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Research Submissions

Neuroimaging for Migraine: The American Headache Society Systematic Review and Evidence-Based Guideline

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Objective.—To provide updated evidence-based recommendations about when to obtain neuroimaging in patients with migraine.

Methods.—Articles were included in the systematic review if they studied adults 18 and over who were seeking outpatient treatment for any type of migraine and who underwent neuroimaging (MRI or CT). Medline, Web of Science, and Cochrane Clinical Trials were searched from 1973 to August 31, 2018. Reviewers identified studies, extracted data, and assessed the quality of the evidence in duplicate. We assessed study quality using the Newcastle-Ottawa Scale.

Results.—The initial search yielded 2269 publications. Twenty three articles met inclusion criteria and were included in the final review. The majority of studies were retrospective cohort or cross-sectional studies. There were 4 prospective observational studies. Ten studies evaluated the utility of CT only, 9 MRI only, and 4 evaluated both. Common abnormalities included chronic ischemia or atrophy with CT and MRI scanning, and non-specific white matter lesions with MRI. Clinically meaningful abnormalities requiring intervention were relatively rare. Clinically significant neuroimaging abnormalities in patients with headaches consistent with migraine without atypical features or red flags appeared no more common than in the general population.

Recommendations.—There is no necessity to do neuroimaging in patients with headaches consistent with migraine who have a normal neurologic examination, and there are no atypical features or red flags present. Grade A Neuroimaging may be considered for presumed migraine for the following reasons: unusual, prolonged, or persistent aura; increasing frequency, severity, or change in clinical features, first or worst migraine, migraine with brainstem aura, migraine with confusion, migraine with motor manifestations (hemiplegic migraine), late-life migraine accompaniments, aura without headache, side-locked headache, and posttraumatic headache. Most of these are consensus based with little or no literature support. Grade C.

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OBJECTIVES

The American Headache Society (AHS) develops guidelines and practice parameters for clinicians. This guideline summarizes evidence from the existing literature about when to recommend neuroimaging in patients with migraine. We specifically reviewed

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studies with either CT or MRI brain imaging, as well as neuroimaging in patients with no concerning signs or exam findings suggestive of secondary headache.

BACKGROUND

Migraine has a worldwide prevalence of 15%-18%[1] and affects over 40 million people in the United States. When and how to use neuroimaging for migraine is a critical issue which confronts every physician who diagnoses and treats migraine. Evidence from the US population based National Ambulatory Medical Care Survey demonstrated that neuroimaging was ordered during 12% of outpatient headache visits between 2007 and 2010.[2]

There are many reasons why physicians may obtain neuroimaging for suspected migraine, including:

- Excluding secondary conditions that mimic migraine.[3]
- Discomfort with migraine as a clinical diagnosis, ie, "our stubborn quest for diagnostic certainty."[4]
- Cognitive bias.[5]
- Busy practice conditions where tests are ordered as a shortcut.
- Addressing the expectations, concerns, and anxiety of patients and family which may be reflected in negative online reviews.[6]
- Addressing the concerns and expectations of referring clinicians ("better safe than sorry").
- Medicolegal issues.[7]

Indiscriminate use of neuroimaging should be avoided. The costs associated with neuroimaging can be significant, and one study estimated nearly $1 billion of annual costs in the United States from neuroimaging.[2] Neuroimaging may also lead to anxiety, further testing, and additional costs from incidental findings which are not clinically significant.[8,9] There are many barriers for obtaining neuroimaging, including cost, as patients may have high deductible insurance plans or lack insurance coverage; lengthy third-party review for payor approval; and insurance companies which consider neuroimaging utilization as a negative in their physician ratings.[10]

Recommendations about the role of neuroimaging in diagnosis of headache vary by specialty. The American Academy of Neurology (AAN) evidence-based review[11] of the role of neuroimaging in non-acute headache patients, published in 2000, recommended: "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)." The AHS' "Choosing Wisely in Headache Medicine" concluded: "Don't perform neuroimaging studies in patients with stable headaches that meet criteria for migraine."[12] The American College of Radiology's "Choosing Wisely" concluded: "Don't do imaging for uncomplicated headache."[13] Neurosurgeons, however, argue against overly restrictive guidelines and for the benefit of neuroimaging of patients with isolated headaches or non-specific symptoms to diagnose brain tumors.[14]

In this systematic review, we aimed to gather evidence about the diagnostic utility (ie, sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV]) of neuroimaging (MRI and CT) in adult patients (ages 18 and older) seeking outpatient treatment for episodic migraine, chronic migraine, progressive migraine,

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migraine with aura, and migraine without aura. Our goal was to answer the question "How often does a CT or MRI of the brain identify potentially symptomatic intracranial abnormalities in this population?" Based on the obtained evidence, we developed a guideline regarding the use of neuroimaging in patients with migraine with a normal neurological examination.

METHODS

Authorship Committee.—The AHS Guideline Committee and the Executive Committee of the Board of Directors accepted the guideline proposal of the working group chair RE and approved the working group. The working group consists of AHS members with expertise in migraine imaging and guideline development. No patients were involved in the development of this guideline. The guideline development process adhered to the standards for systematic reviews of the Institute of Medicine of the National Academies.[15] The AHS provided meeting rooms during annual society meetings and arranged for conference calls for group discussions.

Systematic Review Eligibility Criteria.—A systematic review was designed to gather evidence on which to base the guideline. To be eligible for inclusion in the review, articles must have included adult females and males ages 18 and over who were seeking outpatient treatment for episodic migraine, chronic migraine, progressive migraine, migraine with aura, migraine without aura and undergoing neuroimaging (MRI or CT). English language articles published from 1973, the time of first CT use, to the time of the search were included. Meeting abstracts and case reports were excluded from the search.

Search Strategy.—Two medical research librarians (recruited by Thomas N. Ward, MD) performed a search on December 5, 2016 and used the following databases: Medline (PubMed), Web of Science, and Cochrane Central Register of Controlled Trials. The search terms included the following: migraine, cluster headache, computed tomography, CT, magnetic resonance imaging, MRI, neuroimaging, imaging, diagnosis, diagnostic imaging, delayed diagnosis, differential diagnosis, early diagnosis, pathophysiology, sensitivity, specificity, predictive value, PPV, NPV, likelihood ratio, or testing. Full search strategies for each database are included in Appendix 1. The search was updated on August 31, 2018 using the same search strategy and databases.

