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Factors associated with significant MRI findings in medical walk-in patients with acute headache

Joris Budweg[a], Till Sprenger[b,c], Anthony De Vere-Tyndall[d], Anne Hagenkord[d], Christoph Stippich[d], Christoph T. Berger[a,e]

[a] Medical Outpatient Clinic, University Hospital Basel, Switzerland

[b] Department of Neurology, University Hospital Basel, Switzerland

[c] Department of Neurology, DKD Helios Klinik Wiesbaden, Wiesbaden, Germany

[d] Division of Diagnostic and Interventional Neuroradiology, Department of Radiology, University Hospital Basel, Switzerland

[e] Department of Biomedicine, Translational Immunology, University Hospital Basel, Switzerland

Summary

QUESTION: Acute headache is a main reason for emergency consultations and can be a symptom of dangerous neurological conditions. We hypothesised that in medical walk-in headache patients with low suspicion of intracranial bleeding significant findings in brain magnetic resonance imaging (MRI) are associated with clinical features.

METHODS: Retrospective chart review on medical outpatient referrals for brain MRI (2010–2014) with the chief complaint "acute headache" (duration <4 weeks). MRI findings were classified by relevance (significant yes/no) and whether they potentially caused headache. Stepwise logistic regression analysis was applied to identify clinical features associated with pathological findings.

RESULTS: Among 513 MRI examinations, acute headache was the second most common reason for a brain MRI (n = 82, 16%). Of those, forty-one (50%) were completely normal, 16 (19.5%) had an "nonsignificant" finding not causing headache, 10 (12%) had a nonsignificant finding potentially explaining the headache, 8 (9.8%) a "significant" finding probably explaining the headache, and 7 (8.5%) a significant finding probably not causing headache. Syncope (odds ratio [OR] 31.4, 95% confidence interval [CI] 1.7–570), vomiting (OR 7.5, 95% CI 1.2–46.4), ophthalmological symptoms (OR 3.9, 95% CI 1.0–15.6) and female gender (OR 3.1, 95% CI 0.7–13.7) were associated with significant MRI findings. A clinical score based on these variables was associated with a significant MRI finding potentially causing headache with high sensitivity and specificity.

CONCLUSION: Among walk-in patients who underwent MRI for acute headache with low suspicion for intracranial bleeding, 20% had a significant MRI finding. A simple clinical score identified all patients with significant findings that explained the headache. If prospectively validated, this might be a useful tool in selecting those walk-in headache patients requiring urgent cranial MRI.

Key word: *headache; walk-in; outpatient; MRI; risk; clinical findings*

Introduction

Acute headache can be a symptom of dangerous neurological conditions, including intracerebral bleeding or cerebral venous thrombosis [1–5]. About 1 to 4% of all emergency visits are due to headache, and the frequency of subjects receiving immediate neuroimaging has massively increased over recent years [1]. To reduce unnecessary examinations and related costs, it is crucial to distinguish clinically subjects who probably have a significant pathology from those with uncomplicated primary headache. It is generally accepted that patients with focal neurological symptoms and those with acute-onset very severe pain ("thunderclap headache") or seizures require immediate computed tomography (CT) neuroimaging to exclude bleeding [3–10]. However, when headache is an isolated symptom, or in cases where only minor additional symptoms or neurological findings are present, this decision remains challenging [2, 6]. Defensive clinical decision making is common and, driven by the fear of missing dangerous conditions, primary care physicians often order neuroimaging studies with a very low diagnostic yield [1]. Despite this relevant clinical problem, only few studies have investigated which patients, presenting with headache in a medical walk-in clinic, need urgent cranial magnetic resonance imaging (MRI) even in the absence of pathological findings in the physical examination. Moreover, most of these studies date back to times when CT or MRI had only just become widely available [1, 6, 7, 11]. With the rapid quality improvements of MRI techniques and the increase in immediate availability of neuroimaging in past years in industrialised countries, this issue warrants revisiting.

We retrospectively investigated potential predictors of a significant pathological finding in cranial MRI examinations of acute headache patients in a medical outpatient clinic in Switzerland.

Methods

Organisation of the medical outpatient unit and triage of emergency department patients

At the Medical Outpatient Clinic of the University Hospital Basel a team of 20 nurses, 15 physicians and 12 administrative assistants manages 18 000–21 000 doctor visits annually. Of those, around 3500 involve walk-in patients. Among the main reasons for encounters at our walk-in clinic are infections (respiratory, urinary tract, gastrointestinal), acute pain including chest pain and headache, minor neurological symptoms, vertigo and hypertension. While 75% of the patients are direct walk-ins, the remaining 25% are referred from the emergency department (ER). At the ER, patients are triaged by an experienced ER nurse using Emergency Severity Index (ESI) levels. Subjects with levels of 4–5, and those with level 3 if appropriate, are referred to our medical walk-in clinic. This excludes any patient with "sudden onset of speech deficits or motor weakness", "seizure", "suspected meningitis (i.e., headache, stiff neck, fever, lethargy)" or "sudden onset of severe headache", as they are deemed ESI level 2 (i.e., "need immediate attention and use of various resources") [12].

