CLINICAL VIGNETTE

Headache: When you hear hoof beats, think of Horses, not Zebras

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A 42-year-old male presents for his annual exam and to establish care. He also seeks advice for a new headache of two weeks. He describes the headache as bilateral frontal, aching, and rates the strength from 1 to 5 on a 10-point scale. He says "it just grabs you", is constant in nature but does worsen by the end of the day. The patient sleeps well as the headache does not wake him from sleep, although the headache is present upon awakening. He denies nausea or vomiting. He admits that his cat has been sleeping next to his head in his bed for the last 3-4 weeks. He has tried aspirin and a visit to his chiropractor, which did not help.

Past medical history was negative. Past surgical history included a varicocelectomy 3 years ago. His father had prostate cancer at age 75. He has no siblings. He has been married for 12 years, has no children, and works as an accountant. They have a pet cat. He is a never smoker, drinks alcohol rarely, and denies marijuana or other drug use. A complete review of systems is positive only for tooth pain, nasal congestion, and the headache, as above.

Exam included normal vital signs. Neurologic exam showed normal cranial nerves, normal strength, sensation and reflexes in upper and lower extremities, memory, gait, and cerebellar tests were all normal. Mental status exam was normal.

The initial differential included allergies and tension headache. He was asked to have the cat sleep in a different room, wash his bedding, and was given a prescription for nasal steroids. A laboratory panel was ordered, and he was asked to follow up in 6 weeks if the headache had not improved.

The patient's labs were significant for a WBC of 3.96 (nl 4.16 – 9.95) and an absolute neutrophil count of 1.60, fasting glucose of 108 and A1c of 5.4%, a total cholesterol of 218, HDL 50, LDL 142, Non-HDL of 168 and Triglycerides of 130, AST 35 (nl 13-47), ALT 91 (nl 8-64), Alkaline phosphatase 199 (nl 37-113). Other CMP, UA and TSH studies were normal. He was referred to a hepatologist for the abnormal ALT and alkaline phosphatase.

The hepatologist's evaluation included ultrasound of the liver and viral and autoimmune serologies, all of which were normal. The ultrasound reported only minor steatosis. He was advised to follow a low-cholesterol, low-fat, low-carbohydrate diet for fatty liver.

The patient returned four months later. He had interval improvement of the headache, until one week prior to the follow-up visit, when he started to implement the recommended dietary changes. The headache was described as originating from the neck and radiating to the entire head, coming and going, though worse at night. It was worse with walking and movement and was now moderate to severe in intensity. It felt better to lie down, and there was no photophobia. Vision was "ok." The patient complained of some dizziness, low energy, and nausea. He had taken low dose ibuprofen without any improvement and tried Chinese herbs, without improvement. He had recently developed a canker sore in his mouth.

Exam included normal vital signs. There was mild pharyngitis in the soft palate and a canker sore on the lower lip, with the remainder of the HEENT exam normal. Given the pharyngitis, cold sore and recent dietary changes, the patient was instructed to use a higher dose of ibuprofen and to return in 2 weeks, if the headache persisted.

Two weeks later, the patient returned. The headache persisted, unchanged without improvement on higher dose ibuprofen twice a day. There was a tactile fever the last two weeks, nausea without vomiting, nasal congestion and transient ear pain. ROS was negative for cough, diarrhea, constipation, rash, or neurologic symptoms.

The differential included a lack of sleep, poor water and food intake, medication induced headache, and URI. He was encouraged to return to his previous regular diet, stop the ibuprofen, and to have a CBC with differential, BMP, ESR and CRP and to return in one week.

The CBC, differential, and BMP were normal with the exception of the non-fasting glucose of 114. Inflammatory markers were normal with ESR of 3 and CRP less than 0.3.

One week later, the patient returned. The headache had improved in severity, though it had not resolved. On the way to his appointment, the patient had a minor car accident. The headache was described as a band of discomfort across the forehead and back of neck, lasting a couple of hours with mild nausea. It was not present every day. He was walking without any balance difficulty, no blurry vision, and able to read a newspaper well. He had no other symptoms.