Study Selection.—The study selection process is detailed in Figure 1. After the search was conducted, RE and BF jointly screened the titles and abstracts of the returned articles and indicated appropriate articles for exclusion or for further review to answer the guideline question. RB then further applied the diagnostic criteria and selected the final list of articles for review. Additional articles were included from the reference lists of review articles and guidelines. Studies of migraine and white matter lesions, case studies, and reviews were excluded.

Data Extraction and Rating the Evidence.—RB assigned 2 members of the guidelines committee as data extractors for each article (RB, RE, BF, MM, and 3 headache medicine fellows independently reviewed 7 or 8 articles each). DT served as the arbiter of this final review. The committee concurred on the use of a standardized data extraction form that included the following: study name, date of extraction, person extracting, publications type (full article or abstract), funding/conflicts of interest, study design, study location, participants/population, sample size, age (mean [SD]), gender (n (%) female), how migraine diagnosis was made, inclusion/exclusion criteria, recruitment methods, aim, dates of study, primary outcome measure, secondary outcome measure, missing data, analysis methods, primary outcome results, secondary outcome results, key conclusions. The extraction form was piloted by RB prior to use by the group. The Newcastle-Ottawa Scale adapted for cross-sectional studies was used for rating risk of bias and quality assessment.[16]

Synthesis of Results.—Results were qualitatively synthesized by MM who summarized the findings of the data extraction. After extraction, we evaluated whether the results were appropriate for pooling and meta-analysis. Due to methodological and statistical heterogeneity among studies, quantitative synthesis was not appropriate.

RESULTS

The initial search yielded 2269 publications. After review of the titles and abstracts, 85 articles were

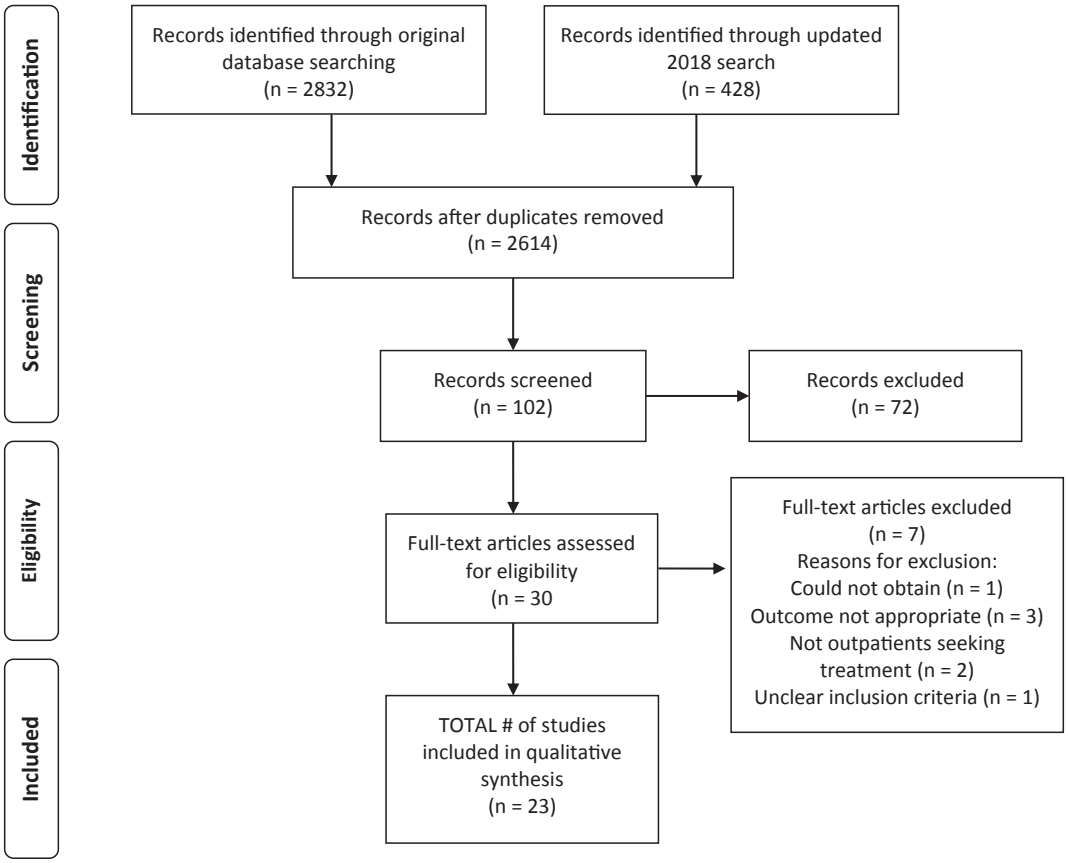

Fig. 1.—Flow diagram of study selection process.

selected by RE and BF for full screening, and 25 meeting the inclusion criteria were chosen for final review and extraction. After excluding 4 articles that were determined to be ineligible after a full review, 21 articles were retained for inclusion in the synthesis of results. Studies of cluster headache were also excluded after determining that none met the review inclusion criteria. The updated search in 2018 yielded 2 new articles that met the inclusion criteria. A total of 23 articles were therefore included in the synthesis (See Table 1). The majority of studies were retrospective cohort or cross-sectional studies. There were 4 prospective observational studies.

While most of the articles (18/23) focused on the use of neuroimaging in the setting of a normal neurological exam and diagnosis of migraine, 5 studies specifically focused on migraine subjects with more worrisome signs or symptoms raising concern for a secondary cause. These included 2 studies of subjects with migraine presenting with acute changes in headache pattern or focal neurological abnormalities,[17,18] long-standing serious migraine (average 20 years) or with "permanent neurological sequelae,"[19] patients with a diagnosis of "non-epileptiform basilar artery migraine,"[20] or disabling migraine requiring hospital admission including hemiplegic or vertebrobasilar migraine.[21] A few studies preceded the recognition of important secondary headaches such as reversible cerebral vasoconstriction syndrome, and the link between migraine and white matter lesions.[20,22] Outpatients seeking care for headache in the clinic were the most common subjects. A few studies included both typical migraine subjects, with and without aura, as well as those with complicated or hemiplegic migraine.