Database search

Patients with referrals for neuroimaging from the medical outpatient clinic were identified via the radiology database of the Department of Radiology at the University Hospital Basel. The study was approved by the local ethics committee (EKNZ 2014–025). MRI scans performed between May 2010 and November 2014 were considered. The clinical indication (i.e., chief complaint) for all MRI was retrieved from the electronic form every physician has to fill out when ordering the examination. Only MRI or MRI-angiograms of the brain were included for further review. The screening process and case identification are outlined in the appendix (supplementary fig. S1). At our medical outpatient clinic, a resident and a senior physician see all walk-in patients. A senior internal medicine physician of the medical outpatient clinic decides which headache patients undergo MRI. As patients with a clinical presentation suspicious for intracranial bleeding, i.e., "red flags" [5, 8, 9] are directly referred for CT scans and/or treated via the ER; our study population was intended to include subjects with very low suspicion for intracranial bleeding. As an approximation of how many of the patients presenting with headache are referred for brain imaging from our clinic, we performed an additional database search of the electronic medical records. We identified all subjects with a primary diagnosis containing the keywords "headache", "cephalalgia", or "migraine". Data on age, gender and whether the patient was referred for imaging were extracted. Those patients with "chronic headache" as the exact diagnosis were excluded. Notably, this search might still have included some patients with headache >30 days or with MRI referrals for other indications.

Chart review and case definition

A retrospective chart review was performed for all patients aged >18 years presenting with the chief complaint of acute headache and in whom a brain MRI had been performed. Chronic headache (defined as headache lasting >28 days with no recent change in pain quality or quantity) and posttraumatic headache were excluded. Data extraction included (if available) demographic characteristics (age, sex, body mass index, smoking status), medication, clinical features (duration and intensity of headache, cluster-like features such as cranial autonomic symptoms, dizziness, ophthalmological symptoms, syncope within the past 3 days, sensory disturbances, paresis, fever) and laboratory analyses (white blood cell count, haemoglobin, thrombocyte count, C-reactive protein and D-dimers) (table 1). Dysaesthesia, hypaesthesia, hyperaesthesia or paraesthesia were summarised as "sensory disturbance", and vision loss, double vision, blurred vision and/or nystagmus as "ophthalmological symptoms". These were counted separately depending on whether they were reported in the patient history or were objective findings in the neurological examination. The neurological examination in our clinic routinely includes pupillary light reaction, eye mobility, cranial nerve testing, upper and lower extremity muscle power, light touch, reflexes, finger-to-nose test and observation of gait. Additional testing was performed when deemed appropriate by the treating physician.

MRI examinations and grading of MRI

The MRI scans were performed on 3 T (n = 45/82; Magnetom Skyra [n = 26], Verio [n = 18] or Prisma [n = 1], all Siemens Healthcare, Erlangen, Germany) or 1.5 T (n = 37/82; Magnetom Avanto [n = 18] or Espree [n = 19], both Siemens Healthcare) scanners. MRI reports were reviewed by two internal medicine physicians from the medical outpatient clinic (JB and CTB). All MRI studies underwent a second look by an experienced neuroradiologist (CS, AH, ADT), who were unaware of the primary report. With input from an experienced neurologist (TS), these second-look MRI findings were then graded as "normal", "nonsignificant" (e.g., sinusitis, age-related microangiopathy) or "significant" (e.g., signs of elevated intracranial pressure, tumour, meningeal enhancement) by consensus. Significant findings were defined as: requirement for additional diagnostic tests (e.g., lumbar puncture, follow-up examinations, serological testing); need for specific treatment (e.g., intravenous antibiotic therapy, anticoagulation); and/or association with substantial morbidity (e.g., multiple sclerosis, vasculitis) [13, 14]. Nonsignificant findings were further divided into unspecific findings of no significance (UFNS) or unknown significance (UFUS). Findings that were potentially causing the patient's headache were labelled as "potentially causing headache". The term "not causing headache" was used if an association was unlikely (table 2).

Statistical analysis

Stepwise binary logistic regression analysis was performed using MiniTab17 software with the following variables: gender, age >40 years, headache onset within the previous 72 hours, pathological neurological examination, fever and/or meningism, sensory disturbance, ophthalmological symptoms, nausea, vomiting, vertigo, and syncope. The analysis had to be limited to these variables on the basis of the completeness of the datasets for all subjects (table 1).

Based on the low event number for some items (e.g., fever, meningism, pain duration categories), some variables from the original chart review were combined. An α-level of 0.15 was applied to enter or remove variables from the model. Prism Software was used for descriptive statistics, receiver operating characteristic (ROC) analysis and data visualisation.