Exam included normal vital signs. A neurologic exam was repeated, showing normal cranial nerves, normal strength and sensation, normal patellar reflexes, and a normal gait. Because of the persistent headache and unclear etiology, the patient was referred to neurology and given an empiric trial of sumatriptan. He was asked to return in one month to follow up after the neurology appointment.

Three weeks later, and approximately ten days before the neurology appointment, the patient returned with his wife because of blurred vision. He no longer had fevers, though his appetite had decreased and he had become weak. He now admitted to being unable to work over the last month and being unable to walk without assistance over the last week. He fatigued easily during conversation and was dehydrated. Weight was down 26 pounds since the first visit. Vital signs were abnormal with a heart rate of 104, blood pressure was 126/90, and respiratory rate of 18. He appeared cachectic and uncomfortable, with temporal wasting, dry mucous membranes, but otherwise had a normal heart, lung and abdominal exam. Complete neurologic exam was not performed, but patient was oriented to person and place. He was sent to the emergency room for dehydration and cachexia.

In the emergency department, the patient reported severe occipital headaches for six-to-eight weeks and denied any other focal neurologic symptoms. His wife noted that his speech and cognition had been worsening over the last few days. Vital signs were essentially unchanged and exam, including a sensory and motor neurologic exam was normal. In the ED while awaiting further evaluation, the patient had a grand mal seizure.

CT showed left temporal, parietal, and occipital subcortical hypoattenuation, which may represent primary glioma or gliomatosis cerebri. There was mass effect with 18mm of rightward midline shift with moderate mass effect upon the midbrain with mild transtentorial herniation, and mild dilatation of the right temporal horn, which suggested a trapped ventricle (Figure 1).

MRI showed a 5.7cm x 5.2cm x 5.7cm peripherally enhancing, peripheral diffusion restricting mass in the left posterior temporal/parietal/occipital lobes, which may be related to intracranial lymphoma (Figure 2).

The patient underwent left craniotomy and biopsy. Intraoperatively the patient's brain was noted to have severe cerebral edema. Gross total removal of the tumor was performed. FISH analysis and pathology was consistent with diffuse large B-cell lymphoma, non-germinal center type. Bone marrow biopsy and PET/CT were negative for metastases.

Discussion

Headache is one of the most common presenting complaints to primary care offices, and only rarely is imaging helpful in diagnosis or treatment. As a result, recommendations for imaging of the head has been written and studied extensively.[1-9] Guideline documents by professional societies are replete with recommendations on when **not** to image, and focus primarily on focal neurologic symptoms as the primary reason for imaging in primary care for headache.[1-3] In this case, the management was by the guidelines and appropriate care was delivered. However, it would have been preferable if the primary care physician made the diagnosis – not the emergency department. Could that have been achieved?

Earlier imaging for non-specific symptoms is universally **not** recommended by professional societies. Although a referral to neurology was made, perhaps ordering an MRI at the time of referral would have been appropriate, but at what cost to the healthcare system? Clinically the patient's presentation waxed and waned, making the diagnosis difficult to suspect. There were no focal neurologic signs or symptoms that would have necessitated imaging; thus, the care was as described. If there was any silver lining to the case, it was the continued close follow up and continuity of care. Dr. Atul Gawande recently commented on the importance of continuity and incremental care.[10]

Two studies by Duarte and Larson investigated neurologic symptoms and the likelihood of finding an abnormality on neuro imaging. Symptoms positively associated with significant findings on imaging included: rapidly increasing headache frequency; history of dizziness or lack of coordination; history of subjective numbness or tingling; and history of headache causing awakening from sleep. These two studies also concluded that a history of syncope, headache accompanied by nausea, or the experience of the "worst headache" of one's life did *not* significantly increase the likelihood of finding a significant abnormality on neuroimaging.[4,5] Other studies by De Benedittis and Sargent reported no patient with significant intracranial abnormalities among those with normal neurological examinations and headaches diagnosed as tension-type headaches.[6,7] However, both studies were small and included a total of around 180 patients. The positive and negative likelihood ratios for a variety of neurological signs and symptoms are presented in Table 1.