CT Neuroimaging Studies.—Ten studies reviewed the results of CT scans in subjects with migraine (Table 2). In some cases, the authors focused on all abnormalities, while others reported only clinically meaningful findings. In 2 studies, Cala and Mastaglia reported 2 subjects with masses felt to be glioma, 6 with cerebral infarcts and 6 with periventricular edema among their

Table 1.—Characteristics of Included Studies

Authors and Year of Publication	Study Location	Sample Size	Age (As Reported in Manuscript)	Sex (n [%] Female)	Imaging Outcome Measures
Akpek et al (1995)[24]	Ankare, Turkey	592	Mean: 44.3, range: 8-88	416 (70.3%)	Normal findings, minor pathologies, or gross intracranial pathology on CT
Cala and Mastaglia (1980)[18]	Perth, Australia	94	Not specified	Not specified	Presence of discrete lesions and their anatomical location on CT
Clarke et al (2010)[43]	Birmingham, England	530 undergoing imaging out of 3655 total headache patients	Mean: 42 (of 3655 total patients)	69% (of 3655 total patients)	Normal, insignificant abnormality, or significant abnormality on CT or MRI
Cooney et al (1996)[31]	Philadelphia, USA	185	Median: 38, range: 15-83	145 (78.4%)	Frequency of white matter abnormalities and association of white matter abnormalities with age, sex, migraine type, duration of symptoms, and the presence or absence of concomitant medical risk factors on MRI
Cuetter and Aita (1983)[21]	USA	435	Range: 17-52	Not specified	Results of head CT scans
Cull (1995)[41]	Scotland and Holland	69	Mean (SD): 51.6 (8.9), range: 40-79	46 (66.7%)	Frequency of abnormalities on CT or MRI
Gozke et al (2004)[32]	Istanbul, Turkey	45	Mean (SD): 40.91 (7.69), range: 19-53	43 (95.5%)	Frequency of abnormalities on cranial MRI and their relationship to age, type of migraine, frequency of attacks, and duration of symptoms
Honningsvag et al (2016)[33]	Nord-Trondelag county, Norway	864	Mean (SD): 58.5 (4.2), range: 50-66	452 (52.3%)	Intracranial abnormalities on MRI
Hungerford et al (1976)[19]	London, UK	53	mean: 42.7	36 (67.9%)	Abnormalities including atrophy or infarcts on CT
Jacome and Leborgne (1990)[39]	Florida, USA	18	Mean: 30, range: 17-57	14 (77.7%)	Abnormalities on MRI and CT
Kahn et al (1993)[25]	Chicago, USA and Winnipeg, Canada	1111	Chicago women: mean: 46.6, range: 18-100 Chicago men: mean: 45.8, range: 18-93 Winnipeg group: not specified	Chicago group: 587 (68.3%) Winnipeg group: not specified	Abnormal findings including chronic, acute and extracranial findings on CT
Kuhn and Shekar (1990)[42]	Illinois, USA	74	Mean: 28, range: 9-39	59 (79.7%)	Abnormalities on MRI or CT
Masland et al (1978)[27]	Arizona, USA	136	Not specified	Not specified	Abnormalities on CT

Table 1.—Continued

Authors and Year of Publication	Study Location	Sample Size	Age (As Reported in Manuscript)	Sex (n [%] Female)	Imaging Outcome Measures
Mathew et al (1977)[23]	Houston, USA	29	For those with abnormal CT scans (10/29): mean: 34.9, range: 18-50	23 (79.3%)	Abnormalities including ventricular enlargement or low density areas on CT
Mullally and Hall (2018)[38]	Boston, USA	100	Mean: 31.5, range: 18-56	86 (86.0%)	Prevalence of incidental brain abnormalities on MRI
Osborn et al (1991)[34]	San Diego, USA	41	Mean: 29.8, range: 18-66	17 (41.5%)	White matter abnormalities on MRI
Paemelaire et al (2005)[47]	Ghent, Belgium	244 total; 80 with definitive migraine diagnosis	Total: mean (SD): 38 (14) Migraine with aura: male: 35 (10) female: 34 (11) Migraine without aura: male: 44 (13) female: 35 (14)	Total: 171 (70%) Migraine with aura: 10 (59%) Migraine without aura: 52 (83.0%)	Frequency of abnormalities on MRA of circle of Willis
Prager and Rosenblum (1991)[35]	Chicago, USA	99	Mean: 40, range: 16-78	72 (72.7%)	White matter abnormalities on MRI and association with diagnosis, age, sex, and length of headache history or history of ergot use
Sargent et al (1979)[26]	Topeka, USA	177	Range: 16-60	138 (78.0%)	Abnormalities on CT and association with age
Soges et al (1988)[36]	Syracuse, USA	24	Mean: 36.8, range: 18-55	16 (66.7%)	Abnormalities on MRI
Valenca et al (2002)[28]	Recife, Brazil	78	Not specified	Not specified	Frequency of abnormalities on CT
Wang et al (2001)[37]	New York, USA	402	Range: 18-85	286 (71.1%)	Major abnormalities on MRI
Wang et al (2019)[40]	China	1070 patients with primary headache; 1070 healthy controls	Headache: mean (SD): 40.1 (12.3) Controls: 40.2 (12.5)	Headache: 725 (67.8%) Controls: 725 (67.8%)	Significant or non-significant abnormalities or normal on CT or MRI