Results

Headache is a frequent referral reason for cranial MRI in younger medical outpatients

Among our medical walk-in patients, acute headache was the second most common reason for brain MRI scans, accounting for 82 of 513 (16%) examinations performed (ap-

Table 1: Characteristics of the clinical cohort.

	All	MRI with significant finding (n = 15)	No significant MRI finding (n = 67)
Age, mean (±SD)	37.8 (±15.7)	38.8 (±22.7)	37.6 (±13.9)
Gender, % female	56%	73%	52%
Symptom duration (n = 82/82, 100%)*			
0–24 h	12%	0%	15%
24–72 h	24%	40%	21%
72 h – 7 d	26%	33%	24%
7–28 d	38%	27%	40%
Headache localisation (n = 74/82, 90.2%)*			
Frontal	41%	46%	34%
Orbital	23 %	20%	19%
Temporal/parietal	43%	46%	36%
Occipital	28%	33%	24%
Generalised	24%	13%	24%
Headache onset (n = 61/82, 74.4%)*			
Hyperacute	3%	0%	4%
Acute	26%	9%	30%
Subacute	21%	27%	20%
Slowly progressive	49%	64%	46%
Headache quality (n = 55/82, 67.1%)*			
Pressing	56%	70%	53%
Pulsating	33%	30%	33%
Stabbing	27%	40%	24%
Pulling	7%	0%	9%
Burning	6%	0%	7%
Additional symptoms (n = 82/82, 100%)*			
Nausea	29.3%	53%	24%
Vomiting	12.2%	33%	8%
Meningism	3.7%	13%	2%
Syncope (within the last 3 days)	4.9%	20%	2%
Fever	2.4%	13%	0%
Ophthalmological symptoms	30.5%	47%	27%
Sensory Disturbance	17.1%	20%	16%
Vertigo	18.3%	20%	18%
Neurological examination (n = 82/82, 100%)*			
Pathological neurological examination	28%	47%	24%
Sensory disturbance	11%	13%	10%
Ophthalmological symptoms	7%	20%	5%
Dysmetria straight walk test	1%	0%	2%
Pronator drift	4%	7%	3%
Unterberger's test pathological	5%	0%	6%
Romberg's test pathological	1%	0%	2%
Dysmetria FTNT	2%	7%	2%
Dysdiadochokinesis	1%	0%	2%
Ptosis	4%	7%	3%
Exophthalmos	1.2%	0%	2%
Paresis N VII	2.4%	0%	3%

FTNT = finger-to-nose test; MRI = magnetic resonance imaging; N VII = cranial nerve VII, facial nerve

* Numbers of subjects for whom the respective data were available from the chart review are indicated as ratio and %.

Information on pain intensity (visual analogue scale [45%], photophobia [43%], phonophobia [32%]) and aggravating/trigger factors (23%) were available in only a subset of patients.

Data on body mass index, smoking status, medication and laboratory results were insufficient for inclusion in further analyses.

Percentages were rounded to the next higher (if ≥0.5), or lower (if <0.5) number.

Table 2: Detailed clinical presentation of patients with significant findings on magnetic resonance imaging.

