Diagnostic Testing for Migraine and Other Primary Headaches

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KEYWORDS

• Headache diagnostic testing • MRI • Computed tomography • Migraine
• Trigeminal autonomic cephalalgias • New daily persistent headache

KEY POINTS

- MRI is usually preferred over computed tomography for the evaluation of headaches.
- Imaging is typically not required for the diagnosis of migraine meeting diagnostic criteria.
- MRI is usually indicated for trigeminal autonomic cephalalgias to exclude secondary causes.

Most primary headaches can be diagnosed without diagnostic testing using a comprehensive history and neurologic and focused general physical examinations.

In some cases, however, diagnostic testing is necessary to distinguish primary from secondary causes that may share similar features. The differential diagnosis of headache is one of the longest in all of medicine, with more than 300 different types and causes. In this article, the reasons for diagnostic testing and the use of neuroimaging, electroencephalography, lumbar puncture, and blood testing are evaluated. The use of diagnostic testing in adults and children who have a normal neurologic examination, migraine, trigeminal autonomic cephalalgias (TACs), and new daily persistent headache (NDPH) is reviewed.

REASONS FOR DIAGNOSTIC TESTING

The indications for diagnostic testing are variable, and neurologists must make decisions on a case-by-case basis when presented with a suspected primary headache if secondary headache is a consideration. Clinical situations whereby neurologists consider diagnostic testing are listed in **Box 1**.

There are many other reasons neurologists recommend diagnostic testing: "our stubborn quest for diagnostic certainty";[1] faulty cognitive reasoning; the medical

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Box 1
Reasons to consider neuroimaging for headaches

Temporal and headache features
1. The "first or worst" headache
2. Subacute headaches with increasing frequency or severity
3. A progressive headache or NDPH
4. Chronic daily headache
5. Headaches always on the same side
6. Headaches not responding to treatment
7. New-onset headaches in patients who have cancer or who test positive for HIV infection
8. New-onset headaches after aged 50
9. Patients who have headaches and seizures
10. Headaches associated with symptoms and signs, such as fever, stiff neck, nausea, and vomiting
11. Headaches other than migraine with aura associated with focal neurologic symptoms or signs
12. Headaches associated with papilledema, cognitive impairment, or personality change

From Evans RW. Headaches. In: Evans RW, editor. Diagnostic testing in neurology. Philadelphia: W.B. Saunders; 1999. p. 2; with permission.

decision rule that it is better to impute disease than to risk overlooking it; busy practice conditions whereby tests are ordered as a shortcut; patient expectations; financial incentives; professional peer pressure, whereby recommendations for routine and esoteric tests are expected as a demonstration of competence; and medicolegal issues.[2,3] The attitudes and demands of patients and families and the practice of defensive medicine are especially important reasons in the case of headaches. In the era of managed care, equally compelling reasons for not ordering diagnostic studies include physician fears of deselection, at-risk capitation, and economic credentialing.[4] Lack of funds and underinsurance continue to be barriers to appropriate diagnostic testing for many patients.

DIAGNOSTIC TESTING OPTIONS

Computed Tomography Versus MRI

Computed tomography (CT) detects most abnormalities that may cause headaches. CT generally is preferred to MRI for evaluation of acute subarachnoid hemorrhage, acute head trauma, and bony abnormalities. There are several disorders, however, that may be missed on routine CT of the head, including vascular disease, neoplastic disease, cervicomedullary lesions, and infections (**Box 2**). MRI is more sensitive than CT in the detection of posterior fossa and cervicomedullary lesions, ischemia, white matter abnormalities (WMA), cerebral venous thrombosis (CVT), subdural and epidural hematomas, neoplasms (especially in the posterior fossa), meningeal disease (such as carcinomatosis, diffuse meningeal enhancement in low cerebrospinal fluid [CSF] pressure syndrome, and sarcoid), cerebritis, and brain abscess. Pituitary pathologic condition is more likely to be detected on a routine MRI of the brain than a routine CT.

Another concern with CT is exposure to ionizing radiation. The average radiation dose of a CT scan of the head (with or without contrast, both studies double the dose) is an effective dose of 2.0 millisieverts (mSv), which is equivalent to 100 chest radiographs.[5] The most common malignancies associated with radiation exposure include leukemia and breast, thyroid, lung, and stomach cancers. The latency period for solid tumors usually is long, an average of 10 to 20 years, with a

Box 2
Causes of headache that can be missed on routine computed tomographic scan of the head

Vascular disease
- Saccular aneurysms
- Arteriovenous malformations (especially posterior fossa)
- Subarachnoid hemorrhage
- Carotid or vertebral artery dissections
- Infarcts
- Cerebral venous thrombosis
- Vasculitis
- White matter abnormalities
- Subdural and epidural hematomas

Neoplastic disease
- Neoplasms (especially in the posterior fossa)
- Meningeal carcinomatosis
- Pituitary tumor and hemorrhage

Cervicomedullary lesions
- Chiari malformations
- Foramen magnum meningioma

Infections
- Paranasal sinusitis
- Meningoencephalitis
- Cerebritis and brain abscess

Other
- Low CSF pressure syndrome
- Neurosarcoid
- Idiopathic hypertrophic pachymeningitis