Figures and Tables

Figure 1.

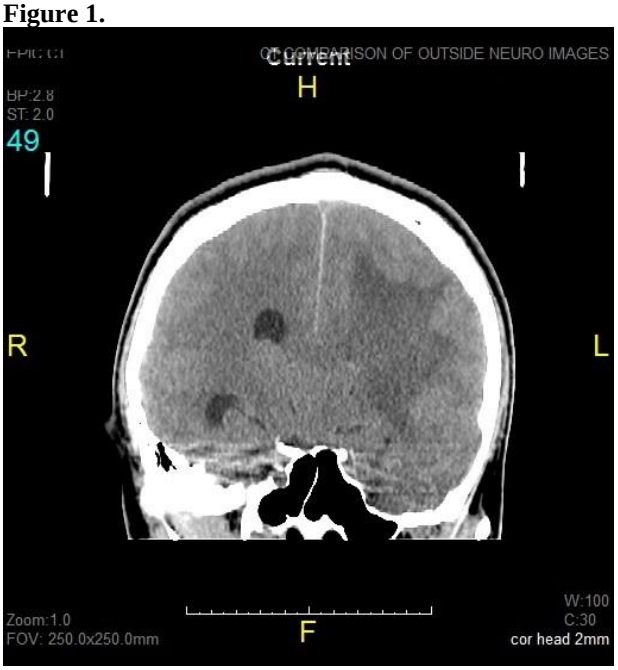

Figure 2.

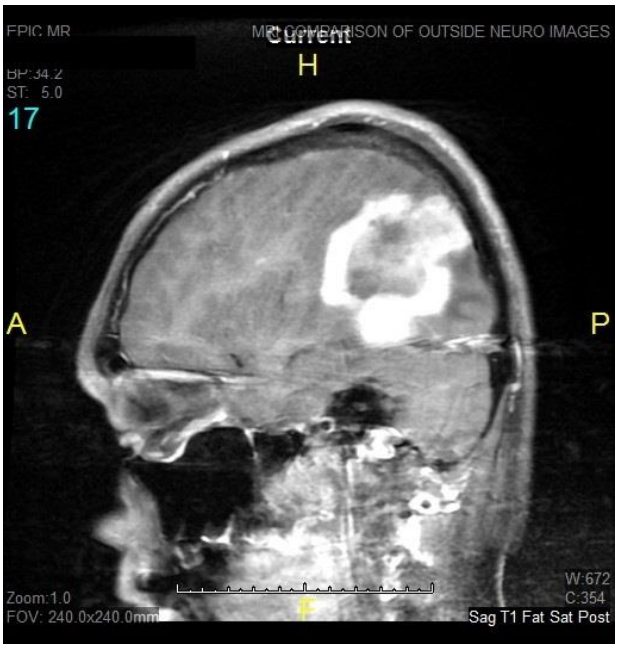

Table 1.

Table 1: Evidence for historical or physical examination findings changing the odds of detecting a significant abnormality on neuroimaging.

Abnormal neurological exam	# Patients	LR positive (95% CI)	LR negative (95% CI)
Cala, 1976	46	1.7 (0.39 to 7.3)	0.71 (0.18 to 2.9)
Carrera, 1977	32	3.0* (2.2 to 4.2)	0 (0 to 11)
Duarte, 1996	100	2.5* (1.2 to 5.3)	0.73 (0.52 to 1.05)
Larson, 1980	40	4.4* (1.9 to 10)	0 (0 to 42)
Mitchell, 1993	350	5.4* (2.2 to 14)	0.62 (0.33 to 1.2)
Any neurololical sign or symptom			
Kahn, 1993	1111	1.1* (1.05 to 1.2)	0.47* (0.25 to 0.89)
Mitchell, 1993	350	6.0* (4.7 to 7.8)	0 (0 to 7.9)
Rapidly increasing headache frequency			
Mitchell, 1993	350	12* (3.1 to 48)	0.73 (0.46 to 1.2)
History of syncope			
Mitchell, 1993	350	0.69 (0 to 340)	1.0 (0.92 to 1.1)
Nausea			
Mitchell, 1993	350	0 (0 to 260)	1.0 (0.93 to 1.1)
Duarte, 1996	100	1.4 (0.69 to 3.0)	0.87 (0.63 to 1.2)
History of headache causing awakening from sleep			
Duarte, 1996	100	1.7 (0.81 to 3.7)	0.78 (0.51 to 1.2)
Mitchell, 1993	350	98* (10 to 960)	0.72 (0.45 to 1.1)
History of dizziness or lack of coordination			
Mitchell, 1993	350	49.0* (3.4 to 710)	0.86 (0.64 to 1.2)
History of subjective numbness or tingling			
Mitchell, 1993	350	49.0* (3.4 to 710)	0.86 (0.64 to 1.2)
"Worst headache of life"			
Mitchell, 1993	350	1.9 (0.30 to 12)	0.93 (0.68 to 1.3)
Headache worse with Valsalva maneuver			
Duarte, 1996	1100	2.3* (1.1 to 4.6)	0.67 (0.42 to 1.1)
Abnormal skull roentgenograph			
Sargent, 1983	88	0 (0 to 29)	1.1* (1.0 to 1.2)