Subject (age, gender)	Critical MRI finding(s)	Duration	Pain evolution	Pain location	Pain quality	Additional symptoms	Pathological examination	Comments	Follow up
HDS 01 (90 y, f)	Acute right occipital ischaemia, **NPH**	72 h – 7 d	Subacute	T, P	n/a	Ophthalmological symptoms*	Yes (ophthalmological)	Anaemia (Hb 115 g/l)	MRI follow-up 5 days later confirmed ischaemia
HDS 04 (24 y, m)	**Suspected pseudotumor cerebri**	7–28 d	n/a	F, T, P	n/a	Syncope, weight loss	No	–	Lost to follow-up
HDS 13 (61 y, f)	Mastoiditis with **meningitis**	24–72 h	Slow progression	n/a	n/a	Ear pain, nausea, vomiting, weight loss, syncope	Yes (dysmetria FTNT, meningism)	Fever, CRP elevation (126 mg/l), leucocytosis (21.4 × 10^9/l), lymphopenia (0.64 × 10^9/l)	LP: CSF compatible with bacterial meningitis
HDS 14 (30 y, f)	Suspected vasculitis	24–72 h	Slow progression	F, O	PU	Phonophobia	No	–	LP and follow-up MRI normal/ unchanged; subsequently repeated classical migraine attacks
HDS 41 (22 y, f)	Suspected vasculitis	24–72 h	Subacute	F	n/a	–	No	Elevated D-Dimer (0.53 µg/ml)	Further evaluation abroad; no information on final diagnosis available
HDS 44 (46 y, m)	Acute left occipital ischaemia	7–28 d	n/a	O	PR	Nausea, vomiting, vertigo, sensory disturbance†	Yes (sensitivity disturbance right arm)	Anaemia (Hb 97 g/l)	MRI not correlating with symptoms, CT >6 months later: no scar
HDS 45 (24 y, f)	Multiple subcortical white matter lesions	24–72 h	n/a	T, P	PR, S, PU	Nausea, vomiting, photophobia/ phonophobia, sensory disturbance	Yes (pathological pyramidal drift test)	Chronic migraine, >5 attacks/month	interpreted as “migrane attack”, no follow up
HDS 48 (19 y, f)	**Bleeding pituitary gland**	24–72 h	Subacute	H	S, PU	Ophthalmological symptoms*, nausea	No	–	several follow up MRI, hormon sampling
HDS 51 (22 y, f)	**Suspected pseudotumor cerebri**	7–28 d	Slow progression	F, O	PR	Ophthalmological symptoms*, nausea, vomiting, vertigo, gait disorder	Yes (ophthalmological*, nystagmus, sensory disturbance†, meningism)	Lymphopenia (0.85 × 10^9/l)	LP: increased open pressure (>50 cm H_2O)
HDS 60 (33 y, m)	Microadenoma pituitary gland	72 h – 7 d	Slow progression	F, T, P, Orb	PR	Ophthalmological symptoms*	No	–	Diagnosis of hormone-inactive adenoma, no MRI follow up
HDS 64 (31 y, m)	Suspected low grade glioma	7–28 d	Slow progression	F	PR	Sensory disturbance†	No	Leucocytosis (10.3 × 10^9/l)	Follow-up MRI after 3 weeks: lesion of unclear aetiology (DD: dysplasia, postinfection, neoplasm)
HDS 69 (84 y, f)	**Haemorrhagic infarction**	24–72 h	n/a	T, P, O, Orb	n/a	Ophthalmological symptoms*, nausea, vertigo	Yes (gait disorder, hemianopsia)	Elevated D-Dimer (>20 µg/ml)	Follow-up MRI 6 months later: regression
HDS 74 (40 y, f)	**Suspected pseudotumor cerebri**	72 h – 7 d	Acute	H	S	Nausea, vomiting	No	–	Lost to follow-up

HDS 78 (38 y, f)	Multiple subcortical white matter lesions, cortical atrophy	72 h – 7 d	Slow progression	T, P, Orb	PR	Ophthalmological symptoms*, nausea	No	–	LP: normal; follow-up MRI 6 months later: no change
HDS 81 (18 y, f)	Complicated sinusitis with **meningitis**	72 h – 7 d	Slow progression	F, T, P, O	PR, S	Ophthalmological symptoms*, facial pain, ptosis	Yes (ptosis)	Fever	Follow-up MRI 4 months later: complete regression

CRP = C-reactive protein; CSF = cerebral spinal fluid; CT = computed tomography; DD = differential diagnosis; F = frontal; Hb = haemoglobin; H = holocephalic; LP = lumbar puncture; n/a = not available; O = occipital; Orb = orbital; P = parietal; PR = pressing; PU = pulsating; S = stabbing; T = temporal
Findings potentially causing headache are in bold type.
* Ophthalmological symptoms include: vision loss, double vision, orbital pain, blurred vision, nystagmus.
† Sensory disturbances include: dys-, hyper-, hypo-, paraesthesia.

pendix table S1). Vertigo/dizziness was the most frequent indication, and chronic headache ranked forth (fig. 1A). Hence, headache accounted for a large number of cranial MRI examinations in our clinic. While the age distribution was wide, headache patients were on average younger than those who had an MRI for other reasons (fig. 1B). In the majority of patients MRI was performed within 3 days of presentation (72%), and in 54% MRI was on the same day. When "any" MRI findings were considered, i.e., including normal anatomical variants or age-related findings without pathological significance (e.g., unspecific white matter T2 hyperintensities), only 50% (41/82) of the MRI examinations were completely normal. Of the rest, 15 had a finding considered significant, of which eight (10%) were probably causing the headache, and seven (9%) were not considered to usually cause headache. Similarly, there were ten (12%) nonsignificant findings causing headache, such as sinusitis, and 16 (19%) nonsignificant findings not causing headache, such as microangiopathy. The main MRI findings were UFNS (20%), sinusitis (11%), and pseudotumor cerebri (4%). UFUS, suspected vasculitis, stroke, neoplasia, bleeding and meningitis were present in two subjects each (2%). An additional database search indicated that during the study period an estimated total of 443 medical outpatients with acute or subacute headache as the primary diagnosis were seen at our clinic. Of those, 134 (30%) had brain imaging (42 CT [9%], 92 MRI [21%]). The age (median 37 years, intercentile range [ICR] 27–48) vs 34 years, ICR 26–47; p = 0.16) and gender distribution (66% [88/134] vs 64% [199/308] women) was comparable between those who underwent imaging and those who did not.

