Neuroimaging Correlates of False-Localizing Signs in Neurology and Neuro-Ophthalmology: An Educational Review

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BACKGROUND

Purpose
The implicit assumption that abnormal neurologic and neuro-ophthalmologic findings are signposts for particular lesions of the neuraxis is tainted by the existence of clinical 'mis-localizing' signs and symptoms, either as false-localizing signs (FLS), when local disturbances of function are distant from a neurologic lesion, or non-localizing signs, when clinical stigmata lack precise neuroanatomic correlation. The pathogenesis of FLSs is uncertain, but neuroimaging has three important clinical roles: FLSs may lead to inappropriate imaging in the first place; imaging can prevent surgical interventions in the wrong location; and more sophisticated neuroimaging techniques are necessary in the quest for accurate diagnosis to solve the dilemma of FLSs. Neuroradiologists should have a sound knowledge of clinically challenging FLSs, since accurate imaging interpretation may greatly contribute to clinical management.

Methods
We review clinical presentations, possible mechanisms, and neuroimaging correlates of numerous neurologic and neuro-ophthalmologic FLSs.

Findings
Neurologic FLSs most often occur in the context of raised ICP. Suggested mechanisms include mechanical distortion resulting in three FLS categories: motor deficits, cranial neuropathies, or spinal cord pathology. Motor system effects include Kernohan's notch syndrome, a hemiparesis FLS from a supratentorial mass causing transtentorial herniation and contralateral midbrain compression by the tentorial free edge above the pyramidal decussation. Frontocerebellar pathway damage, e.g. post ACA infarct, may result in an FLS 'cerebellar syndrome'. We also discuss FLSs manifesting as neuropathies affecting many of the cranial nerves. Notably, CN6 palsies are the most common FLS with raised ICP (in 14%). Spinal cord FLSs occur with lesions around foramen magnum or the lower cervical/upper thoracic cord resulting in distant myelopathies and radiculopathies. We also illustrate numerous other neuro-ophthalmologic FLSs, as seen in transient monocular visual loss, complex visual hallucinations, other ocular motility disturbances (divergence paresis, convergence insufficiency, and skew deviation), and the localizing pitfalls of anisocoria, including Horner and Raeder syndromes.

Summary
FLSs are clinical signs that violate the expected clinico-anatomical concordance on which clinical examination is predicated. This presentation will aid in identifying and understanding the imaging correlates of FLSs for improved patient management.

SIGNIFICANCE

James Stansfield Collier (1870 – 1935) first introduced the concept of false localizing signs in 1904 after review of 161 consecutive cases of intracranial tumors. He found that 20 of the 161 (12.4%) cases were associated with false localizing signs¹⁴.

Subsequent physicians, neurologists and neurosurgeons alike, observed other examples of false localizing signs based off their clinical exam and subsequent patient diagnoses. Historically the awareness of false localizing signs was important so as to prevent misdiagnosis, delayed treatment, or even incorrect/unnecessary therapies.

However the rapid advent of new technologies, including improved imaging studies, has demonstrated that many of the previously described false localizing signs are due to true underlying pathophysiology.

Many of the described false localizing signs are due to increased intracranial pressure, whether idiopathic, benign, or malignant in etiology. Increased intracranial pressure can cause distortion or disturbances of the cranial nerves, oftentimes related to compression of the brainstem. Other causes are related to underlying vasculopathy, including ischemic changes.

Awareness of how and why clinical symptoms may not be concordant with expected findings should aid in faster accurate diagnoses, improved imaging protocolling, and decreased patient anxiety.