Table 2.—Studies Using CT Only for Evaluation

Study	Subjects	Results	Conclusions
Cala and Mastaglia[18]	94 subjects with migraine presenting with acute changes in headache pattern or focal neurological abnormalities	The majority of scans (69/94, 73%) were normal, but 2 were found to have unsuspected masses likely to be glioma. Other significant abnormalities included cerebral infarcts (6/94, 6%), and periventricular edema (transependymal cerebrospinal fluid flow or microangiopathy) (6/94, 6%)	CT is a useful screening test for patients with a change in symptoms or new exam findings
Mathew et al[23]	29 total: 4 with hemiplegic migraine, 5 vertebrobasilar migraine, 11 migraine without aura, 9 migraine with aura. Many of the subjects had concerning signs or symptoms such as weakness, memory loss, ataxia, confusion, anxiety or tremor	Most of the patients (19/29, 66%) had normal CT scans. Abnormalities included 4 subjects with ventricular enlargement, in which 2 had associated parenchymal low density areas. Six patients had 1 or more areas of low density. In 3 patients these low-density abnormalities resolved 3 months later	The authors suggested these CT abnormalities represented edema from blood-brain barrier alterations rather than infarction
Cuetter and Aita[21]	435 subjects	Only 1 patient had a significant CT exam abnormality – showing a choroid plexus papilloma of the 4th ventricle. After surgery, there was no change in headache pattern	CT scanning provided "little diagnostic value in patients with classic migraine"
Akpek et al[24]	592 subjects	40 (8%) had minor abnormalities: including: 16 with cerebral or cerebellar atrophy, 12 with chronic ischemia, 9 with possible pseudotumor cerebri, 3 with venous angioma, 2 with empty sella, 2 with ventricular asymmetry, 1 with basal ganglia calcifications, and 1 with a subcutaneous fibroma. No subject had major abnormalities	Patients with chronic headache and a normal exam do not need urgent imaging
Kahn et al[25]	1111 subjects	10.8% were abnormal. Abnormalities included: acute infarction (44, 4.0%), primary neoplasm 18, (1.6%), subarachnoid hemorrhage 14 (1.3%), subdural hematoma 12 (1.1%), metastatic neoplasm 12 (1.1%), vascular abnormalities such as aneurysm or AVM 11 (1.0%), hydrocephalus 9 (0.8%). Extracranial abnormalities included sinusitis or skull metastasis	CT scans are most useful for identifying serious causes of headache in those with risk factors such as thunderclap headache, abnormal exams, old age, elderly, fever, neurological exam changes and seizure
Masland et al[27]	136 subjects	19 (14%) had abnormalities including: 14 with cerebral atrophy, 2 with evidence of small infarcts, 1 with AVM, 1 with astrocytoma, 1 with meningioma, and 1 had a saccular aneurysm of the anterior communicating artery. CT scans did not show abnormalities during migraine attacks, including 2 patients with complicated migraine. The 2 patients with severe intracranial pathology also had recent clinical changes including progressive hemiparesis and focal seizure	CT during migraine and in those with uncomplicated migraine is unlikely to change management. However, CT is effective in detecting significant neurologic disease in patients with new clinical changes

Table 2.—Continued

Study	Subjects	Results	Conclusions
Hungerford et al[19]	53 subjects	Almost ½ of subjects (25/53, 47%) had abnormalities on imaging, including 6 with generalized atrophy, 8 with focal atrophy, 6 with infarcts and 5 with other abnormalities. Of the 13 patients with "permanent neurological sequelae," 11 had CT abnormalities	In retrospect, some of these patients likely had secondary causes of headache such as stroke or reversible cerebral vasoconstriction syndrome
Sargent et al[26]	138 patients with headache, 82 with migraine	Of the patients with migraine, 20 of 82 had an abnormality such as generalized or focal atrophy	The average age of migraine patients with an abnormal CT was 42.29 years compared to 33.33 years with a normal CT ($P < .001$) suggesting age is a risk factor for CT abnormalities
Valenca et al[28]	78 subjects: 34 with migraine, 35 with tension-type, and 9 with both disorders	While many subjects had abnormal CT findings (38.5%), most were considered incidental. Abnormalities included inflammatory sinus disease (19.2%), cysticercosis (3.9%), unruptured cerebral aneurysm (2.6%), basilar impression (2.6%), intracranial lipoma (2.6%), arachnoid cyst (2.6%), empty sella (2.6%), intracranial neoplasm (2.6%), and colloid cyst (1.3%)	The authors concluded CT abnormalities are common but do not usually change management

94 subjects presenting with acute changes in headache pattern or the presence of focal neurologic abnormalities.[17,18] Hungerford et al found abnormalities in almost half of their subjects (25/53) including 6 with generalized atrophy, 8 with focal atrophy, and 5 with other abnormalities.[19] Cuetter and Aita reported only 1 clinically significant abnormality in their 435 subjects with migraine: a choroid plexus papilloma of the 4th ventricle.[21] Mathew et al reviewed results in hospitalized subjects with significant complications and found abnormalities in 10/29 subjects including 4 with ventricular enlargement, and 6 with 1 or more areas of low density.[23] Akpek retrospectively evaluated 592 subjects who had CT for migraine and found that 40 (8%) had minor abnormalities but none had major abnormalities. The abnormalities included 16 with cerebral or cerebellar atrophy, 12 with chronic ischemia, 9 with possible pseudotumor cerebri, 3 with venous angioma, 2 with empty sella, 2 with ventricular asymmetry, 1 with basal ganglia calcifications, and 1 with a subcutaneous fibroma.[24] Kahn et al[25] reviewed findings in 1111 patients presenting at 2 large teaching hospitals for acute non-traumatic headache; About 10.8% was abnormal. Abnormalities included acute infarction (44, 4.0%), primary neoplasm 18, (1.6%), subarachnoid hemorrhage 14 (1.3%), subdural hematoma 12 (1.1%), metastatic neoplasm 12 (1.1%), vascular abnormalities such as aneurysm or AVM 11 (1.0%), and hydrocephalus 9 (0.8%). Sargent et al[26] studied 82 subjects migraine and found 20 of 82 had abnormalities such as generalized or focal atrophy, with increasing prevalence in older subjects. Masland et al studied 136 subjects with migraine and during acute migraine attacks[27] and reported that 19 (14%) had abnormalities including 14 with cerebral atrophy, 2 with evidence of small infarcts, 1 with AVM, 1 with astrocytoma, 1 with meningioma, and 1 had a saccular aneurysm of the anterior communicating artery. CT scans did not show abnormalities during migraine attacks, and the 2 patients with severe intracranial pathology also had recent clinical changes including progressive hemiparesis and focal seizure suggesting a need for neuroimaging. Valenca et al reviewed findings in 78 patients: 34 with migraine, 35 with tension-type, and 9 with both disorders.[28] Abnormalities were common but mostly incidental including inflammatory sinus disease (19.2%), cysticercosis (3.9%),

unruptured cerebral aneurysm (2.6%), basilar impression (2.6%), intracranial lipoma (2.6%), arachnoid cyst (2.6%), empty sella (2.6%), intracranial neoplasm (2.6%), and colloid cyst (1.3%).