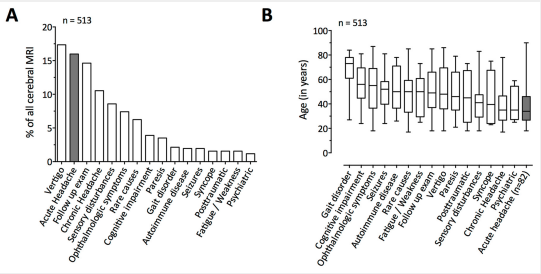

Figure 1
Acute headache is a leading indication for cerebral magnetic resonance imaging (MRI) in medical outpatients. **(A)** Indications for brain MRI referrals at our medical outpatient clinic are displayed. Indications were ranked by % of all ordered brain MRI during the study period. Absolute numbers and more detailed definitions are listed in table S1 (appendix). **(B)** Age distribution per indication is displayed, ranked by decreasing age. The line indicates the median age, the box the second and third quartiles, and the whiskers indicate the range.

Differences in the patient history and clinical examination of subjects with or without significant pathological findings

The significant MRI findings found in our study covered various pathologies (fig. 2). Neuroradiological signs of pseudotumor cerebri represented the most frequent entity, being present in three patients. Meningeal enhancement (i.e., meningitis) related to sinusitis or mastoiditis, occipital ischaemia, suspected vasculitis, multiple subcortical white matter lesions, and an intracranial bleed were each found in two subjects. A probable low-grade glioma and a microadenoma of the pituitary gland were each seen once. Clinical presentations of the subjects with and without significant MRI findings are summarised in table 1. Data on symptom duration and pain location were reported in almost all (90.2% and 100%, respectively) subjects. In contrast, data on pain development and pain quality were only available for 74% and 67% of patients, respectively. Data on pain severity, which were recorded on a visual analogue scale were often lacking (available in 45%), as were data on factors that might have been helpful in the classification of headache: photophobia/phonophobia, trigger factors for sinusitis (e.g., bending head down) or cluster headache (e.g., tearing, eye redness, ptosis) were assessed in only 43%, 32% and 23%, respectively. Patients with significant MRI findings complained more frequently of nausea, vomiting, syncope (within the previous 3 days), ophthalmological symptoms, fever or meningism, whereas the other symptoms were equally distributed. Almost half (47%) of the patients with a significant MRI finding had a finding in the neurological examination. However, a clinical finding was also reported in 24% with a normal MRI scan. The individual symptoms, findings and outcome in patients with significant MRI findings are summarised in table 2. In summary, some symptoms or findings were more frequently found in patients with significant MRI findings, but none of these could firmly discriminate them from patients with normal MRI.

A clinical score predicts significant MRI findings that explain headache

We then tested whether a model based on symptoms and clinical findings could be used to predict which patients had secondary headache due to a significant pathological

MRI finding. Binary stepwise logistic regression identified the best model, based on four of the included variables: syncope, vomiting, ophthalmological symptoms, and female gender (fig. 3A). Weighted by the odds ratio, we generated a clinical score with two points if syncope was present and one point for each of the other factors (appendix, fig. S2). This was used in a ROC analysis to visualise the same data. With a cut-off of two points, this score was associated with a pathological MRI with a sensitivity of 100% and a specificity of 82% (fig. 3B).

The clinical decision as to which of the acute headache patients in the non- ER setting needs urgent cranial MRI is challenging. Given the availability and accessibility within 24 hours of MRI scans in our institution, acute headache patients without red flags for intracranial bleeding [1, 5, 6] frequently undergo head MRI instead of CT scans. Presumably, MRI is more readily accessible in Switzerland than in other countries. Hence, Swiss hospital physicians may have a lower threshold for ordering brain imaging even in the absence of clear warning signs. This allowed us to study MRI findings in the setting of low pretest risk for intracranial bleeding in a medical outpatient clinic, which probably also reflects many patients seen in private practice offices. In our study population of adult medical walk-in patients, we found that female gender, a history of syncope (within the 3 days before presentation), vomiting and ophthalmological symptoms were associated with significant findings on MRI. More specifically, the combination of these variables allowed subjects with a significant MRI finding probably causing headache to be predicted with an accuracy of 100%. Given the retrospective study design, the fact that only headache patients who had MRI were considered in the analysis, and the fact that no additional unrelated cohort of patients was used to validate the score, these findings need prospective confirmation. Moreover, our findings are not applicable to an ER setting, as in ER headache patients other symptoms (e.g., thunderclap headache, loss of consciousness, paresis) or findings (e.g., intracranial bleeding, artery dissection) may be much more prevalent and warrant immediate CT head scans. Obviously, patients with red

