LEARNING OBJECTIVES

1. To point out that clinical features are not adequate to exclude an aneurismal cause of isolated third cranial nerve palsy.

2. To point out that computed tomographic angiography (CTA) is now the preferred method of emergently ruling out an intracranial aneurysm as the cause of third cranial nerve palsy except in children and pregnant women, in whom magnetic resonance angiography (MRA) is the preferred method.

3. To point out that these methods are reliable only if they interpreted by physicians with adequate training and experience in neuroradiology and that such expertise may not be available in non–tertiary care medical centers. For that reason, CTA and MRA studies performed in non–tertiary care settings for this indication may have to be reviewed by experts before an aneurysm can be excluded and before patients undergo the more invasive and dangerous catheter angiography.

CME QUESTIONS

1. Which of the following sets of clinical findings would indicate the need for emergent intracranial vascular imaging?
   a. Fixed, dilated pupil, complete ptosis, complete adduction, supraduction, and infraduction palsies.
   b. Isocoria with normally constricting pupil, partial ptosis, adduction, supraduction, and infraduction palsies.
   c. Slightly mydriatic and partially constricting pupil, complete ptosis, complete adduction, supraduction, and infraduction palsies.
   d. All of the above.

2. Which of the following intracranial vascular imaging studies is preferred for the emergent evaluation of acute, isolated third cranial palsy in non–pregnant adults?
   a. Computed tomographic angiography (CTA)
   b. Magnetic resonance angiography (MRA)
   c. Digital subtraction angiography (DSA)

3. In a patient with an acute, isolated third nerve palsy who has undergone a reportedly “negative” CTA or MRA in a community (non–tertiary care) hospital, the recommended approach by the neuro-ophthalmologist is:
   a. Perform DSA
   b. Repeat CTA (MRA) with higher contrast dye injection
   c. Have the CTA (MRA) reviewed by a neuroradiologist

KEY WORDS

1. Third nerve palsy
2. Intracranial aneurysm
3. Intracranial vascular imaging
4. Computed tomographic angiography
5. Magnetic resonance angiography

ABSTRACT

Although intracranial aneurysms are an uncommon cause of isolated third nerve palsy, they must be promptly identified in order to prevent rupture with dire consequences. Clinical features—patient age, arteriosclerotic risk factors, pain, and ophthalmic findings—are not reliable in excluding aneurysms, so that all patients should undergo emergent computed tomographic angiography (CTA). CTA is now viewed to be as accurate as magnetic resonance angiography (MRA) and as reliable and safer than routine digital subtraction angiography (DSA) for detecting aneurysms greater than 3–4mm in size. To avoid the heavy radiation exposure of CTA, children and pregnant women should undergo MRA as the first procedure. If CTA produces equivocal results, then MRA should be performed if a non–invasive approach is desired. If there is a continued high suspicion of aneurysm, then 3D rotational DSA should be performed. If CTA is unequivocally negative, MRI should be performed to exclude a non–aneurysmal cause if clinical features do not support a microvascular ischemic cause. There is reason to doubt whether CTA (or MRA) as currently performed and interpreted in non–tertiary care medical centers is adequate to exclude aneurysms causing third nerve palsy. Therefore, patients with third nerve palsies and negative non–invasive intracranial vascular imaging in
whom the clinical suspicion of aneurysm is high should be referred promptly to a tertiary care center for review of the non–invasive studies prior to undergoing catheter angiography.

THE CHALLENGE
In the presence of a new-onset, non–traumatic isolated third cranial nerve palsy, the detection of a berry aneurysm compressing the nerve is the paramount concern. When the patient has normal consciousness, the development of such a palsy is not usually a sign that the aneurysm has ruptured and bled, but that it has recently expanded to compress the adjacent third nerve. Recent expansion often foretells imminent rupture with subarachnoid hemorrhage—within days, even hours. Rupture carries 66% mortality and, at best, serious neurologic morbidity arising chiefly from vasospasm and secondary stroke, as well as the consequences of having to repair an aneurysm under difficult circumstances.

On the other hand, repair of an expanding but unruptured aneurysm, whether by surgical or endovascular methods, has a high chance of restoring the patient to normal neurologic health. Hence, there is a premium on finding it before it ruptures. Where else does a physician have an opportunity to make such a difference?

THE ANEURYSM
Berry aneurysms that cause isolated third cranial nerve palsies are usually situated at the junction of the supraclinoid internal carotid and posterior communicating arteries (ICA–PComA) or, less commonly, at the junction of the basilar and posterior cerebral artery (BA–PCA) or superior cerebellar artery (BA–SCA). The relative prevalence of these aneurysms as a cause of non–traumatic isolated third cranial nerve palsy is not well documented because reported series are undoubtedly biased by accrual in tertiary care centers. The reported series in adults suggest a proportion as high as 56%, but those of us who have examined many patients with isolated third nerve palsy know that the proportion is likely to be much, much lower—probably less than 10%. The most common cause in adults is microvascular ischemia, probably accounting for more than 90% of cases. The other non–aneurysmal causes—inflammation, neoplastic infiltration, non–aneurysmal compression—are exceedingly rare.