Many of these early CT studies report frequent abnormalities, findings such atrophy, chronic ischemia, basal ganglia calcifications, sinus disease or ventricular enlargement, very few of these changed the diagnosis or led to intervention. Many of the reported abnormalities such as atrophy likely reflect normal aging.[29] The prevalence of unruptured intracranial aneurysms in these studies was similar to the general population.[30] While there were some serious abnormalities, in one study, the 2 patients with severe pathology had a progressive hemiparesis and another with seizure.[27] Other abnormalities occurred among subjects in studies specifically focused on hospitalized subjects [25] or in those with new changes in headache or exam abnormalities.[18]

MRI Neuroimaging Studies.—Nine studies reviewed the results of MRI studies in subjects with migraine (Table 3). Cooney et al retrospectively analyzed 185 consecutive patients with migraine to correlate MRI abnormalities such as white matter lesions with patient demographics and clinical features.[31] Only 30 of the 185 (16%) had white matter abnormalities, with a higher prevalence in subjects over 50 and those with risk factors such as hypertension, heart disease, or diabetes mellitus.[31] Gozke et al[32] studied 45 patients with migraine: 20 with aura and 25 without. White matter foci were noted in 13/45 subjects (28.8%) and significantly more common in those with aura (8/20, 40%) compared to those without (5/25, 20%). There was 1 patient each with frontoparietal cortical atrophy and heterotopy – felt to be incidental findings. Honnigsvag reviewed MRI findings in a population-based cross-sectional study of adults aged 50-65 who had participated in previous Nord-Trøndelag Health Studies (HUNT).[33] Patients with any headache disorder had a higher rate of any intracranial abnormality as compared with the non-headache population (29% vs 22%), including major (11% vs 10%) and minor (17% vs 13%) categories. However, when white matter hyperintensities were removed from the analysis, this association disappeared. While abnormalities were common in both groups including venous angioma, multiple sclerosis, carotid disease, AVM, and pituitary tumor, there was no significant difference between headache and headache-free groups.[33] Osborn et al[34] reviewed MRI findings in a relatively younger group of migraine subjects, with a mean age of 29.8 years. They detected white matter lesions in 5 of the 41 patients (12%) which were less common in those under 40 years old (5.5%). Prager and Rosenblum retrospectively reviewed 77 subjects with migraine, to determine if white matter abnormalities were associated with clinical features such as diagnosis, sex, age, number of years with symptoms, and history of vasoactive medication.[35] These abnormalities were common in subjects with (44%) and without (47%) aura, and more common with advancing age. Soges et al[36] investigated 24 patients with migraine, including 7 without aura and 17 with aura. They determined that white matter lesions were common in those with aura (4/7, 57%) and those without aura (7/17, 41%). They also reported addition 3 large cortical abnormalities in the group with aura multiple bilateral focal white matter lesions in another subject. Wang et al[37] retrospectively reviewed neuroimaging findings in 402 subjects referred for headache by a neurologist including 161 subjects with migraine. Major abnormalities were significantly less common in those with migraine, the only abnormality was a petrous apex cholesterol cyst in a 58-year-old woman. Mullally and Hall[38] sought to determine if patients who request neuroimaging for headache would be more likely to have serious abnormalities. Of 100 subjects with a migraine diagnosis, including 41 with chronic migraine, and normal neurological examination, most scans were normal (82%) but 17% had insignificant abnormalities. One patient had a serious abnormality: a meningioma that eventually required surgery and radiation therapy. Jacome and Leborgne[39] specifically studied 18 patients with a diagnosis of "non-epileptiform basilar migraine" and found an abnormality in 12/18. Of these, 6 had mildly enlarged sulci, 1 had moderately large ventricles and T2 focal signal abnormalities, 1 had cerebellar vermal hypoplasia, 1 had basal ganglia calcifications, and 2 had a single white matter lesion.

In addition to abnormalities noted on CT, MRI studies frequently showed white hyperintensities and occasionally pituitary abnormalities. These studies primarily focused on outpatients with migraine with no indication of exam abnormalities. Other than the

Table 3.—Studies Using MRI Only for Evaluation

Study	Subjects	Results	Conclusions
Jacome and Leborgne[39]	Diagnosis of "non-epileptiform basilar artery migraine." (21) Exclusion criteria included objective abnormalities such as an abnormal neurological exam or EEG, as well as a diagnosis of epilepsy on anti-epileptic treatment	Of these 18 subjects, 6 had mild cortical sulci enlargement. One had moderate ventricular enlargement and focal T2 signal abnormalities in the centrum semiovale. Another subject had basal ganglia calcifications, and another cerebellar vermis hypoplasia. Two had 1 single T2 white matter lesion. Six of the 12 subjects had a CT study prior to MRI which did not show the MRI abnormalities. Six of the 18 subjects had both normal CT and MRI	The authors concluded MRI was more sensitive than CT for abnormalities. Neither CT nor MRI demonstrated a biomarker for the disorder, with the exception of the patient with cerebellar hypoplasia. The authors also mentioned the white matter abnormalities were not typical for demyelinating disease
Cooney et al[31]	185 consecutive patients with migraine in the same department. Their goal was to correlate MRI abnormalities such as white matter lesions with patient demographics and clinical features	Only 30 of the 185 (16%) had white matter abnormalities. These abnormalities were more common in patients over age 50 but did not correlate with clinical features such as length of disease, sex or migraine subtype. Only 6% of subjects who were under age 50 and had no significant medical problems such as hypertension, heart disease, or diabetes mellitus had white matter abnormalities (24)	The authors suggested white matter abnormalities may not be migraine related, and may be incidental findings related to other clinical variables such as age
Gozke et al[32]	45 patients with migraine: 20 with aura and 25 without	White matter foci were noted in 13/45 subjects (28.8%) and significantly more common in those with aura (8/20, 40%) compared to those without (5/25, 20%). There was a non-significant difference for longer mean migraine duration in those with white matter foci. There was 1 patient each with frontoparietal cortical atrophy and heterotopy – felt to be incidental findings	The authors concluded that "there are no specific MRI findings peculiar for migraine" but that white matter foci are common, especially in those with aura
Honnigsvag et al [33]	Population-based cross-sectional study which included adults aged 50-65 who had participated in previous Nord-Trøndelag Health Studies (HUNT)	Patients with any headache disorder had a higher rate of any intracranial abnormality overall (29% vs 22%), including major (11% vs 10%) and minor (17% vs 13%) categories. However, when white matter hyperintensities were removed from the analysis, this association disappeared. Persons with migraine were not more likely to have cysts, aneurysm, cerebral infarctions, meningioma, or microhemorrhages. There were a large number of significant abnormalities in both headache and headache-free groups including venous angioma, multiple sclerosis, carotid disease, AVM, and pituitary tumor but there was no significant difference between headache and headache-free groups	The author concluded that persons with migraine are more likely to have white matter hyperintensities. Other neuroimaging abnormalities do not appear more common in those with migraine