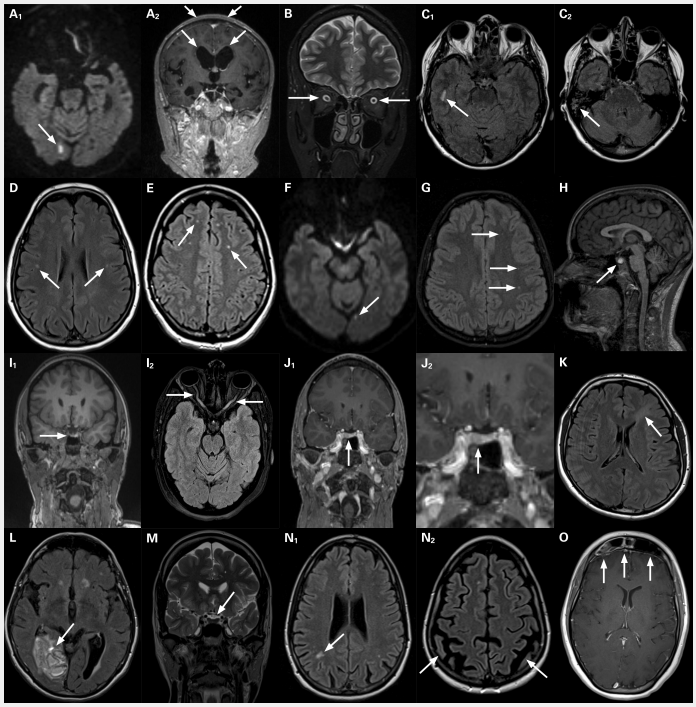

Figure 2
Magnetic resonance imaging (MRI) of acute headache patients from a medical walk-in clinic display a variety of significant findings. MRI scans indicating the significant findings in our study are displayed. White arrows indicate the main pathological finding(s).
A HDS 1, acute ischemia occipital right (A_1), normal pressure, hydrocephalus (A_2)
B HDS 4, suspected pseudotumor cerebri
C HDS 13, meningitis (C_1) complicating mastoiditis (C_2)
D HDS 14, suspected vasculitis
E HDS 41, suspected vasculitis
F HDS 44, acute ischemia occipital left
G HDS 45, multiple subcortical white matter lesions
H HDS 48, bleeding pituitary gland
I HDS 51, suspected pseudotumor cerebri ($I_{1,2}$)
J HDS 60, microadenoma of the pituitary gland ($J_{1,2}$)
K HDS 64, suspected low grade glioma
L HDS 69, hemorrhagic infarction
M HDS 74, suspected pseudotumor cerebri
N HDS 78, multiple subcortical white matter lesions (e.g. N_1), cortical atrophy (N_2)
O HDS 81, complicated sinusitis with meningitis

flags might also present to a walk-in clinic or to primary care physicians, who need to be aware of these. Consequently, our data are only intended to help the decision process in patients without red flags.

Older studies in ER settings or on unselected headache patient populations linked syncope, older age, associated symptoms, focal neurological findings, or vomiting/nausea to pathological imaging findings [8, 15–17], whereas others found no association with any finding and the investigators concluded that imaging is needed in every recent onset headache [18]. We addressed this question in a population of medical walk-in patients. In contrast to previous studies, we here report individual risk factors for pathological MRI findings and performed statistical modelling to test for independent effects of such variables. Since patients with severe neurological symptoms are directly referred to the ER at our hospital, our walk-in population is characterised by a low prevalence of patients with clinical findings highly suggestive of a focal pathology (e.g., hemiplegia, amaurosis, or aphasia), and thus is distinct from ER headache patients. However, 23 out of 82 patients in our study presented with (mostly minor) abnormal findings in the clinical examination. Because of the unspecific nature of most of these findings, it is of little surprise that a pathological examination did not clearly increase the accuracy of outcome prediction in our model. Nevertheless, abnormal findings in the clinical examination were more common in patients with pathological MRI. The heterogeneity of the clinical findings, however, precluded including a subanalysis in the regression model. Also, unlike many neurologists or ER physicians, our physicians did not assess papilloedema in the clinical examination; thus we cannot comment on whether this would have resulted in different findings. As a result of these limitations and the relatively low number of events, and since the clinical examination was not performed in a highly standardised, predefined manner (reporting bias), we cannot exclude the possibility that specific clinical examination findings might predict significant MRI findings in larger, prospective studies. The observation that some headache characteristics that might have allowed classification of the headache were poorly recorded (and probably poorly sought by the treating physician) indicates that headache history-taking by internal medicine specialists in a real-life setting needs to be improved. Given that the history may hint at specific primary headache diagnoses, such as cluster headache, migraine, etc., this may also impact further diagnostic strategies.

In our study, 15 of the 82 patients with headache had a significant finding on cranial MRI, which was substantially higher than we expected on the basis of the literature on unselected patients with headache [1, 6, 7, 11]. Potential explanations are the improvement in MRI technique with the introduction of 3-Tesla MRI, which has been linked to increased detection of pathological findings [19, 20], the study setting of a medical outpatient clinic of a university hospital, or a selection bias as a result of investigating only subjects who had an MRI scan and not all consecutive headache patients. It could, however, also indicate that the physicians made good judgement calls when ordering MRI. Notably, our findings are not applicable to an ER setting, and their translation to the setting of private practice needs to take the limitations of the study into account. Moreover, our study population represents rather young headache patients and the findings are thus not unrestrictedly applicable to older patient groups.