From Evans RW. Diagnostic testing for migraine and other primary headaches. Neurol Clin. 2009 May;27(2):393-415; with permission.

persistent lifelong risk. Leukemia has an earlier latency period with an increased risk 2 to 5 years after radiation exposure. The pediatric population is at increased risk, as a result of increased radiosensitivity and more years of remaining life, for potentially developing cancer. Consider the radiation exposure of some patients who have multiple trips to an emergency department, have migraine and multiple CT scans, and also have multiple CT scans of the head and sinuses in an outpatient setting. For a single CT scan of the head, the estimated lifetime-attributable risk for death from cancer by age is approximately as follows: age 10 years, 0.025%; age 20 years, 0.01%; and age 50 years, 0.003%.[6] Although these are small numbers, are individual studies justified? Up to 2% of all cancer deaths in the United States may be attributable to radiation exposure associated with CT use. The Food and Drug Administration has estimated that exposure to 10 mSv (equivalent to 1 CT of the abdomen) may be associated with an increased risk for developing fatal cancer in one of every 2000 patients.[7]

Thus, MRI generally is preferred over CT for evaluation of headaches. The yield of MRI may vary depending on the field strength of the magnet, the use of paramagnetic contrast, the selection of acquisition sequences, and the use of magnetic resonance (MR) angiography (MRA) and MR venography (MRV). MRI may be contraindicated, however, in the presence of an aneurysm clip or pacemaker. In addition, approximately 8% of patients are claustrophobic, approximately 2% to the point at which they cannot tolerate the study.

Neuroimaging During Pregnancy and Lactation

When there are appropriate indications, neuroimaging should be performed during pregnancy.[8] With the use of lead shielding, a standard CT scan of the head exposes the uterus to less than 1 mrad. The radiation dose for a typical cervical or intracranial arteriogram is less than 1 mrad. The fetus is most susceptible to the teratogenic effects of radiation between the second and 20th weeks of embryonic age[8] with a threshold radiation dose estimated at between 5 and 15 rad.[9] There is no known risk associated with iodinated contrast use during pregnancy or in breastfeeding women, and contrast may be used when indicated.[10]

MRI is more sensitive for rare disorders that may occur during pregnancy, such as pituitary apoplexy, CVT (with the addition of MRV), and metastatic choriocarcinoma.

There is no known risk associated with MRI during pregnancy.[11–13] There may be an increased risk of tissue heating at field strengths more than 1.5 T of uncertain significance.

According to the 2013 American College of Radiology Guidance Document for Safe Practices,[14]

Present data have not conclusively documented any deleterious effects of MR imaging exposure on the developing fetus. Therefore, no special consideration is recommended for the first, versus any other, trimester in pregnancy. Nevertheless, as with all interventions during pregnancy, it is prudent to screen females of reproductive age for pregnancy before permitting them access to MR imaging environments. If pregnancy is established, consideration should be given to reassessing the potential risks versus benefits of the pending study in determining whether the requested MR examination could safely wait to the end of the pregnancy before being performed.

a. *Pregnant patients can be accepted to undergo MR scans at any stage of pregnancy if, in the determination of a level 2 MR personnel-designated attending radiologist, the risk-benefit ratio to the patient warrants that the study be performed. The radiologist should confer with the referring physician and document the following in the radiology report or the patient's medical record:*
   1. *The information requested from the MR study cannot be acquired by means of nonionizing means (eg, ultrasonography).*
   2. *The data are needed to potentially affect the care of the patient or fetus during the pregnancy.*
   3. *The referring physician believes that it is not prudent to wait until the patient is no longer pregnant to obtain this data.*

MR contrast agents should not be routinely provided to pregnant patients.

The decision to administer a gadolinium-based MR contrast agent to pregnant patients should be accompanied by a well-documented and thoughtful risk-benefit analysis.

The American College of Obstetricians and Gynecologists concluded that breastfeeding should not be interrupted after gadolinium administration.[15]

Electroencephalography

The electroencephalogram (EEG) was a standard test for evaluation of headaches in the pre-CT scan era. Gronseth and Greenberg[16] reviewed the literature from 1941 to 1994 on the usefulness of EEG in the evaluation of patients who had headache. Most of the articles had serious methodologic flaws. The only significant abnormality reported in studies with a relatively nonflawed design was prominent driving in response to photic stimulation (the H response) in migraineurs who had a sensitivity

ranging from 26%[17] to 100%[18] and a specificity from 80%[19] to 91%.[18] This finding, although interesting, is not necessary for the clinical diagnosis of migraine. If the purpose of the EEG is to exclude an underlying structural lesion, such as a neoplasm, CT or MRI imaging is far superior.

A report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN) suggests the following practice parameter: "The electroencephalogram (EEG) is not useful in the routine evaluation of patients with headache. This does not exclude the use of EEG to evaluate headache patients with associated symptoms suggesting a seizure disorder such as atypical migrainous aura or episodic loss of consciousness. Assuming head imaging capabilities are readily available, EEG is not recommended to exclude a structural cause for headache."[16] The AAN's choosing wisely recommendations include, "Don't perform EEGs for headaches."[17]

A report of the Quality Standards Subcommittee of the AAN and the Practice Committee of the Child Neurology Society[18] makes the following pediatric recommendations: "EEG is not recommended in the routine evaluation of a child with recurrent headaches, as it is unlikely to provide an etiology, improve diagnostic yield, or distinguish migraine from other types of headaches (Level C; class II and class III evidence)."