Table 3.—Continued

Study	Subjects	Results	Conclusions
Osborn et al[34]	41 Subjects, with a mean age of 29.8 years	White matter lesions were detected in 5 of the 41 patients (12%) but were less common in those under 40 years old (5.5%). One of the patients with complicated migraine had white matter lesions, but no other significant abnormalities were seen	
Prager and Rosenblum[35]	77 subjects with migraine	White matter abnormalities were common in subjects with (44%) and without (47%) aura, and more common with advancing age	White matter changes are common in migraine and more common in older patients
Mullally and Hall[38]	100 subjects with migraine and a normal neurological examination, including 41 with chronic migraine	Most scans were normal (82%) but 17% had insignificant abnormalities. One patient had a serious abnormality: a meningioma that eventually required surgery and radiation therapy.	Given that the prevalence of this tumor in the general population is similar, the authors concluded brain MRI should not be performed as part of the evaluation of migraine without a clear clinical indication
Soges et al[36]	24 subjects: 17 migraine with aura, 7 migraine without aura. The authors did not clearly define migraine or specify how secondary causes of headache were ruled out	T2-weighted studies demonstrated white matter lesions more frequently in those with aura (4/7, 57%) than those without aura (7/17, 41%). In addition, among those with aura there were large cortical abnormalities similar to infarcts in three patients and multiple bilateral focal white matter lesions in one patient	The authors noted the cortical lesions correlated with neurological deficits, but the periventricular changes were not
Wang et al[37]	402 subjects referred for headache by a neurologist. Headache types included: migraine (161 subjects), tension-type (71), mixed (27), atypical (64), or other (79)	The study focused on major abnormalities of possible clinical significance, not white matter abnormalities. Major abnormalities were significantly less common in those with migraine than in other types of headache. The only abnormality among the migraine subjects was a petrous apex cholesterol cyst in a 58 year old woman	If anything, patients with migraine are less likely to have significant neuroimaging abnormalities than those with non-migraine headaches

patient with meningioma, there were no serious abnormalities requiring intervention.

Studies Using Both CT and MRI.—Four studies included subjects with either CT or MRI imaging. Wang[40] compared neuroimaging results between 1070 subjects with headache (including 665 with migraine) and 1070 healthy gender and age matched controls, without "red flags" or abnormal exam findings. None of the 382 subjects undergoing CT had significant abnormalities. Of the 688 subjects receiving MRI, only 4 subjects with headache had significant imaging abnormalities (0.58%), including 3 of the migraine subjects (0.67%). Abnormalities included 2 subjects with hydrocephalus and 2 with tumors of the throat and nose. There were 5 abnormalities in the healthy controls (0.73%) which was not significantly different.[40] Cull[41] studied CT and MRI abnormalities in 69 subjects presenting with "late-onset migraine" starting after the age of 40 with the majority of subjects (86%) having aura. When available, carotid ultrasound and laboratory testing was also reviewed. About 93% had normal neuroimaging. Abnormalities included 4 subjects with evidence of a previous cerebral infarction, and 3 with mild-moderate carotid atheroma on ultrasound scanning. Kuhn and Shekar reviewed CT and MRI findings in 74 pediatric and adult subjects (age 9-39, mean 28) with classic migraine. MRI revealed multiple foci of bright signal on T2 MRI in 19 of the 74 subjects (26%) which were not detected on CT. Focal or generalized ventricular enlargement or sulcal prominence was present in 26 subjects both on CT and MRI. One patient with homonymous hemianopsia had an occipital lobe infarct – seen on both MRI and CT.[42] Clarke et al reviewed CT and MRI findings in sequential new patients who had neuroimaging over a 5-year period.[43] Of the 167 patients with a diagnosis of migraine, only 2 (1.2%) had significant abnormalities and both had known possible secondary causes of headache. One abnormality was a Chiari malformation in a patient with a history of Moya-Moya disease and extracranial-intracranial bypass surgery, and another presenting with blurred vision and early morning headache with known Dandy-Walker syndrome was found to have a blocked shunt (Table 4).

These studies with CT or MRI demonstrated frequent abnormalities but with similar incidence to those in the general population or control groups. Exam abnormalities such as vision loss or history of neurosurgery predicted significant pathology in CT or MRI.

Quality Assessment.—The quality of studies included in this review was generally poor. Scores on the Newcastle-Ottawa Scale for cross-sectional studies ranged from 0 to 6 (Table 5). The majority of studies received either a 0 (9 studies) or a 1 (6 studies). Only 1 study each received a 5 or 6. No studies received the score of >7 required to be considered high quality. Only 1 study, Honningsvag et al[33] , was rated as being truly representative of the population of interest. The majority of studies included in this review were based on either consecutive recruitment from a healthcare setting, or were convenience samples. No paper described a sample size calculation. Three studies[20,22,33] reported that outcomes were determined by independent blind assessment. Most radiographic outcomes were determined by radiologists who were aware of the indication for imaging. Based on the methodological flaws of the included studies, further good quality studies are needed.

