (Adie) pupil, a pharmacologically dilated pupil, or a pupil that is mechanically damaged (as may occur with posterior synechiae).

The presence of head and periorbital pain is not helpful in establishing the cause of the third nerve palsy. Although most third nerve palsies caused by aneurysms present with pain, many vasculopathic palsies also produce pain that, in some cases, may be intense. In older adults, vasculitis (e.g. giant cell arteritis) must also be considered.

An acute, isolated, pupil-sparing but otherwise complete third nerve palsy in a patient over 50 years with appropriate vascular risk factors does not necessarily require neuroimaging but should prompt a general medical evaluation, with attention to serum glucose levels, systemic blood pressure, serum lipids, and sedimentation rate. If progression occurs, if other cranial neuropathies develop, or if the expected recovery does not ensue within 3 months, then neuroimaging should be performed to search for a mass or infiltrative lesion at the base of the skull or within the cavernous sinus. Occasionally, scans need to be repeated to discover a mass, especially if it is contained within the cavernous sinus. Lumbar puncture may be needed to detect carcinomatous meningitis, inflammation, or infection.[9]

Management of the clinical vignette

- This patient's findings suggest a partial TNP.
- The current recommendations for the management of any patient with an acute onset of TNP is straight-forward: the recommendation in this situation is to proceed directly to a non-invasive neuroimaging study.
- CTA is the imaging modality of choice as it is slightly more sensitive than MRA in detecting small aneurysms, it is quick to perform and more readily available.
- However, it is important that this study is interpreted by an experienced neuroradiologist. If this study is negative the chance of missing an aneurysmal compression of the third nerve is exceedingly small.
- If CTA is normal and the patient is 50 years or older with vascular risk factors, it is reasonable to observe the patient for 2 to 3 months with the presumptive diagnosis of microvascular TNP.
- If microvascular TNP is unlikely, magnetic resonance imaging (MRI) with MRA is the appropriate next step to image the course of the third nerve to exclude other causes.
- If MRI is normal, consider neuromuscular junction disorders (most commonly myasthenia gravis).

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