Lumbar Puncture

MRI or CT scan always is performed before a lumbar puncture for evaluation of headaches except in some cases where acute meningitis is suspected. Lumbar puncture can be diagnostic for meningitis or encephalitis, meningeal carcinomatosis or lymphomatosis, subarachnoid hemorrhage, and high (eg, pseudotumor cerebri) or low CSF pressure. In cases of blood dyscrasias, the platelet count should be 50,000 or greater before safely performing a lumbar puncture. The CSF opening pressure always should be measured when investigating headaches. When measuring the opening pressure, it is important for patients to relax and at least partially extend the head and legs to avoid recording a falsely elevated pressure.

After neuroimaging is performed, lumbar puncture often is indicated in the following circumstances: the first or worst headache, headache with fever or other symptoms or signs suggesting an infectious cause, a subacute or progressive headache (eg, in an human immunodeficiency virus [HIV]-positive patient or a person who has carcinoma), and an atypical chronic headache (eg, to rule out pseudotumor cerebri in an obese woman who does not have papilledema).

There are many potential complications of lumbar puncture, the most common of which is low CSF pressure headache, which occurs approximately 30% of the time using the conventional bevel-tip or Quincke needle.[19] The risk for headache can be reduced dramatically to approximately 5% to 10% by using an atraumatic needle, such as the Sprotte or Whitacre, and replacing the stylet before withdrawing the needle.[20]

Blood Tests

Blood tests generally are not helpful for the diagnosis of headaches. There are many indications, however, such as the following: erythrocyte sedimentation rate or C-reactive protein to consider the possibility of temporal arteritis in a person 50 years or older who has new-onset migraine, because only 2% of migraineurs have an onset at age 50 years or older; erythrocyte sedimentation rate, rheumatoid arthritis factor, and antinuclear antibody test in patients who have headache and arthralgia to evaluate for possible collagen vascular disease, such as lupus[21]; monospot in teenagers who have headaches, sore throat, and cervical adenopathy; complete blood cell count

(CBC), liver function tests, HIV test, or Lyme antibody test in some patients who have a suspected infectious basis; an anticardiolipin antibody and lupus anticoagulant in migraineurs who have extensive WMA on MRI; thyroid-stimulating hormone because headache may be a symptom in 14% of cases of hypothyroidism; CBC because headache may be a symptom when the hemoglobin concentration is reduced by one-half or more; serum urea nitrogen and creatinine to exclude renal failure, which can cause headache; serum calcium because hypercalcemia can be associated with headaches; CBC and platelets because thrombotic thrombocytopenic purpura can cause headaches; and endocrine studies in patients who have headaches and a pituitary tumor.

In addition, blood tests may be indicated as a baseline and for monitoring for certain medications, such as valproic acid for migraine prophylaxis, carbamazepine for trigeminal neuralgia, and lithium for chronic cluster headaches.

HEADACHES AND A NORMAL NEUROLOGIC EXAMINATION

Neuroimaging Studies in Adults

The yield of abnormal neuroimaging studies in studies of patients who have headaches as the only neurologic symptom and normal neurologic examinations depends on several factors, including the duration of the headache, study design (prospective vs retrospective), who orders the scan, and the type of scan performed. The percentage of abnormal scans may be higher when ordered by neurologists or a tertiary care center compared with primary care physicians representing case selection bias. In reported CT scan series, the yield may vary depending on the generation of scanner and whether iodinated contrast was used. The yield of MRI may vary depending on the field strength of the magnet, the use of paramagnetic contrast, the selection of acquisition sequences, and the use of MR angiography.

Frishberg[22] reviewed 8 CT scan studies of 1825 patients who had unspecified headache types and varying durations of headache. The summarized findings from these studies are combined with 4 additional studies of 1566 CT scans in patients who had headache and normal neurologic examinations[21,23–25] for a total of 3389 scans. The overall percentages of various pathologic conditions are as follows: brain tumors, 1%; arteriovenous malformations (AVMs), 0.2%; hydrocephalus, 0.3%; aneurysm, 0.1%; subdural hematoma, 0.2%; and strokes (including chronic ischemic process), 1.1%.

Combining 3 studies of patients who had chronic headaches and a normal neurologic examination with 1282 patients, the only clinically significant pathologic condition was 1 low-grade glioma and 1 saccular aneurysm.[21,23,26]

Weingarten and colleagues[26] extrapolated various types of data from 100,800 adult patients who belonged to a health maintenance organization. The estimated prevalence (in patients who had chronic headache and a normal neurologic examination) of a CT scan demonstrating an abnormality requiring neurosurgical intervention may have been as low as 0.01%. It is not certain whether detection of additional pathologic condition on MRI scan would change this percentage. For example, complaints of headache with a normal neurologic examination may be seen in patients who have Chiari type I malformation, which is easily detected on MRI but not CT scans. Pituitary hemorrhage can produce a migrainelike acute headache with a normal neurologic examination.[27] Pituitary infarction, with severe headache, photophobia, and CSF pleocytosis, initially can be similar to aseptic meningitis or meningoencephaitis.[28] Pituitary pathologic condition is more likely to be detected on a routine MRI than CT scan.