DISCUSSION

This systematic review included 23 articles which attempted to assess the value of neuroimaging in migraine. The methods for selecting subjects varied considerably among studies. Some specifically included subjects with worrisome features. Other studies retrospectively analyzed findings of CT or MRI after they were ordered by physicians. Only a few prospectively studied patients with migraine. In the few cases in which neuroimaging lead to the discovery of clinically meaningful abnormalities, many had abnormal exam findings such as homonymous hemianopsia,[42] progressive hemiparesis and focal seizures,[27] or previously diagnosed secondary causes of migraine including brain surgery.[43] While white matter abnormalities are common in those with long-standing migraine, they more likely represent a consequence of migraine, rather than a cause of the disorder.[22] Another limitation is that some of these studies were performed over 40 years ago. These studies predate recent headache classification and do not differentiate episodic and chronic migraine.

Another discrepancy was the definition of neuroimaging abnormalities. Early studies reported cerebral

Table 4.—Studies Using Either MRI or CT for Evaluation

Study	Subjects	Results	Conclusions
Cull[41]	69 subjects, with "late-onset migraine" after age 40. The majority (86%) had were migraine with aura. When available, carotid ultrasound and laboratory testing was also reviewed	Most subjects (93%) had normal neuroimaging. Four of the subjects had evidence of a previous cerebral infarction, and 3 had evidence of mild-moderate carotid atheroma on ultrasound scanning. However, none of the subjects had findings which would change clinical management such as brain cancer or a vascular malformation	Routine neuroimaging of late-onset migraine is unlikely to be of value in patients with a normal exam and no worrisome clinical features
Kuhn and Shekar[42]	17 subjects with migraine with aura. Included both pediatric and adult subjects (age 9-39, mean 28)	In 19 of the 74 subjects (26%) MRI revealed multiple foci of bright signal on T2 MRI which were not detected on CT. Focal or generalized ventricular enlargement or sulcal prominence was present in 26 subjects both on CT and MRI. One patient with homonymous hemianopsia had an occipital lobe infarct – seen on both MRI and CT	MRI is more sensitive for detecting lesions than CT, but not brain atrophy
Clarke et al[43]	167 subjects with migraine	Only 2 (1.2%) had significant abnormalities and both had known secondary causes of headache. One abnormality was a Chiari malformation in a patient with a history of Moya-Moya disease and extracranial-intracranial bypass surgery. The other presented with blurred vision and early morning headache with known Dandy-Walker syndrome and was found to have a blocked shunt	The authors concluded it is best to selectively image in patients with exam abnormalities or worrisome signs or symptoms
Wang et al[40]	1070 subjects with headache, including 665 with migraine, and 1070 controls. Subjects with red flags raising concern for headache or abnormal exam findings were excluded	None of the 382 subjects undergoing CT had significant abnormalities. Of the 688 subjects receiving MRI, only 4 subjects with headache had significant imaging abnormalities (0.58%), including 3 of the migraine subjects (0.67%). Abnormalities included 2 subjects with hydrocephalus and 2 with tumors of the throat and nose. There were 5 abnormalities in the healthy controls (0.73%) which was not significantly different	Neuroimaging in patients with migraine or other primary headache who do not have exam abnormalities or red flags is unneeded and a poor use of health care resources

Table 5.—Study Quality Assessment Using a Modified Newcastle Ottawa Scale for Cross-Sectional Studies[15]

	Selection												Comparability		Outcome						
Study	1a	1b	1c	1d	2a	2b	3a	3b	3c	4a	4b	4c	1a	1b	1a	1b	1c	1d	2a	2b	Quality Score
Akpek et al[24]		*				*	*					*					*			*	1
Cala and Mastaglia[18]		*				*	*					*						*		*	1
Clarke et al[43]		*				*		*		*							*			*	1
Cooney et al[31]		*				*			*	*			*	*	*				*		5
Cuetter and Aita[21]		*				*	*				*							*		*	1
Cull[41]			*			*			*			*							*		*	0
Gozke et al[32]			*			*			*	*								*	*		2
Honningsvag et al[33]	*					*		*		*			*	*	*				*		6
Hungerford et al[19]			*			*			*			*							*		*	0
Jacome and Leborgne[39]			*			*			*			*							*		*	0
Kahn et al[25]		*				*	*				*		*				*		*		3
Kuhn and Shekar[42]		*				*			*			*						*		*	0
Masland et al[27]			*			*			*		*							*		*	0
Mathew et al[23]				*		*			*		*						*			*	0
Mullally and Hall[38]		*				*			*	*							*			*	1
Osborn et al[34]		*				*			*		*						*			*	0
Paemelaire et al		*				*	*			*								*	*		3
Prager and Rosenblum[35]		*				*	*					*	*	*				*		*	3
Sargent et al[26]		*				*		*			*						*			*	0
Soges et al[36]				*		*			*			*						*		*	0
Valenca et al[28]			*			*			*	*								*		*	1
Wang et al[37]		*				*	*					*	*	*				*	*		4
Wang et al[40]		*				*		*		*			*	*	*					*	4

Maximum scores: Selection = 5, Comparability = 2, Outcome = 3, Total Quality Score = 10.

atrophy and white matter foci on MRI as significant abnormalities, but more recent studies have focused on clinically meaningful abnormalities that require observation or treatment. This review specifically focuses on neuroimaging for migraine, and excludes other common primary headache disorders such as the trigeminal autonomic cephalalgias and facial pain disorders. Only 9 of the studies exclusively studied MRI. Compared to CT, MRI does not pose a risk of radiation and may identify abnormalities commonly missed on CT located in the pituitary or posterior fossa, venous sinuses, and optic nerve.[44,45] For patients with disorders such as low or high cerebrospinal fluid pressure or Chiari malformation, a normal CT may be falsely reassuring. As MRI is widely available, carries no known biologic risk, and had significantly increased sensitivity, The American Headache Society and other organizations now recommend MRI over CT for patients presenting with subacute or chronic headache for those patients who need neuroimaging.[12] In patients at high-risk for having significant abnormalities, the judicious use of MRI may actually improve outcomes and decrease medical costs.[46]

Most of the studies in this review predate advances in MRI technology such as stronger magnet sizes, ultra-high-field magnetic resonance angiography, and the ability to obtain thinner slices for specific regions such the pituitary or brainstem.[48] These advances offer physicians more choices in selecting exams, and communication between referring providers and radiology can ensure more appropriate imaging. The studies in this review did not assess a role for non-invasive angiography or venography in the evaluation of migraine. Given its potential for toxicity,[49] there is no indication for the routine use of gadolinium contrast in the imaging of migraine, unless there is a high index of suspicion for another disorder such as multiple sclerosis or brain cancer.