* p<0.05

Appendix

Summary: "Evidence-Based Guidelines in the Primary Care Setting: Neuroimaging in Patients with Non-Acute Headache" from the 2008 US Headache Consortium.[1]

Evidence Grade

Grade A. Multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings.

Grade B. Some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal. For instance, either few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant to the recommendation. An example of the last point would be the case where trials were conducted using a study group that differed from the target group for the recommendation.

Grade C. The US Headache Consortium achieved consensus on the recommendation in the absence of relevant randomized controlled trials.

Neurological Examination

Finding: An abnormal neurological examination increases the likelihood of finding significant intracranial pathology (e.g., brain tumor, arteriovenous malformation, hydrocephalus) on neuroimaging. The absence of any abnormalities on neurological examination reduces the odds of finding a significant abnormality on imaging.

Recommendation: Neuroimaging should be considered in patients with nonacute headache
and an unexplained abnormal finding on the neurological examination (Grade B).

Neurological Symptoms

Finding: Headache worsened by Valsalva maneuver, headache causing awakening from sleep, new headache in the older population, or progressively worsening headache may indicate a higher likelihood of significant intracranial pathology, as reported in several small studies. (One study reported that a history of headache worsening with Valsalva maneuver significantly increased the odds of finding a significant intracranial abnormality on neuroimaging, most commonly a Chiari malformation. In general, however, the absence of signs and symptoms is less reliable and informative than their presence.

Recommendation: Evidence is insufficient to make specific recommendations regarding neuroimaging in the presence or absence of neurological symptoms (Grade C).

Migraine and a Normal Neurological Examination

Finding: Meta-analysis of patients with migraine and a normal neurological examination found a rate of significant intracranial lesions of 0.18% (2/1000; previously reported rates of finding intracranial lesions with CT and MRI ranged from 0.3% to 0.4%). Neuroimaging is thus unlikely to reveal an abnormality on MRI or CT scanning in patients with migraine and a normal neurological examination.

Recommendation: Neuroimaging is not usually warranted for patients with migraine and normal neurological examination. (Grade B). For patients with atypical headache features or patients who do not fulfill the strict definition of migraine (or have some additional risk factor), a lower threshold for neuroimaging may be applied (Grade C).

Tension-type Headache and Normal Neurological Examination

Finding: In two studies of imaging in patients with tension-type headache (one study specified as chronic tension-type headache) and normal neurological examinations, no significant lesions were demonstrated.

Recommendation: Data were insufficient to make an evidence-based recommendation regarding the use of neuroimaging for tension-type headache (Grade C).

Effectiveness of CT vs. MRI

Finding: Based on the limited data in the studies reviewed here, MRI appears to be more sensitive in finding white matter lesions and developmental venous anomalies than CT, a result that could be expected based upon the characteristics of the two.

Recommendation: Data were insufficient to make any evidence-based recommendations regarding the relative sensitivity of MRI compared with CT in the evaluation of migraine or other nonacute headache (Grade C).

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