Wang and coworkers[29] retrospectively reviewed the medical records and MRI images of 402 adult patients (286 women and 116 men) who had been evaluated

by the neurology service and who had a primary complaint of chronic headache (a duration of 3 months or more) and no other neurologic symptoms or findings. Major abnormalities (a mass, caused mass effect, or was thought the likely cause of patient's headache) were found in 15 patients (3.7%) and included glioma, meningioma, metastases, subdural hematoma, AVM, hydrocephalus (3 patients), and Chiari I malformations (2 patients). They were found in 0.6% of patients who had migraine, 1.4% of those who had tension headaches, 14.1% of those who had atypical headaches, and 3.8% of those who had other types of headaches.

Tsushima and Endo[30] retrospectively reviewed the clinical data and MR studies of 306 adult patients (136 men and 170 women) all of whom were referred for MRI evaluation of chronic or recurrent headache with a duration of 1 month or more, had no other neurologic symptoms or focal findings at physical examination, and had no prior head surgery, head trauma, or seizure: 55.2% had no abnormalities, 44.1% had minor abnormalities, and 0.7% (2) had clinically significant abnormalities (pituitary macroadenoma and subdural hematoma). Neither contrast material enhancement (195) nor repeated MRI (23) contributed to the diagnosis.

Sempere and colleagues[31] reported a study of 1876 consecutive patients (1243 women and 633 men), aged 15 or older, mean age 38 years, who had headaches that had an onset at least 4 weeks previously and who were referred to 2 neurology clinics in Spain. One-third of the headaches were new onset, and two-thirds had been present for more than 1 year. Subjects had the following types: migraine (49%), tension (35.4%), cluster (1.1%), posttraumatic (3.7%), and indeterminate (10.8%). Normal neurologic examinations were found in 99.2% of the patients. CT scan was performed in 1432 patients and MRI in 580; 136 patients underwent both studies.

Neuroimaging studies detected significant lesions in 22 patients (1.2%), of whom 17 had a normal neurologic examination. The only variable or red flag associated with a higher probability of intracranial abnormalities was an abnormal neurologic examination with a likelihood ratio of 42. The diagnoses in these 17 patients were pituitary adenoma (3), large arachnoid cyst (2), meningioma (2), hydrocephalus (2), and Arnold-Chiari type I malformation, ischemic stroke, cavernous angioma, AVM, low-grade astrocytoma, brainstem glioma, colloid cyst, and posterior fossa papilloma (one of each). Of these 17 patients, 8 were treated surgically, including for hydrocephalus (2), and pituitary adenoma, large arachnoid cyst, meningioma, AVM, colloid cyst, and papilloma (one of each).

The rate of significant intracranial abnormalities in patients who had headache and normal neurologic examination was 0.9%. Neuroimaging studies discovered incidental findings in 14 patients (75%): 3 pineal cysts, 3 intracranial lipomas, and 8 arachnoid cysts. The yield of neuroimaging studies was higher in the group with indeterminate headache (3.7%) than in the migraine (0.4%) or tension-type headache (0.8%) groups. The study does not provide information on WMA in migraineurs. MRI performed in patients who had normal CT revealed significant lesions in 2 cases: a small meningioma and an acoustic neurinoma. No saccular aneurysms were detected; MR angiography was not obtained.

Wang and colleagues[32] recruited 1070 health controls and 1070 primary headache patients (including 665 with migraine of all types, 93 with chronic migraine, and 338 with tension-type headaches, 99 with the chronic type) from the Chinese People's Liberation Army General Hospital, who then underwent either CT or MRI scans. Abnormal scans were found in the following: 0.67% in migraine (3/665 with MRI and 0/291 with CT) compared with 0.73% abnormal scans in controls. Abnormalities in

migraineurs were 2 with hydrocephalus and 2 with tumors of the throat and nose. They concluded, "The present study found that neuroimaging was unnecessary for the primary headache patients."

The studies do not give information about the detection of paranasal sinus disease, however, which may be the cause of some headaches. For example, sphenoid sinusitis may cause a severe, intractable, new-onset headache that interferes with sleep and is not relieved by simple analgesics. The headache may increase in severity with no specific location. There may be associated pain or paresthesias in the facial distribution of the fifth nerve and photophobia or eye tearing with or without fever or nasal drainage. The headache may mimic other causes, such as migraine or meningitis.[33]

The American College of Radiology Choosing Wisely recommended, "Don't Image for uncomplicated headache."[34]

Headache and a normal neurologic examination neuroimaging in children

Many studies have investigated the findings of neuroimaging in children who had headaches with a normal neurologic examination. The yield of clinically significant abnormalities is low (0.9%–1.2%).[35] A few studies are reviewed.

Chu and Shinnar[36] obtained brain imaging studies in 30 children, aged 7 or younger, who had headaches and were referred to pediatric neurologists. The studies were normal except for 5 that had incidental findings.

Maytal and coworkers[37] obtained MRI or CT scans or both in 78 children, aged 3 to 18, who had headaches. With the exception of 6 patients, the neurologic examinations were normal. The studies were normal except for incidental cerebral abnormalities in 4 and mucoperiosteal thickening of the paranasal sinuses in 7.