In spite of these differences, the medical evidence to date appears fairly consistent. Subjects with concerning clinical or exam features frequently have abnormalities which require attention and should be imaged. Neuroimaging may be considered for presumed migraine for the following reasons: atypical in nature, prolonged or persistent aura, increasing frequency, severity, or change in clinical features, first or worst migraine, migraine with brainstem aura, migraine with confusion, hemiplegic migraine, late-life migrainous accompaniments, aura without headache, side-locked headache, and posttraumatic headache. While criteria have been promoted to guide recognition of secondary headache, so called "red flags" such as fever, immunosuppression, papilledema, or pregnancy, especially in combination increase the chances of secondary headache.[50] These signs and symptoms guide neuroimaging selections such as ordering angiography for suspected reversible cerebral vasoconstriction syndrome, or gadolinium enhancement for suspected low pressure headache.

However, there is no evidence that routine imaging for migraine meeting International Classification of Headache Disorders 3rd edition criteria (at least 5 attacking of migraine without aura and at least 2 attacks of migraine with aura)[51] is more likely to reveal meaningful abnormalities compared to the general healthy population in the absence of worrisome features. Several studies affirm that routine neuroimaging for migraine meeting the criteria is more likely to identify incidental abnormalities than identify serious problems, potentially creating anxiety or leading to further work-up.

Reducing the overutilization of neuroimaging is a high priority as we move toward value-based care delivery models.[52] In many cases, clinicians may overestimate the patient's desire to receive neuroimaging.[53] The threshold to perform neuroimaging varies considerably from provider to provider, even among specialists.[54]

While some clinicians may request neuroimaging hoping to ease the anxiety of their patients,[55] the initial reduction in anxiety is lost at 1 year follow-up in a study of chronic daily headache.[56] However, neuroimaging significantly reduced costs for patients with high levels of psychiatric co-morbidity. Rather than routine neuroimaging of migraine patients, an alternative approach is to establish a strong relationship and educate the patient about the low yield of neuroimaging. Informing and involving patients in the decision-making process may increase patient satisfaction and improve outcomes.

If the headache is resistant to migraine treatment or has changes in migraine character, reevaluation may be necessary. Reassure patients that neuroimaging can be performed at a later date should new symptoms or signs develop. Patients with potential warning signs

of catastrophic headache (eg, thunderclap headache, neurologic deficits) in need of urgent attention rarely present in an outpatient setting and are an exception.

This review does not touch on emerging neuroimaging research such as functional neuroimaging,[57] or studies generally used to investigate secondary headache disorders such as CSF flow studies[58] or MRI venograms to assess for the presence of transverse sinus stenosis.[59]

Recommendations.—It is not necessary to do neuroimaging in patients with headaches consistent with migraine who have a normal neurologic examination. **Grade A** (strong recommendation, high quality evidence).

1. Neuroimaging may be considered for presumed migraine for the following reasons: unusual, prolonged, or persistent aura; increasing frequency, severity, or change in migraine clinical features, first or worst migraine, migraine with brainstem aura, confusional migraine, hemiplegic migraine, late-life migrainous accompaniments, migraine aura without headache, side-locked migraine, and posttraumatic migraine. Most of these are consensus based with little or no literature support. **Grade C** (strong recommendation, low quality evidence).

Disclaimer.—This guideline does not mandate any particular course of medical care and is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients.

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APPENDIX 1: Search Strategy

MEDLINE (PUBMED)

The search was run in December 2016 and August 2018. Equivalent search strategies were run in Web of Science and Cochrane Central Register of Controlled Trials on the same dates.

Search	Query
#1	Search "Migraine Disorders" [Mesh] or "Cluster Headache" [Mesh] or Migrain * [tiab] or Cluster headache * [tiab] or Cluster type headache * [tiab] or Cluster like headache*[tiab]
#2	Search "magnetic resonance imaging" [MeSH] or "Tomography, X-Ray Computed" [Mesh] or "Neuroimaging" [Mesh] or "Diagnostic Imaging" [Mesh:NoExp] or "Radiography" [subheading] or MRI [tiab] or Magnetic resonance imaging [tiab] or CT [tiab] or Computed tomography [tiab] or Computerized tomography[tiab] or Computer assisted tomography [tiab] or Neuroimag * [tiab] or Imaging [tiab]
#3	Search "Diagnosis" [Mesh:NoExp] or "Diagnostic Imaging" [Mesh:NoExp] or "Delayed Diagnosis" [Mesh] or "Diagnosis, Differential" [Mesh] or "Early Diagnosis" [Mesh] or "diagnosis" [Subheading:NoExp] or "Sensitivity and Specificity" [Mesh] or "physiopathology" [Subheading] or Diagnos* [tiab] or Specificity [tiab] or Predictive value * [tiab] or PPV [tiab] or NPV [tiab] or Likelihood Ratio * [tiab] or Testing [tiab] or Test [tiab] or Tests [tiab] or Tested [tiab]
#4	Search (#1 and #2 and #3)
#5	Search (#1 and #2 and #3) Filters: Publication date from 1973/01/01
#6	Search (#1 and #2 and #3) Filters: Publication date from 1973/01/01; English
#7	Search "Meeting Abstracts" [Publication Type] or "Case Reports" [Publication Type] Filters: Publication date from 1973/01/01; English
#8	Search (#6 not #7) Filters: Publication date from 1973/01/01; English