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Clinical Pearls in Neurology

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See end of article for correct answers to questions.

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At the 2001 Annual Conference of the American College of Physicians, a new teaching format to aid physician learning, Clinical Pearls, was introduced. Clinical Pearls is designed with the 3 qualities of physician-learners in mind. First, we physicians enjoy learning from cases. Second, we like concise, practical points that we can use in our practice. Finally, we take pleasure in problem solving.

In the Clinical Pearls format, speakers present a number of short cases in their specialty to a general internal medicine audience. Each case is followed by a multiple-choice question answered live by attendees using an audience response system. The answer distribution is shown to attendees. The correct answer is then displayed and the speaker discusses teaching points, clarifying why one answer is most appropriate. Each case presentation ends with a Clinical Pearl, defined as a practical teaching point that is supported by the literature but generally not well known to most internists.

Clinical Pearls is currently one of the most popular sessions at the American College of Physicians meeting. As a service to its readers, *Mayo Clinic Proceedings* has invited a selected number of these Clinical Pearl presentations to be published in our Concise Reviews for Clinicians section. "Clinical Pearls in Neurology" is one of them.

CASE 1

A 70-year-old man with a history of smoking and hypertension is seen in urgent care 3 hours after awakening with first-ever acute vertigo, vomiting, and imbalance in the absence of headache or other focal neurologic or otologic symptoms. Vertigo persists even while sitting upright with his head still. He is unable to walk unassisted due to ataxia.

Question

Which physical examination test is *most useful* in this setting to differentiate between acute vestibular neuritis and cerebellar infarction?

a. Head impulse test (HIT)
b. Dix-Hallpike test
c. Cover testing for skew deviation
d. Romberg test
e. Examination for Babinski sign

Discussion

Distinguishing an acute peripheral vestibulopathy (vestibular neuritis) from a posterior circulation infarction in the acutely vertiginous patient is challenging. Focal neurologic signs are often lacking in cerebellar infarction. Proper management differs widely between the 2 conditions, and computed tomography has poor sensitivity for brainstem and cerebellar ischemic strokes in the acute setting. The Dix-Hallpike test is used specifically to test for benign paroxysmal positional vertigo (BPPV), which is unlikely in this case given the persisting vertigo while sitting still. Romberg test may be abnormal in both conditions (although patients with cerebellar infarction may have such severe truncal ataxia as to be unable to sit or stand), and the Babinski sign would be absent in both. Fortunately, several features elicited on bedside examination have been found to be very useful for distinguishing benign from dangerous causes of acute vertigo (Supplemental Table, available online at http://www.mayoclinicproceedings.org).

The head impulse test is a simple bedside examination technique to evaluate the integrity of the vestibulo-ocular reflex (VOR) generated from stimulating each horizontal semicircular canal.[1] With the patient watching the examiner's nose, the examiner very rapidly rotates the patient's head 15 degrees to one side and watches to see if the VOR is able to keep the eyes fixed on the examiner's nose. In a peripheral vestibulopathy, rapid rotation toward the side of the lesion does not generate a sufficient VOR to keep the eyes on target, and a small "catch-up" saccadic (fast) eye movement will be required immediately after the head rotation to refixate on the target (Supplemental Video 1, available online at http://www.mayoclinicproceedings.org). However, acute vertigo from a cerebellar infarction spares the VOR and results in a normal HIT. In addition, skew deviation (supranuclear vertical eye misalignment) can be assessed at the bedside with alternate cover testing and is a specific but quite insensitive marker for brainstem or cerebellar lesions in acute vertigo. Finally, spontaneous nystagmus direction reflects the origin of the vertigo: Acute peripheral vestibulopathy produces unidirectional horizontal nystagmus with quick phases beating away from the side of the lesion, whereas central lesions may cause direction-changing gaze-evoked nystagmus and/or dominantly vertical or torsional spontaneous nystagmus. The combination of these 3 examination findings (HIT, skew deviation, and spontaneous nystagmus direction) appears to be more sensitive than diffusion-weighted magnetic resonance imaging (MRI) in acute vertigo.[2]

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Clinical Pearl

The HIT is the most sensitive and specific bedside test for distinguishing central from peripheral causes in the acute vestibular syndrome when other focal neurologic or otologic findings are lacking.

CASE 2

A 66-year-old woman is seen for evaluation of a 3-week history of positional vertigo episodes. Symptoms began 2 days after bumping her head under a counter. Since then, she may experience 20-second-long episodes of vertigo upon rolling over in bed or first sitting up in the morning, and she feels unsteady making quick head turns while walking. She has no history of vertigo or other neurologic symptoms. Examination is normal. Dix-Hallpike test is negative bilaterally, without producing any vertigo or nystagmus.