Wöber-Bingöl and colleagues[38] prospectively obtained MRI scans in 96 children, aged 5 to 18, who had headaches and normal neurologic examinations and who were referred to an outpatient headache clinic. The studies were normal except for 17 (17.7%) who had incidental findings.

Lewis and Dorbad[39] retrospectively reviewed records of children, aged 6 to 18, who had migraine and chronic daily headache with normal examinations. Of 54 patients who had migraine who underwent CT (42) or MRI (12) scans, the yield of abnormalities was 3.7%, none clinically relevant. Of 25 patients who had chronic daily headache who underwent CT (17) or MRI (8) scans, the yield of abnormalities was 16%, none clinically relevant.

Carlos and colleagues,[40] in a retrospective chart review, identified all pediatric migraine patients who had a CT or MRI to investigate their headaches. Ages ranged from 3 to 18. Of the 93 patients, 35 had CT, 14 had MRI, and 9 had both. Twenty-two had abnormalities, but none was thought related to the patients' headaches.

Alehan[41] prospectively obtained neuroimaging (49 MRI scans and 11 CT scans) in 60 of 72 consecutive children diagnosed with migraine or tension-type headaches. Ten percent had findings related to their headache with no neoplasms, and no patients required surgery.

Occipital headaches in children have been thought to be rare and suggestive of serious intracranial pathologic condition. However, in a retrospective study of 308 children $\leq$18 years of age referred to a headache clinic for headache with a normal neurologic examination, headaches were solely occipital in 7% and occipital-plus in 14%. Occipital pain alone or with other locations was not significantly associated with clinically significant intracranial pathologic condition on neuroimaging.[42] In children with occipital headaches consistent with migraine or another primary headache disorder with a normal neurologic examination, the yield of neuroimaging is low.[43]

Headaches upon awakening and sleep interruption owing to headache have been commonly regarded as a potential sign of raised intracranial pressure. In a study of 102 children aged between 5 and 17 years, including 77% with headache upon awakening, 19% with sleep interruption owing to headache, and 4% with both, neuroimaging was performed in 101 of the cohort. Imaging was normal in 97 and showed nonsignificant findings in 4.[44] All had primary headaches or medication overuse except for 1 with sinusitis. This symptom alone is not an indication for routine neuroimaging.

Guidelines

A report of the Quality Standards Subcommittee of the AAN and the Practice Committee of the Child Neurology Society[17] makes the following recommendations:

1. Obtaining a neuroimaging study on a routine basis is not indicated in children who have recurrent headaches and a normal neurologic examination (level B; class II and class III evidence).
2. Neuroimaging should be considered in children who have an abnormal neurologic examination (eg, focal findings, signs of increased intracranial pressure, significant alteration of consciousness), the coexistence of seizures, or both (level B; class II and class III evidence).
3. Neuroimaging should be considered in children in whom there are historical features to suggest the recent onset of severe headache or change in the type of headache or if there are associated features that suggest neurologic dysfunction (level B; class II and class III evidence).

The American College of Radiology appropriateness criteria recommend that for children with primary headache, "There is no role for radiography in patients with primary headache."[45]

Risk/Benefit and Cost/Benefit of Neuroimaging

Table 1 summarizes the estimated risks and benefits of neuroimaging in patients who have headaches and normal neurologic examinations (radiation exposure and the increased long-term risk for cancer are discussed previously). Many anxious patients and their family members are not reassured even after a long discussion about the low yield of neuroimaging. Howard and colleagues[46] performed a randomized control trial in a London headache clinic of 150 patients with chronic daily headache (76 were randomized to the offer of a brain scan and 74 were treatment as usual). Patients offered a scan were less worried about a serious cause of the headaches at 3 months, although this was not maintained at 1 year. However, patients with high levels of psychiatric morbidity offered a scan had significantly less costs owing to lower utilization of medical resources.

For other patients, the scan may produce anxiety when nonspecific abnormalities are found, such as incidental findings or anatomic variants[47,48] or white matter lesions. The author suspects that many neurologists have seen patients who have isolated headaches referred by primary care physicians with a request to rule out multiple sclerosis when white matter lesions associated with migraine are detected.

Although the cost of finding significant pathologic condition is high, many payers have significantly reduced the cost of neuroimaging. Cost/benefit estimates should include the cost to physicians of malpractice suits filed when patients who have significant pathologic condition do not have neuroimaging[49] and the cost to patients and society of premature death and disability of undetected treatable lesions.

Table 1
Balance sheet. CT or MRI in patients with headache and normal neurologic examinations. Technology: CT with intravenous contrast or MRI without contrast. Indications: (1) migraine and (2) any headache

	CT, %	MRI, %	No Test
Health outcomes			
Benefits			
Discovery of potentially treatable lesions			
1. Migraine	0.3	0.4	0
2. Any headache	2.4	2.4	0
Relief of anxiety	30	30	0
Harms			
Iodine reaction			
Mild	10	—	—
Moderate	1	—	—
Severe	0.01	—	—
Death	0.002	—	—
Claustrophobia			
Mild	5	15	0
Moderate (needs sedation)	1	5–10	—
Severe (unable to comply)	1–2	—	—
False-positive studies	No data	No data	—
Cost (charges)	Varies widely depending on payer		—

Data from Frishberg BM. The utility of neuroimaging in the evaluation of headache in patients with normal neurologic examinations. Neurology 1994;44:1196.