THE ARGUMENT
But even if aneurysm is a rare cause of third nerve palsy, excluding it is of prime importance. In that process, how much help do we get from clinical features? Not enough.

The Rule of the Pupil states that third cranial nerve palsies that "involve the pupil" (cripple the iris sphincter) are often aneurysms and that those that "spare the pupil" (leave the sphincter intact) are rarely aneurysms. This Rule is not reliable enough in deciding which patients need imaging. When imaging meant catheter angiography with its attendant risks, we fussed over how to modify The Rule to help us determine who did and did not need catheter angiography. Now that we possess non–invasive methods of sensitively imaging cerebral aneurysms, everyone with a new non–traumatic, isolated third nerve palsy—even those in whom the risk of aneurysm appears low—should undergo a prompt non–invasive intracranial imaging study. In adults, that study should be a computed tomography angiogram (CTA). In children and pregnant women, it should be a magnetic resonance angiogram (MRA). The clinical features (patient age, presence of arteriosclerotic risk factors, degree of ophthalmoplegia and mydriasis) that we formerly used to determine who should undergo catheter angiography should now determine how much scrutiny is applied to a reported “negative” non–invasive imaging study. The critical unresolved issue, of course, is whether the quality and interpretation of the non–invasive study is adequate to rule out an aneurysm. There is evidence, mostly anecdotal, that radiologists without special training and experience in detecting intracranial aneurysms will overlook those that cause third nerve palsies. For this reason, it may be advisable to have a “negative” non–invasive study reviewed at a tertiary care center before the diagnosis is dismissed or before the patient undergoes a catheter cerebral angiogram.

CLINICAL INDICATORS
Clinical features can shade the index of suspicion of an aneurysm, but are not reliable enough to exclude it.

Age. Berry aneurysms become clinically manifest between ages 20 and 60—an enormous age span. Younger and older people do not show manifestations very often, but there are plenty of reports of aneurysm at the extremes of age.

Arteriosclerotic risk factors. Because microvascular ischemia is such a predominant cause of isolated third nerve palsy in adults, and because this condition is nearly always associated with hypertension, diabetes, and other conventional risk factors, clinicians often tote up these factors in deciding whether aneurysm can be dismissed as a cause. But patients with arteriosclerosis can also have aneurysms, and there is evidence that berry aneurysms expand—and may become manifest—when arteries are battered by hypertension, diabetes, cholesterol, and other factors associated with arteriosclerosis.

Pain. Headache and periocular pain are reported in as few as 30% of patients with aneurysmal third nerve palsy, making it impossible to exclude aneurysm in the absence of pain. Pain excruciating enough to overshadow the ptosis and diplopia is present in at least 50% of patients with ischemic third nerve palsy, further diminishing its usefulness as a discriminator.

Ophthalmoplegia, ptosis, and the pupil. The relationship between the degree of impairment of somatic (external)
and parasympathetic (internal) motor functions has been the focus of debate about how to predict the likelihood of aneurysm in third nerve palsy. The bottom line is that aneurysms are likely to “involve” the pupil, but not reliably enough to exclude aneurysm if the pupil is “spared.” Pupil-sparing is especially apt to be present with compressive aneurysms if the ophthalmoplegia is incomplete, and particularly if the inferior division of the third cranial nerve is spared. Pupil involvement occurs in as many as 20% of patients with ischemic third nerve palsies, but anisocoria of more than 1.5 mm is exceedingly rare. (By the way, everyone knows—or ought to know—that isolated mydriasis and ptosis are not caused by aneurysm. Those findings do not merit vascular imaging!)

Time course of ophthalmic manifestations. Although expansion of an aneurysm usually produces acute manifestations, subacute, and even chronic clinical evolution is well documented.

IMAGING

The only reasons not to perform intracranial vascular imaging are: 1) the study results would not alter management; 2) the study is unacceptably hazardous; and 3) the study is unreliable.

Altering management. The argument that brain imaging results would not alter management in patients with unruptured but symptomatic aneurysms applies only to elderly ill patients who would not tolerate intervention or to patients who would refuse it. With the advent of endovascular aneurysm techniques, which carry lower morbidity than surgery and offer an alternative for poor surgical candidates, that argument has become “inoperative.”