Question

What should be the *next step* in evaluation or management?

a. Vestibular function testing
b. MRI of the brain and internal auditory canals
c. Testing for horizontal canal BPPV (hc-BPPV)
d. Epley maneuver
e. Meclizine and reassurance

Discussion

The patient's history strongly suggests BPPV, the most common vestibular disorder with a cumulative incidence of nearly 10% by age 80 years.[3] Benign paroxysmal positional vertigo is caused by dislodged otoconia from the labyrinthine utricle that float into a semicircular canal and render it abnormally excited by changes in head position with respect to gravity. Few conditions other than BPPV cause brief, purely positional episodes of isolated vertigo. Cerebellar or craniocervical junction abnormalities can cause positional nystagmus that is typically purely vertical or torsional, persists for the duration that the head position is maintained, and does not produce severe vertiginous symptoms.

Benign paroxysmal positional vertigo affecting the posterior semicircular canal (pc-BPPV) occurs in 85% of patients, causing a transient mixed upbeat/torsional nystagmus on the Dix-Hallpike test. Once the affected side is determined, it can be treated effectively with the Epley canalith repositioning procedure. About 10% of BPPV affects the horizontal canal (hc-BPPV). Symptoms are essentially identical to those of pc-BPPV, so it should be suspected with the typical history when Dix-Hallpike test is negative. A supine roll test (Supplemental Figure, available online at http://www.mayoclinicproceedings.org)[4,5] should be performed from the supine position by turning the head 90 degrees to the right and then to the left. Nystagmus elicited in hc-BPPV is horizontal and changes direction depending on which ear is down. Most commonly, the horizontal nystagmus beats toward the ground (geotropic) with the head to either side, and the strongest nystagmus occurs with the affected ear down. If all positional testing results are negative but the history suggests BPPV, it is more useful to repeat positional testing another day than to order an MRI.

Several treatment options exist for hc-BPPV, the simplest of which is the Lempert (barbecue roll) maneuver[4]: With the patient supine and the affected ear down, the head (and body as required) is rotated in 90-degree increments toward the healthy side, holding each position for 10 to 30 seconds, until the patient makes a full circle with the affected ear down again. The patient is then simultaneously returned to supine face up and rapidly sat up. Like the Epley maneuver for the posterior canal, the concept is to move the head in such a way as to liberate the otoconia from the canal back into the utricle.

Clinical Pearl

Horizontal canal BPPV is less common than pc-BPPV but is also treatable with a simple repositioning maneuver in the office.

CASE 3

A 41-year-old woman sees you for a 3-year history of spontaneous episodes consisting of vertigo, nausea, vomiting, and imbalance, each lasting hours to a few days. She has had a total of 10 attacks and reports a concurrent headache with 3 of them; she usually has associated photophobia. Sometimes the episodes seem triggered by missed meals, stress, or menses. She feels well between attacks. You elicit a lifelong history of motion sickness and a 20-year history of occasional migraine headaches without aura. Her grandmother had Ménière disease, and 2 family members have migraine.

Question

What is the *most likely* cause of this patient's recurrent spontaneous episodes of vertigo?

a. Vestibular migraine (VM)
b. Ménière disease
c. Vertebrobasilar insufficiency
d. Superior canal dehiscence syndrome
e. Basilar-type migraine

Discussion

Ménière disease is a condition producing attacks of vertigo, tinnitus, fluctuating ipsilateral hearing loss, and aural fullness typically lasting 2 to 3 hours and is

thought to result from distortion of the membranous labyrinth leading to endolymphatic hydrops. The absence of auditory symptoms and the history of some episodes lasting for days would make Meniere disease unlikely in this case. Vertebrobasilar insufficiency would be an unlikely cause of episodes lasting hours to days and recurring over years. Superior canal dehiscence syndrome is an uncommon condition in which dehiscence of the thin petrous bone separating the roof of the superior semicircular canal from the middle cranial fossa leads to sound- and pressure-induced auditory and vestibular symptoms. Manifestations may include brief episodes of noise- or Valsalva maneuver–induced vertigo, hyperacusis for bone-conducted sound (such as pulsatile tinnitus and hearing one's own voice loudly in the affected ear), and apparent conductive hearing loss on audiometry, none of which is present in this patient.