Following guidelines does not indemnify the physician in a malpractice suit.[2,50] Until physicians are indemnified in malpractice cases when they follow guidelines, one might consider what a jury would consider indications for neuroimaging rather than one's peers.

NEUROIMAGING IN MIGRAINE

Incidence of Pathologic Condition

Combining 16 MRI and CT scan studies for a total of 1625 scans of patients with various types of migraine, the studies found no significant pathologic condition except for 4 brain tumors (3 of which were incidental findings) and 1 AVM (in a patient who had migraine and a seizure disorder).[51] Sempere and colleagues[31] found a similarly low yield of 0.4%.

Mullally and Hall[52] performed a prospective study on 100 subjects with a diagnosis of migraine (45 without aura, 14 with aura, and 41 with chronic migraine) and a normal neurologic examination who had MRI scans of the brain solely at their request. The duration of headaches ranged from 4 months to 40 years. MRI scans were normal in 82 and found clinically insignificant abnormalities in 17. MRI was abnormal in 1 patient (chronic migraine without aura) finding a meningioma requiring surgery and radiotherapy that is similar to the yield of brain tumor in the general asymptomatic population. The investigators conclude, "Brain MRI obtained at the specific request of patients with a diagnosis of migraine in the presence of normal neurologic

examination results has a yield that is equivalent to that of the general asymptomatic population. Patients do not seem to have more insight than the examining clinician with regard to detecting underlying structural abnormalities, and brain MRI should not performed as part of the routine evaluation of migraine without a clear clinical indication."

A meningioma is not necessarily an incidental finding in a migraineur. Evans and colleagues[53] reported a 47-year-old woman with a left frontal secretory meningioma that mimicked transformed migraine with and without aura. As discussed above, there is potential harm to the patient and physician's medicolegal liability if these rare cases are not detected.

Wang and colleagues[32] recruited 1070 health controls and 1070 primary headache patients (including 665 with migraine) from the Chinese People's Liberation Army General Hospital who then underwent either CT or MRI scans. Abnormal scans were found in the following: 0.67% in migraine (3/665 with MRI and 0/291 with CT) compared with 0.73% abnormal scans in controls. Abnormalities in migraineurs were 2 with hydrocephalus and 2 with tumors of the throat and nose. They conclude, "The present study found that neuroimaging was unnecessary for the primary headache patients."

White Matter Hyperintensities and Subclinical Infarcts

WMA are foci of hyperintensity on proton density, fluid attenuation inversion recovery, and T2-weighted images in the deep and periventricular white matter resulting from interstitial edema or perivascular demyelination. WMA are easily detected on MRI but are not seen on CT scan. The percentages of WMA for all types of migraine range from 4% to 59% and in controls from 0% to 31%.[54]

The clinical significance of WMA is not known. There might be microvascular damage because of gliosis, demyelination, and loss of axons.[55]

WMA are not specific to migraine and can be present in nonmigraine headaches and older age. Depending on the number, distribution, and location, there may be a secondary cause, such as multiple sclerosis, cerebral autosomal dominant arteriopathy with subclinical infarcts and leukoencephalopathy, or mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes.

In the general population-based MRI study in the Norwegian county of Nord-Trondelag (HUNT MRI),[56] having tension-type headache or developing headache in middle age was linked to extensive WMA. Migraine did not increase the odds of having extensive WMA.

Silent infarctlike lesions (ILLs) have been reported in migraineurs typically located in the cerebellum, subcortex, and deep gray matter. The cause, nature, and clinical significance are not clear.[57] Evaluation for stroke risk factors is appropriate.

In a metaanalysis of WMA and ILLs,[54] there was an association for migraine with aura (odds ratio 1.68) but not for migraine without aura. The association of ILLs was greater for migraine with aura than without, but there was no association for either type of migraine compared with controls.

In a study of female twins aged 30 to 60 years in the population-based Danish Twin Registry,[58] there was no evidence of an association between silent brain infarcts, WMA, and migraine with aura. A prospective study found no association of WMA and cognitive changes in migraineurs.[59]

Practice Parameters

A report of the Quality Standards Subcommittee of the AAN[54] makes the following recommendation: "Neuroimaging is not usually warranted in patients with migraine and a normal neurologic examination (Grade B)." The American Headache Society

Choosing Wisely[60] recommendation is the following: do not perform neuroimaging studies in patients with stable headaches that meet criteria for migraine.

Although the yield is low, **Box 3** lists some reasons to consider neuroimaging in migraineurs. There are numerous migraine mimics.[61]

Trigeminal Autonomic Cephalalgias

TACs are primary headache syndromes characterized by severe unilateral headaches typically associated with ipsilateral cranial autonomic features, such as lacrimation, conjunctival injection, nasal congestion, and rhinorrhea. TACs include cluster headache, paroxysmal hemicrania, hemicrania continua (HC), and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), with cluster headache the most common.[62] **Table 2** provides the clinical features.