Interestingly, we found that female gender represented a risk factor for significant MRI findings in headache patients who underwent MRI. Sex-related differences in disease presentation and severity can affect outcome, as demonstrated in other diseases [22]. Because of the sex distribution of some diseases, including multiple sclerosis, stroke, systemic lupus erythematosus or migraine, women may have a higher risk for some brain pathologies. However, given the relatively low OR and the wide CI for the association with female gender, we cannot rule out a coincidental finding. Importantly, in our study we found no evidence for a gender bias regarding referrals for brain imaging [23].

From a health economics perspective, unnecessary MRI causes high costs, and may prolong the in- or outpatient clinic stay. Moreover, a relatively high number of nonsignificant findings are seen when cranial MRI is conducted in unselected patients. Awareness of such findings, which are non-significant in a medical sense, can still cause significant discomfort and anxiety in patients. If prospectively validated our clinical score may contribute to reducing imaging for headache, especially in high resource countries, where imaging is readily available and significantly contributes to increasing healthcare costs.

Without prospective validation, our findings do not rule out significant findings in patients without these factors; thus, imaging might still be warranted in specific situations with a significant grade of suspicion for secondary headache. This specifically applies to cerebral venous thrombosis,

A

Variable	Odds Ratio	95% CI
Female Gender	3.08	(0.69 - 13.68)
Ophthalmologic symptoms	3.93	(0.99 - 15.63)
Syncope	31.38	(1.73 - 569.86)
Vomiting	7.45	(1.20 - 46.41)

B

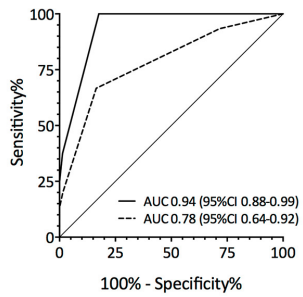

Figure 3

Statistical modelling and data visualisation using a ROC analysis of factors associated with significant magnetic resonance imaging (MRI) findings in headache patients. **(A)** Factors identified in binary, stepwise logistic regression analysis to be associated with significant MRI findings. **(B)** ROC analysis of a clinical score based on syncope (2 points), vomiting (1 point), ophthalmological symptoms (1 point), and female gender (1 point). Visualisation of a score cut-off of 2 points is displayed. Line indicates ROC analysis for "all significant findings that potentially caused headache". Dotted line indicates ROC analysis for 'all significant findings'. Score point distribution in the groups is indicated in figure S2 (appendix). AUC = area under the curve; ROC = receiver operating characteristic

one of the much feared causes of headache in younger individuals. Although it is rare, reports on cerebral venous thrombosis with isolated headache in the absence of any other clinical findings indicate that, in the respective risk settings [24], our clinical score may not exclude the small possibility of such rare events [25, 26]. Although D-dimer values have a good negative predictive value for cerebral venous thrombosis, they have been shown to fail in ruling it out in those with isolated headaches [2, 25] and in pregnant women. In our cohort, no patient had a cerebral venous thrombosis; D-dimers were assessed in only 15/82 patients (18.3%) and were therefore not included in the statistical model.

In conclusion, our data suggest that medical walk-in patients with a history of syncope (within the last 3 days), or at least two of the other factors, an MRI should be performed, and symptomatic therapy without brain imaging is inappropriate. Without confirmation in an independent cohort, our data cannot be used to exclude patients from undergoing imaging. Such validation would preferably be done in a prospective setting and systematically include laboratory testing as well as a standardised neurological examination.

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Correspondence: *Christoph T. Berger, MD, University Hospital Basel, Medical Outpatient Clinic, Petersgraben 4, CH-4031 Basel, christoph.berger[at]usb.ch*

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Appendix

Supplementary figures and table

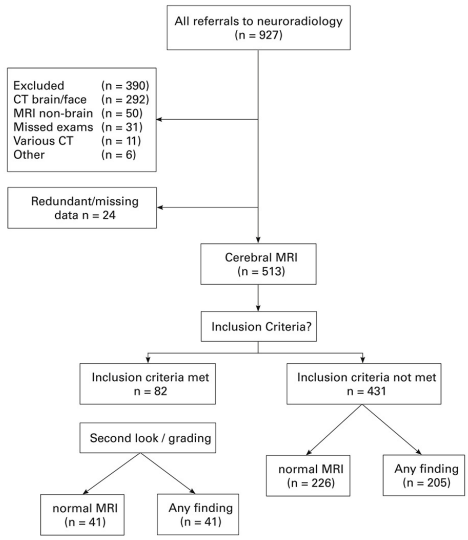

Figure S1
Patient screening and case identification tree.