Vestibular migraine (or migrainous vertigo) is the most common cause of recurrent spontaneous episodes of vertigo, with a prevalence estimated at 1% in the general population.[6] Studies from tertiary dizziness clinics[7,8] have found that among patients who have chronic recurrent attacks of vertigo without otologic symptoms and no other cause for their symptoms, 61% to 87% are also migraine sufferers. Vestibular migraine affects predominantly women, peaks in the third to fifth decades, and is typically preceded by migraine headaches for years (although the headaches may be mild enough not to be mentioned by the patient). The pathophysiology of VM remains unclear but likely involves central and peripheral vestibular pathways. It is diagnosed by history (and typically normal examination findings), although tests may be needed to rule out other conditions. Diagnostic criteria include episodic vestibular symptoms of at least moderate severity in which migrainous symptoms (headache, photophobia, phonophobia, aura) accompany at least 2 attacks in a patient with a current or previous history of migraine.[9] Supporting features include vertigo precipitated by food triggers, sleep irregularities, or hormonal changes; strong family history of migraine; and reduction in attacks with migraine preventative medications. Less than 10% of VM patients meet criteria for basilar-type migraine, which requires 2 or more basilar-distribution neurologic symptoms lasting between 5 and 60 minutes. Although both VM and Meniere disease can cause vertigo lasting for hours, findings favoring VM include vertigo attacks also lasting a day or more and only minimal or bilateral aural symptoms with a normal audiogram.

Clinical Pearl

Vestibular migraine is a common but underdiagnosed cause of recurrent vertigo most commonly affecting young to middle-aged women. Diagnosed on clinical grounds, management typically begins with migraine preventive strategies similar to those for migraine headaches.

CASE 4

Your 62-year-old patient returns 1 month after neurologic consultation confirming your suspicion of idiopathic Parkinson disease (PD) causing new-onset asymmetric rest tremor, rigidity, bradykinesia, and a shuffling gait. A treatment regimen of carbidopa/levodopa, 25/100-mg tablets 3 times per day with meals, was initiated and has been titrated up to 2½ tablets per dose. Very little benefit has been noticed, however.

Question

What is the *most likely* cause of the poor medication response?

a. He should have been given controlled-release carbidopa/levodopa
b. He should be taking the carbidopa/levodopa on an empty stomach
c. He should titrate up to 3 tablets per dose
d. A dopamine agonist would be more potent
e. He has a different disorder such as multiple system atrophy or progressive supranuclear palsy

Discussion

In the absence of additional clinical features such as dementia, autonomic failure, or cerebellar ataxia, the presence of asymmetric parkinsonism with rest tremor suggests a diagnosis of idiopathic PD. Initial levodopa treatment is the most efficacious therapy, and a good clinical response to a proper trial provides confirmatory diagnostic evidence for idiopathic PD.

When levodopa was introduced in the 1960s, nausea and vomiting were frequent problems due to premature conversion of levodopa to dopamine outside the brain, which then stimulates the brainstem chemoreceptor trigger zone to cause nausea. Taking levodopa with food helped reduce nausea. Unfortunately, if taken with food, levodopa must compete with other ingested large neutral amino acids to cross the intestinal mucosa and blood-brain barrier via saturable transport mechanisms, leading to reduced bioavailability of the medication.[10] The addition of carbidopa to levodopa formulations in 1973 reduced peripheral conversion of levodopa to dopamine and greatly improved tolerability. The tradename Sinemet is derived from *sin* (Latin), meaning *without*, and *emet* (Greek), meaning *emesis*. Still, well-meaning pharmacists may instruct patients to take it with food. Carbidopa/levodopa is best started as 25/100-mg immediate-release (yellow) tablets in 3 doses, each given 1 hour before meals or 2 hours

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www.mayoclinicproceedings.org

after meals. Each dose is titrated from one-half or 1 tablet in half-tablet increments up to 3 tablets based on clinical benefit, which is typically seen at 400 to 800 mg/d of levodopa.[11] Individual doses above 3 tablets have little added benefit and are more likely to cause peak-dose dyskinesias. If nausea develops, it is usually mild, resolves with continued administration, and can be countered with soda crackers (low protein) eaten with each dose. Most newly treated patients do not have short-duration responses or clinical fluctuations with this regimen. Immediate-release carbidopa/levodopa is also substantially cheaper than any alternative.

Clinical Pearl

Carbidopa/levodopa should be taken on an empty stomach to maximize absorption and bioavailability. If nausea develops, it is usually mild, transient, and countered by eating a few soda crackers.

CASE 5

A healthy 32-year-old woman with a 1-year history of increasingly frequent episodic unilateral headaches associated with nausea, photophobia, and phonophobia is evaluated in the clinic between headaches. Neurologic examination is normal. She undergoes MRI and magnetic resonance angiography (MRA) of the head, which demonstrate a 4-mm saccular aneurysm at the junction of the internal carotid and ophthalmic arteries. There is no known personal or family history of ruptured or unruptured aneurysms.