Hazards. The hazards of CTA stem from radiation exposure and contrast load. Under most circumstances, those hazards can be justified, except in children and pregnant women. The hazards of MRA are essentially nonexistent, as the preferred study sequence (time-of-flight, TOF) does not require intravenous contrast. DSA, the “gold standard” for imaging intracranial aneurysms, carries a risk of stroke of up to 2%, a proportion that may be higher in older patients with arteriosclerosis. The greater contrast load of DSA—approximately twice that used for CTA—may be hazardous in older patients and in those with impaired renal function. Therefore, DSA is now reserved for patients in whom CTA or MRA has produced equivocal results. It can also be justified for patients in whom CTA or MRA is negative, but in whom clinical features propound a very high suspicion of aneurysm.

Sensitivity and specificity. As compared to DSA, CTA and MRA are highly and equally sensitive in diagnosing intracranial aneurysms—upwards of 95%—if the aneurysm is 3 mm in diameter or larger. There is now ample evidence that nearly all aneurysms that produce third nerve palsy are at least 4 mm in diameter, so they should be evident on CTA or MRA. With the development of the multi-slice detector CTA and refined post-processing, most radiologists are supporting this modality over MRA as the first choice in the evaluation of intracranial aneurysms (except in children and pregnant women) due to its speed of acquisition and immunity to signal loss artifacts related to low or turbulent flow and in-plane dephasing that occurs with TOF MRA. The specificity of CTA and MRA for intracranial aneurysm is acceptably low and DSA will usually resolve the false positives.

However, the sensitivity of CTA and MRA in the detection of intracranial aneurysms critically depends on the following factors: 1) Is the image acquisition adequate? 2) Is the post processing adequate? and 3) Do the interpreters of the studies have enough skill and/or experience to recognize an aneurysm at the appropriate locations?

1) Image acquisition. There are no published guidelines on the minimum standards for imaging acquisition in the detection of aneurysms. At our institution, neuroradiologists recommend that CTA images be acquired at no larger than 1.25 mm slice thickness. Appropriate MRA acquisition involves balancing complex variables in addition to slice thickness less than 1 mm such as field of view, matrix size, and scan times. 3T field strength provides better detection ability. For DSA, 3D rotational techniques are advised. There are no published data on how often or to what degree these standards are being followed.

2) Post–processing. There are no published guidelines on post–processing standards. At our institution, neuroradiologists recommend that CTA images be post processed in axial, coronal, and sagittal reformatted planes utilizing less than 3 mm non–gapped reconstructions. MRA studies should be reviewed using raw axial acquisitions and maximum intensity projections. There are no published data on how often post–processing standards are being followed.

3) Interpretation. Here’s the rub. The sensitivity studies are all reported from tertiary care centers where neuroradiologists are experienced in interpreting intracranial vascular imaging. One very small study compared the ability of general radiologists and neuroradiologists in the detection of aneurysm and found neuroradiologists to be more sensitive. That study cautioned that there are many confounders on intracranial vascular imaging, especially for aneurysms at the skull base, and that sensitivity for aneurysms of <5 mm diameter was no better than 60% for relatively small aneurysms even by neuroradiologists. In a study comparing interpretation of head and neck cancer patient images by neuroradiologists and general radiologists, a change in the interpretation occurred in 42% of cases, leading to substantial alteration in management. There are no published data on what proportion of intracranial imaging studies are being interpreted by general radiologists, who have received an average of 4–6 months’ exposure to neuroradiology in residency training, during which they probably saw at most 10–20 aneurysms.
CONCLUSIONS

The overall probability that an aneurysm is causing isolated non-traumatic third nerve palsy is low. Even so, the clinician’s paramount concern is to exclude it before it ruptures and causes morbidity and mortality. Treatment of an unruptured aneurysm is a relatively low-risk procedure, especially with endovascular techniques, and is effective in preventing rupture.

Clinical features of a third nerve palsy do not provide adequate criteria to exclude aneurysm. Advances in CTA and MRA have progressed to the point that they are as sensitive (and almost as specific) as routine DSA in identifying aneurysms responsible for third nerve palsy and with fewer hazards than DSA. CTA is the preferred emergent imaging modality because it is widely available and can be done quickly without excessive hazard. Therefore, every non-pregnant adult patient with an isolated third cranial nerve palsy should undergo emergent CTA. In children and pregnant women, MRA is the first choice. If the CTA result is equivocal, then DSA, preferably in the 3D rotational mode, should be performed if there is a high clinical suspicion of aneurysm. If CTA is unequivocally negative, MRI should be performed to exclude a non-aneurysmal cause if clinical features do not support a diagnosis of microvascular ischemia.

There is anecdotal evidence that radiologists in non–tertiary care medical centers may overlook intracranial aneurysms in patients with third nerve palsies. Therefore, patients who have a “negative” CTA (or MRA) in whom the clinical suspicion of aneurysm is high should have the non–invasive study reviewed at a tertiary care center before the diagnosis of aneurysm is dismissed or before undergoing catheter angiography.

PREFERRED ANSWERS

1. d
2. a
3. c

REFERENCES

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