REFERENCES

1. Zhang C.H. et al. Kernohan-Woltman notch phenomenon: a review article. *British Journal of Neurosurgery*. 2017;31(2):159-166.
2. Caballer M. et al. Kernohan-Woltman Notch Phenomenon Secondary to a Subdural Hematoma in a Young Man. *Clin Neuroradiol*. 2015;25:435-436.
3. Park J.M. and Kim J.H. False localizing sign caused by schwannoma in cervical spinal canal at C1-C2 level. *Medicine*. 2018;97:36(e12215).
4. Langfitt T.W. and Elliott F.A. Pain in the Back and Legs Caused by Cervical Spinal Cord Compression. *JAMA*. 1967;200(5):382-385.
5. Scott M. Lower extremity pain simulating sciatica: Tumors of the high thoracic and cervical cord as causes. *JAMA*. 1956;160:528-534.
6. Sonstein W.J. et al. False Localizing Signs in Upper Cervical Spinal Cord Compression. *Neurosurgery*. 1996;38(3):445-449.
7. Houten J.K. et al. Cervical Myelopathy without Symptoms in the Upper Extremities: Incidence and Presenting Characteristics. *World Neurosurgery*. 2019;132:e162-e168.
8. Hellman M.A. et al. Thoracic sensory level as a false localizing sign in cervical spinal cord and brain lesions. *Clinical Neurology and Neurosurgery*. 2013;115:54-46.
9. Laurence A.G. et al. Unilateral Fixed Dilation of the Pupil as a False-localizing Sign with Intracranial Hemorrhage: Case Report and Literature Review. *Neurosurgery*. 2001;49(5):1251-1256.
10. Broder J. A resume of the principal diagnostic features of subdural hematoma. *Bull NY Acad Med*. 1943;19:169-176.
11. Jefferson G. The tentorial pressure cone. *Arch Neurol Psychiatry*. 1938;40:857-876.
12. Ritter A.M. et al. Brain stem blood flow, pupillary response, and outcome in patients with severe head injuries. *Neurosurgery*. 1999;44:941-948.
13. Larner A.J. False localizing signs. *J Neurol Neurosurg Psychiatry*. 2003;74(4):415-418.
14. Collier J. The false localizing signs of intracranial tumour. *Brain*. 1904;27:490-508.
15. Furtado S.V., Mohan D., Hegde A.S. Ophthalmic segment aneurysmal subarachnoid hemorrhage presenting with contralateral abducens nerve palsy: A false localizing sign. *Optometry*. 2010;81:450-453.
16. Capobianco D.J., Brazis P.W., Cheshire W.P. Idiopathic Intracranial Hypertension and Seventh Nerve Palsy. *Headache*. 1997;37:286-288.
17. Kersner C. Seventh nerve palsy as a false localizing sign in benign intracranial hypertension. *J R Soc Med*. 2010;103:412-414.
18. Nayak N. et al. Unusual clinical presentation of hypertensive cerebellar hemorrhage. *Asian J Neurosurg*. 2011;6(2):123-124n
19. Ro L. et al. Concurrent Trigeminal, Abducens, and Facial Nerve Palsies Presenting As False Localizing Signs: Case Report. *Neurosurgery*. 1995;37(2):322-325
20. Castillo M. and Kramer L. Raeder Syndrome: MR Appearance. *AJNR*. 1992;112:1121-1123.
21. Lepore F.E. False and non-localizing signs in neuro-ophthalmology. *Neuro-ophthalmology*. 2002;13:371-374

CRANIAL NEUROPATHIES

Patient with left temporal hematoma, but on clinical exam had contralateral fixed pupil dilation⁹

Oculomotor nerve:

- Multiple reported cases of false localizing contralateral fixed pupil dilation from supratentorial pathology, especially SDH¹⁰, calling into question the classic axiom of "Hutchinson's pupil" (unilateral mydriasis secondary to mass effect on the oculomotor nerve from a supratentorial lesion)
- **Theories:** a) extrinsic compression of the third nerve against the free edge of the contralateral tentorium and b) "dynamic axial brainstem distortion" where buckling of the brainstem from increased supratentorial pressure leads to impairment of blood supply and subsequent brainstem dysfunction^{11,12}
- Anisocoria also occurs in 20% of population

Abducens nerve:

- Abducens palsy has a variety of etiologies, most commonly underlying vasculopathies such as diabetes and hypertension
- CN VI palsy may also be a false localizing sign that actually indicates underlying idiopathic intracranial hypertension
- **Theories:** a) compression of the nerve against petrosphenoid ligament of Dorello's canal or ridge of petrous temporal bone¹³ or b) stretch or strain of CN VI when there is posteroinferior displacement of the brainstem due to the fact that CN VI is the only CN that is directed anteriorly (as opposed to oblique orientation of other CNs)¹³

Patient with left lateral gaze palsy, found to have SAH secondary to a ruptured aneurysm (not shown). Palsy could be due to combination of sudden increased intracranial hypertension from SAH, as well displacement of ectatic basilar artery that compresses the left CN VI (arrow on MRI)¹⁵

Facial nerve:

60 y/o with acute onset facial asymmetry, inward deviation of left eye, and gait imbalance. Found to have hypertensive left cerebellar ICH. Abducens and facial nerve palsies resolved after conservative management with antihypertensive and antiemetic medications¹⁴

- FLS of facial nerve (CN VII) palsies are infrequent compared to CN VI palsies, but can also occur in increased intracranial pressure
- Reported cases of FL CN VII palsies resolved after lowering of the elevated ICP¹⁶

- **Theories:** a) pressure related stretching of the intracranial portion of CN VII, before it enters petrous temporal bone, or b) early CN VII fibers wrap around the nucleus of CN VI and any damage at CN VI may also involve lower motor fiber of CN VII¹⁷

Trigeminal nerve:

A left cerebellopontine angle mass causing brainstem distortion. Patient presented with contralateral CN V sensory disturbance, CN VI and CN VII palsies¹⁸

- FLS of trigeminal neuralgia and trigeminal disturbances other than neuralgia in cases of contralateral intracranial tumors, posterior fossa > supratentorial
- **Theories:** a) extrinsic compression of the nerve between brainstem and petrous bone or b) distortion at point where CN V enters Meckel's cave¹⁹

Raeder Syndrome:

Patient with Raeder's syndrome, found to have left cavernous ICA narrowing (above) and distal cervical ICA marked narrowing (left)²⁰

- Unilateral trigeminal neuralgia and oculosympathetic palsy
- Facial sweating preserved, in contrast to Horner's syndrome

- **Theory:** pathology in middle cranial fossa, pericarotid, disturbing postganglionic trigeminal nerve and oculopupillary sympathetic fibers traveling with distal cervical ICA. Sparing of sympathetic fibers traveling with ECA, thus preserving facial sweating

MOTOR DEFICITS

Kernohan's notch

- Hemiparesis ipsilateral to site of cerebral lesion
- Etiologies include mass lesion, subdural hematomas, extradural hematomas
- **Theory:** Results from compression of the contralateral cerebral peduncle against the edge of the tentorium
- Causes damage to the descending corticospinal tract above medullary decussation

Left SDH and temporal IPH with signal abnormality in contralateral cerebral peduncle¹

Right SDH and signal abnormality in contralateral crus cerebri²

SPINAL CORD PATHOLOGY

- Cervical cord compression by mass or degenerated disc material can cause lumbar disk syndrome or sciatica like leg pain, but clinically may lack symptoms of limitation in back mobility or a positive reaction to the straight leg raising test⁴
- Marked kyphotic curvature of thoracic spine can also manifest as sciatica
- **Theories:** may be due to irritation of the spinothalamic tract⁵, but newer theories include anterior spinal artery ischemia and venous obstruction⁶

Patient with right sciatica symptoms and right lateral recess narrowing at L4-L5, nonresponsive to multiple epidural injections³

Patient p/w progressive weakness of lower limbs and decreased sensation of lower limbs up to T10 sensory level, but with normal thoracic imaging. Found to have severe cervical myelopathy and symptoms resolved after surgical intervention⁸

Same patient subsequently found to have right C1-C2 schwannoma with cord compression. After total mass resection (right), patient's right sciatica symptoms resolved¹

- Other false localizing presenting symptoms include lower extremity weakness, midthoracic pin level, loss of sensation caudal to the level of the upper leg⁷
- Further imaging of the cervical cord should be pursued in patients with thoracic sensory level symptoms, but normal findings on thoracic imaging⁸

Various patterns of perceived sensory loss in patients with cervical myelopathy, but without symptoms in upper extremities⁷

NEURO-OPHTHALMOLOGY

Sign	False Localization	True Localization
Papilledema	Raised intracranial pressure e.g. brain tumor	Leading cause of optic disk swelling in late life is anterior ischemic optic neuropathy. Accurate identification of hyaline bodies of the optic nerve, congenitally "tilted" disks, or papillitis, could also prevent needless neuroimaging procedures in search of intracranial masses.
Transient monocular blindness	Not only occlusive ipsilateral internal carotid artery disease	Ocular migraine. Transient visual obscurations with papilledema or other causes of disk swelling. Uhthoff symptom with demyelinating optic neuropathy. Subacute attacks of narrow-angle glaucoma, or momentary photopsias induced by vitreous traction ("Moore's lightning streaks") may explain interruption of normal monocular vision in a patient mistakenly thought to have carotid artery atherosclerosis.
Visual hallucinations	Pre-geniculate (elementary hallucinations) or post-geniculate visual loss (complex hallucinations)	Epilepsy; Bonnet syndrome with alteration of normal input at any point along afferent visual pathways
Divergence paresis	Raised intracranial pressure	Instead of focal "divergence center", multiple or diffusely distributed neural structures may govern divergence, or alternatively, sites of convergence inhibition may be defective
Convergence insufficiency	Disruption of Perlia's nucleus, a median group of cells acting as a convergence center, lying between right and left oculomotor nuclei	Possible human analogous cells of "near response neurons" found in mesencephalic reticular formation of rhesus monkeys
Vertical divergence	Superior or inferior oblique palsies	Lesions of midbrain, pons, medulla, cerebellum, and peripheral vestibular apparatus. Can be demyelinating, neoplasia, trauma, or infarct related
Anisocoria and Horner syndrome	Midline pupil ipsilateral to lesion disrupting the 3 neuron ocular sympathetic pathway	Raeder's syndrome; cluster headache or carotid artery dissection