Question

What are the *most appropriate* interpretation and course of action at this time?

a. Headaches are migraines. Aneurysm is incidental. No further action required
b. Enlarging aneurysm is likely causing headaches. Emergent coiling/clipping is needed
c. Aneurysm is incidental, but rupture risk is high. Needs urgent intervention
d. Rupture risk is 10% in the next 6 months. Obtain prompt cerebrovascular consultation
e. Rupture risk is extremely low. Reassure patient. Routine cerebrovascular consultation to consider options and surveillance

Discussion

Intracranial aneurysms are acquired lesions at intracranial arterial branching sites. About 2% of the general population or 3 to 6 million Americans harbor intracranial aneurysms, which are increasingly detected with routine use of advanced neuroimaging. About 25,000 aneurysmal subarachnoid hemorrhages occur each year in the United States, so most aneurysms do not rupture; however, the case fatality rate from rupture is 30% to 40%. Women have aneurysms 3 times as commonly as men. Patients with coarctation of the aorta or adult polycystic kidney disease have a prevalence of 10% and should be screened with MRA.

Rupture risk is most closely linked to aneurysm size and location, although smoking, hypertension, and a personal or family history of subarachnoid hemorrhage also increases rupture risk. Fortunately, aneurysms most commonly affect the anterior circulation (internal carotid, middle or anterior cerebral arteries) and are less than 7 mm in size, both features associated with an extremely low rupture rate.[12] The 5-year cumulative rupture rate for anterior circulation aneurysms smaller than 7 mm is nearly 0%. However, a 7- to 12-mm posterior cerebral or vertebrobasilar aneurysm has a 14.5% 5-year rupture rate. Thus, this woman with migraine can be reassured, queried for conditions or family history that would increase rupture risk, and referred routinely for cerebrovascular evaluation. Follow-up imaging is typically performed at 6 months and then yearly for 3 years since 5% to 10% of aneurysms will grow during this time, especially if they are larger when first detected (83% if over 12 mm).[13] Younger patients with posterior circulation aneurysms or aneurysms smaller than 7 mm may be candidates for treatment with coiling or clipping, whereas risks and benefits must be more carefully weighed in older patients.

Clinical Pearl

Intracranial aneurysm rupture rates are exceedingly low with asymptomatic aneurysms smaller than 7 mm affecting the anterior circulation. Larger size and posterior location as well as personal and family risk factors increase the rupture rate.

CASE 6

You are seeing a 58-year-old woman in the clinic because she awoke that morning with complete left-side ptosis. She had complained of dull left orbital pain the day before. Her history is significant for migraines, hypertension, and diabetes mellitus. Examination reveals complete left-side ptosis, 2 mm of anisocoria (left pupil larger than right), and impaired left ocular motility. She cannot adduct the eye past the primary position, has impaired upgaze, and develops intorsion on attempted downgaze (Supplemental Videos 2 and 3, available online at http://www.mayoclinicproceedings.org). The rest of the examation findings are normal.

Question

What are the *most likely* diagnosis and *best* next step?

a. Ophthalmoplegic migraine; sumatriptan
b. Isolated third cranial nerve palsy; angiography
c. Ischemic fourth cranial nerve palsy; erythrocyte sedimentation rate
d. Myasthenia gravis; refer for edrophonium test
e. Dorsal midbrain infarction; MRI with diffusion-weighted imaging

Discussion

The patient has an acute, isolated, complete third (oculomotor) cranial nerve palsy. The third cranial nerve travels from the midbrain to the orbit to innervate the superior, inferior, and medial recti, the inferior oblique, levator palpebrae, and the iris sphincter and ciliary muscles of the lens. Abduction from the lateral rectus (abducens nerve) is intact. Intorsion on downgaze implies preserved superior oblique (fourth cranial nerve) function. Although myasthenia gravis can mimic virtually any ocular motor palsy, its onset is rarely so acute, unilateral, and specific for third cranial nerve–innervated muscles (and the pupil is unaffected in myasthenia gravis). Ophthalmoplegic migraine most commonly affects the third cranial nerve but is rare, typically preceded by prolonged migraine headache, and mainly affects children.