There are many secondary causes of TACs. It can be difficult in some cases to determine causality with a lesion that can be incidental. de Coo and colleagues[63] propose the following categories: probably secondary (when there was a dramatic improvement of the headache after treatment of the underlying lesion); possibly secondary (when the patient was treated but did not become headache free, or was not treated, but where a causal relation was possible based on previous experience with other patients); and unknown (patients in which a causal relation between the phenotype and the lesion was less likely or at least unclear).

Secondary cluster headaches

There are numerous causes of secondary cluster headaches or clusterlike headaches.[64,65] Vascular causes include the following: carotid and vertebral artery dissection, pseudoaneurysm of intracavernous carotid artery, anterior communicating artery aneurysm, AVMs (occipital lobe, middle cerebral artery territory, in soft tissue above ear, frontal lobe, and corpus callosum), infarction (cervical cord and lateral medullary),

Box 3
Reasons to consider neuroimaging in migraineurs

- Unusual, prolonged, or persistent aura
- Increasing frequency, severity, or change in clinical features
- First or worst migraine
- Migraine with brainstem aura
- Confusional
- Hemiplegic
- Late-life migraine accompaniments
- First onset ≥50 years of age
- Aura without headache
- Headaches always on the same side?
- Posttraumatic
- Patient or family and friend request

From Evans RW. Diagnosis of headaches and medico-legal aspects. In: Evans RW, Mathew NT, editors. Handbook of headache. 2nd edition. Philadelphia: Lippincott-Williams & Wilkins; 2005. p. 21; modified, with permission.

Table 2
Comparison of the trigeminal autonomic cephalalgias

	Cluster Headache[1]	Paroxysmal Hemicrania[2]	SUNCT/SUNA[3]	HC[4]
Ratio of female to male	1:3	Slightly more women	1:1.5	2:1
Pain				
Quality	Sharp, stabbing, throbbing	Sharp, stabbing, throbbing	Sharp, stabbing, throbbing	Baseline: aching; exacerbations: sharp, stabbing, throbbing
Severity	Very severe	Very severe	Severe	Baseline: mild to moderate; exacerbations: moderate to severe
Attacks				
Frequency (per day)	1–8[a]	5–50	1 to hundreds	Constant
Duration (min)	15–180	2–30	0.01–10[b]	Baseline: 3 mo or more; exacerbations: 30 min to 3 d
Ratio of episodic to chronic	90:10	35:65	10:90	15:85[c]
Associated features				
Restlessness	90%	80%	65%	70%
Circadian periodicity	82%[5]	Rare	Rare	Rare
Triggers				
Alcohol	Yes	Yes	No	Yes
Nitroglycerin	Yes	Yes	No	Rare
Neck movements	No	Yes	Yes	No
Cutaneous	No	No	Yes	No
Treatment response				
Oxygen	70%	No effect	No effect	No effect
Sumatriptan 6 mg subcutaneous	90%	20%	Rare effect	No effect
Indomethacin	Rare effect	100%	No effect	100%

Abbreviation: SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms.
[a] Cluster headache frequency is officially 1 headache every other day up to 8 per day.[6]
[b] SUNCT and SUNA duration is 1 to 600 s.
[c] For HC, the ratio of episodic to chronic refers to the ratio of remitting to unremitting attacks.
From Burish M. Cluster Headache and Other Trigeminal Autonomic Cephalalgias. Continuum (Minneap Minn). 2018 Aug;24(4,Headache):1137-1156, with permission.

frontotemporal subdural hematoma, trigeminal root compression, pontine cavernous angioma, external jugular vein thrombosis, petrosal venous compression of trigeminal nerve, segmental cavernous carotid ectasia, and indirect carotid-cavernous fistula. Tumors include the following: pituitary, hypothalamic, meningiomas (parasellar, sphenoidal, tentorial, and high cervical), epidermoid tumor (behind the dorsum sella turcica and clivus), nasopharyngeal carcinoma, C3 root fibrosis, lipoma at C1-2, and glioblastoma multiforme involving the cingulate gyrus. Infective causes include maxillary sinusitis, orbitosphenoidal aspergillosis, and herpes zoster ophthalmicus. Posttraumatic or surgery include facial trauma, following enucleation of eye, and cataract surgery. Dental are impacted wisdom tooth and following dental extraction. Miscellaneous causes are cervical syringomyelia, Chiari malformation, idiopathic intracranial hypertension, and multiple sclerosis.

Levy and colleagues[66] reported a series of 84 consecutive patients who had pituitary tumors (65% macroadenomas). Using International Headache Society (IHS) classification, 4 met criteria for SUNCT, 3 for cluster, and 1 for HC. Cavernous sinus invasion was present in 2 of the 3 cluster cases. Of the 4 SUNCT cases, 2 were prolactinomas and 2 were growth hormone–secreting tumors. Although information is provided on response of all headaches to treatment, response to treatment of the TACs is not provided.