An enlarging posterior communicating artery aneurysm is the dreaded and presumed cause of an acquired isolated third cranial nerve palsy until proven otherwise. Since microvascular ischemia within the third cranial nerve is a more common cause in older patients with vascular risk factors, the "rule of the pupil" traditionally helped predict the likelihood of an aneurysm. Because the pupillomotor fibers sit on the surface of the nerve, a compressive aneurysmal third cranial nerve palsy would be expected to cause a dilated pupil. Thus, an otherwise *complete* isolated third cranial nerve palsy that *spared* the pupil was presumed to be ischemic. An erythrocyte sedimentation rate (to rule out giant cell arteritis) and serum glucose level were determined, and the patient could be closely observed for expected recovery within 8 to 12 weeks. The footnote to the rule was that if there was *incomplete* ptosis or ophthalmoparesis, a normal pupil provides no reassurance against an aneurysm. Given the risks of catheter cerebral angiography, this rule has proved useful in guiding selection of those who need angiography.

Unfortunately, clinical features do not allow perfect guidance on the aneurysm risk. The presence of headache or orbital pain is nonspecific. Up to 20% of patients with microvascular ischemic third cranial nerve palsy have anisocoria, but rarely more than 1.5 mm difference. Although microvascular ischemia is much more likely in a pupil-*sparing* complete third cranial nerve palsy, the high morbidity of an enlarging symptomatic aneurysm and imperfect discrimination on clinical grounds support some neuroimaging in all acquired isolated third cranial nerve palsies, regardless of pupil status, especially in patients younger than age 50 years. Fortunately, given the continued improvements in computed tomographic angiography (CTA) and MRA at detecting clinically relevant aneurysms smaller than 4 mm,[14] experts now generally recommend prompt CTA or MRA in virtually all patients with acquired isolated third cranial nerve palsy.[15]

Clinical Pearl

When the pupil is affected in an acquired isolated third cranial nerve palsy, the risk of an enlarging aneurysm is high, and urgent vascular imaging is required, generally with cerebral angiography. Even when the pupil is spared, CTA or MRA are now generally recommended, given the high morbidity of aneurysmal rupture.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

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REFERENCES

1. Halmagyi GM, Curthoys IS. A clinical sign of canal paresis. *Arch Neurol*. 1988;45(7):737-739.
2. Kattah JC, Talkad AV, Wang DZ, Hsieh YH, Newman-Toker DE. HINTS to diagnose stroke in the acute vestibular syndrome: three-step bedside oculomotor examination more sensitive than early MRI diffusion-weighted imaging. *Stroke*. 2009;40(11):3504-3510.
3. von Brevern M, Radtke A, Lezius F, et al. Epidemiology of benign paroxysmal positional vertigo: a population based study. *J Neurol Neurosurg Psychiatry*. 2007;78(7):710-715.
4. Fife TD, Iverson DJ, Lempert T, et al; Quality Standards Subcommittee, American Academy of Neurology. Practice parameter: therapies for benign paroxysmal positional vertigo (an evidence-based review): a report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2008;70(22):2067-2074.
5. Baloh RW, Jacobson K, Honrubia V. Horizontal semicircular canal variant of benign positional vertigo. *Neurology*. 1993;43(12):2542-2549.
6. Neuhauser HK, Radtke A, von Brevern M, et al. Migrainous vertigo: prevalence and impact on quality of life. *Neurology*. 2006;67(6):1028-1033.
7. Lee H, Sohn SI, Jung DK, et al. Migraine and isolated recurrent vertigo of unknown cause. *Neurol Res*. 2002;24(7):663-665.

8. Cha YH, Lee H, Santell LS, Baloh RW. Association of benign recurrent vertigo and migraine in 208 patients. *Cephalagia*. 2009;29(5):550-555.
9. Neuhauser H, Lempert T. Vestibular migraine. *Neurol Clin*. 2009;27(2):379-391.
10. Contin M, Martinelli P. Pharmacokinetics of levodopa. *J Neurol*. 2010;257(suppl 2):S253-S261.
11. LeWitt PA. Levodopa for the treatment of Parkinson's disease. *N Engl J Med*. 2008;359(23):2468-2476.
12. Wiebers DO, Whisnant JP, Huston J III, et al; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;362(9378):103-110.
13. Burns JD, Huston J III, Layton KF, Piepgras DG, Brown RD Jr. Intracranial aneurysm enlargement on serial magnetic resonance angiography: frequency and risk factors. *Stroke*. 2009; 40(2):406-411.
14. Vaphiades MS, Cure J, Kline L. Management of intracranial aneurysm causing a third cranial nerve palsy: MRA, CTA or DSA? *Semin Ophthalmol*. 2008;23(3):143-150.
15. Trobe JD. Searching for brain aneurysm in third cranial nerve palsy. *J Neuroophthalmol*. 2009;29(3):171-173.

CORRECT ANSWERS: Case 1: a. Case 2: c. Case 3: a. Case 4: b. Case 5: e. Case 6: b.