Pituitary adenomas account for up to 17% of all primary brain tumors with a prevalence as high as 115 per 100,000. With the exception of pituitary hemorrhage or infarction, there is likely only a small subset of patients with headaches directly caused by pituitary disease.[67]

Secondary paroxysmal hemicrania

Secondary causes or associations include the following: head trauma; thrombocytopenia; temporal arteritis; pituitary and parasellar lesions; cerebral hemorrhage; cerebral metastasis; AVM, meningioma (cavernous sinus and anterior clinoid; aneurysm (cavernous segment); cavernous sinus dural fistula after carotid artery aneurysm embolization; with use of phosphodiesterase inhibitors; clinically isolated syndrome; and orbital metastaic leiomyosarcoma.[65,68]

Secondary short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/short-lasting unilateral headache attacks with autonomic features

Secondary causes or associations include the following: pituitary tumors; posterior fossa tumors; frontotemporal meningioma; compression of trigeminal nerve by superior cerebellar artery; vertebral artery dissection with dorsolateral medullary infarct, right pontine capillary telangiectasia, and developmental venous anomaly; multiple sclerosis, lung adenocarcinoma, acute and previous infection with herpes zoster in the first trigeminal distribution; viral meningitis; and postradiation to a pituitary adenoma.[63,65]

Secondary hemicrania continua

Rarely, HC may have a secondary cause, which includes the following[65,69]: vascular (cervical internal carotid and vertebral artery dissection, unruptured cavernous internal artery aneurysm, venous malformation of the right masseter, and pontine stroke); neoplasms (nasopharyngeal carcinoma of the nasopharynx, mesenchymal tumor of the sphenoid, adenocarcinoma or small cell carcinoma of the lung, prolactinoma, osteoid osteoma of the ethmoid sinus, benign pineal cyst, and cerebellopontine angle epidermoid); infection (sphenoid sinusitis, HIV, dental disease, and leprosy); and miscellaneous (head trauma, hypertrophic pachymeningitis, transdermal nitroglycerin patch,

following cranial surgery, C7 root irritation owing to disc herniation, inflammatory orbital pseudotumor, and scleritis).

Patients meeting IHS criteria for a TAC rarely have a secondary cause for their headache detected on neuroimaging. Appropriate testing is indicated, however, especially if atypical symptoms and/or signs or risk factors for secondary causes are present. MRI of the brain and MRA of the neck may be indicated. CT of the chest may be considered in smokers.

Secondary new daily persistent headache

NDPH is described by the *International Classification of Headache Disorders, 3rd edition* (*ICHD-3*)[70]: "Persistent headache, daily from its onset, which is clearly remembered. The pain lacks characteristic features, and may be migraine-like or tension-type-like, or have elements of both." The diagnostic criteria are the following:

A. Persistent headache fulfilling criteria B and C
B. Distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours
C. Present for longer than 3 months
D. Not better accounted for by another *ICHD-3* diagnosis

Box 4 lists some primary and secondary causes of new daily headache present for more than 3 months that may have a normal neurologic examination. Some of these secondary disorders may have a thunderclap or sudden onset of severe headache (primary NDPH can have a thunderclap onset[71]), whereas others may develop gradually over 1 to 3 months. Chronic migraine and chronic tension-type headaches increase in frequency over time and are not daily from onset, whereas HC can be daily from onset.

Tests to be considered depending on the case include blood tests (such as CBC, serum chemistries, thyroid function, erythrocyte sedimentation rate and C-reactive

Box 4
Differential diagnosis of new daily headaches present for more than 3 months

Primary headaches
- New daily persistent headache
- Chronic migraine
- Chronic tension-type
- Hemicrania continua

Secondary headaches (NDPH mimics)
- Primary with medication overuse
- Infection (chronic meningitis, Lyme disease, infectious mononucleosis, postmeningitis headache, sphenoid sinusitis, post-Dengue)
- Neoplasms (primary and metastatic)
- Vascular (chronic subdural hematoma, cervical artery dissection, reversible cerebral vasoconstriction syndrome, subarachnoid hemorrhage, dural arteriovenous fistula, hypertension, cerebral venous thrombosis, arteriovenous malformation)
- Posttraumatic headaches
- High and low cerebrospinal fluid pressure (pseudotumor cerebri, postlumbar puncture, spontaneous intracranial hypotension)
- Inflammatory (temporal arteritis and Behçet syndrome[73])
- Miscellaneous (temporal arteritis, Chiari malformation, a single Valsalva event,[74] intranasal contact point, multinodular goiter,[75] cervicogenic, temporomandibular joint dysfunction)

From Evans RW. Diagnostic testing for migraine and other primary headaches. Neurol Clin. 2009 May;27(2):393-415; with permission.

protein in patients 50 years of age and older, Lyme antibodies, and heterophile antibodies), MRI of the brain with and without contrast, MRV of the brain, and MRA of the head and neck (if there is a thunderclap or severe sudden onset).[72]

Guideline

The European Headache Federation[76] has the following recommendations: "Brain MRI with detailed study of the pituitary area and cavernous sinus, is recommended for all TACs. When three consecutive preventive treatments fail additional MRA brain and carotid/vertebral arteries may be required and in the presence of a (partial) Horner's syndrome, additional imaging of the apex of the lung may be warranted, especially in smokers. Pituitary function testing should be considered in refractory TAC patients in addition." Evaluation for lung cancer is a consideration in HC especially in smokers.

For NDPH, "A gadolinium-enhanced brain MRI with MRV and a lumbar puncture with CSF manometry can be indicated in selected patients."

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