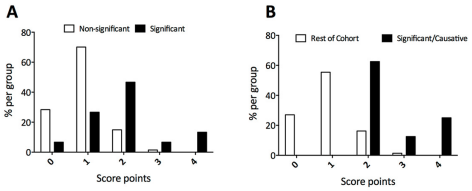

Figure S2

Distribution of the score points. The scores in the groups (A) with (black bars) vs without (open bars) significant findings; and (B) those with significant findings explaining headache (black bars) vs the rest of the cohort (open bars) are displayed. Data is expressed as % subjects per group. The 4-point score consisted of: syncope (2 points), vomiting (1 point), ophthalmological symptoms (1 point), and female gender (1 point).

Table S1: Reasons for referral for brain magnetic resonance imaging.	
Reason	**n (%)**
Vertigo	89 (17.3%)
Acute headache	82 (16.0%)
Follow-up examinations*	75 (14.6%)
Chronic headache (chronic headache, migraine)	54 (10.5%)
Sensitivity disorder (includes paraesthesia, hypaesthesia, hyperaesthesia, etc.)	44 (8.6%)
Ophthalmological symptoms	38 (7.4%)
Rare causes (tinnitus, Horner's syndrome, aphasia, non-headache pain such as jaw, neck, face, or ear pain, transient global aphasia, high blood pressure, hearing problems, Wallenberg syndrome, tremor, follow-up, abnormal neurological examination, acromegaly, unknown)	32 (6.2%)
Cognitive impairment (including dementia)	20 (3.9%)
Paresis	18 (3.5%)
Gait disorder	11 (2.1%)
Epilepsy	10 (1.9%)
Autoimmune disease	10 (1.9%)
Posttraumatic	8 (1.6%)
Fatigue / generalised weakness	8 (1.6%)
Syncope	8 (1.6%)
Psychiatric disorders	6 (1.2%)
Total	**513 (100%)**
* This summarises any examination that was ordered to follow up on a previous finding and included various conditions such as infections, intracranial bleeding, stroke, aneurysms, autoimmune diseases or neoplasia.	

Figures (large format)

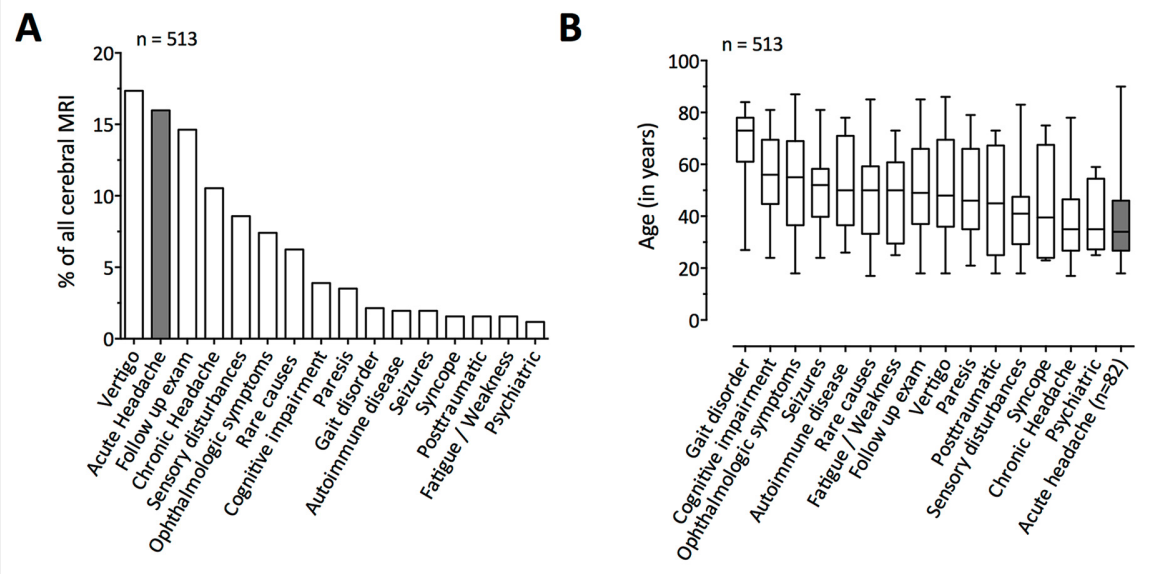

Figure 1
Acute headache is a leading indication for cerebral magnetic resonance imaging (MRI) in medical outpatients. **(A)** Indications for brain MRI referrals at our medical outpatient clinic are displayed. Indications were ranked by % of all ordered brain MRI during the study period. Absolute numbers and more detailed definitions are listed in table S1 (appendix). **(B)** Age distribution per indication is displayed, ranked by decreasing age. The line indicates the median age, the box the second and third quartiles, and the whiskers indicate the range.

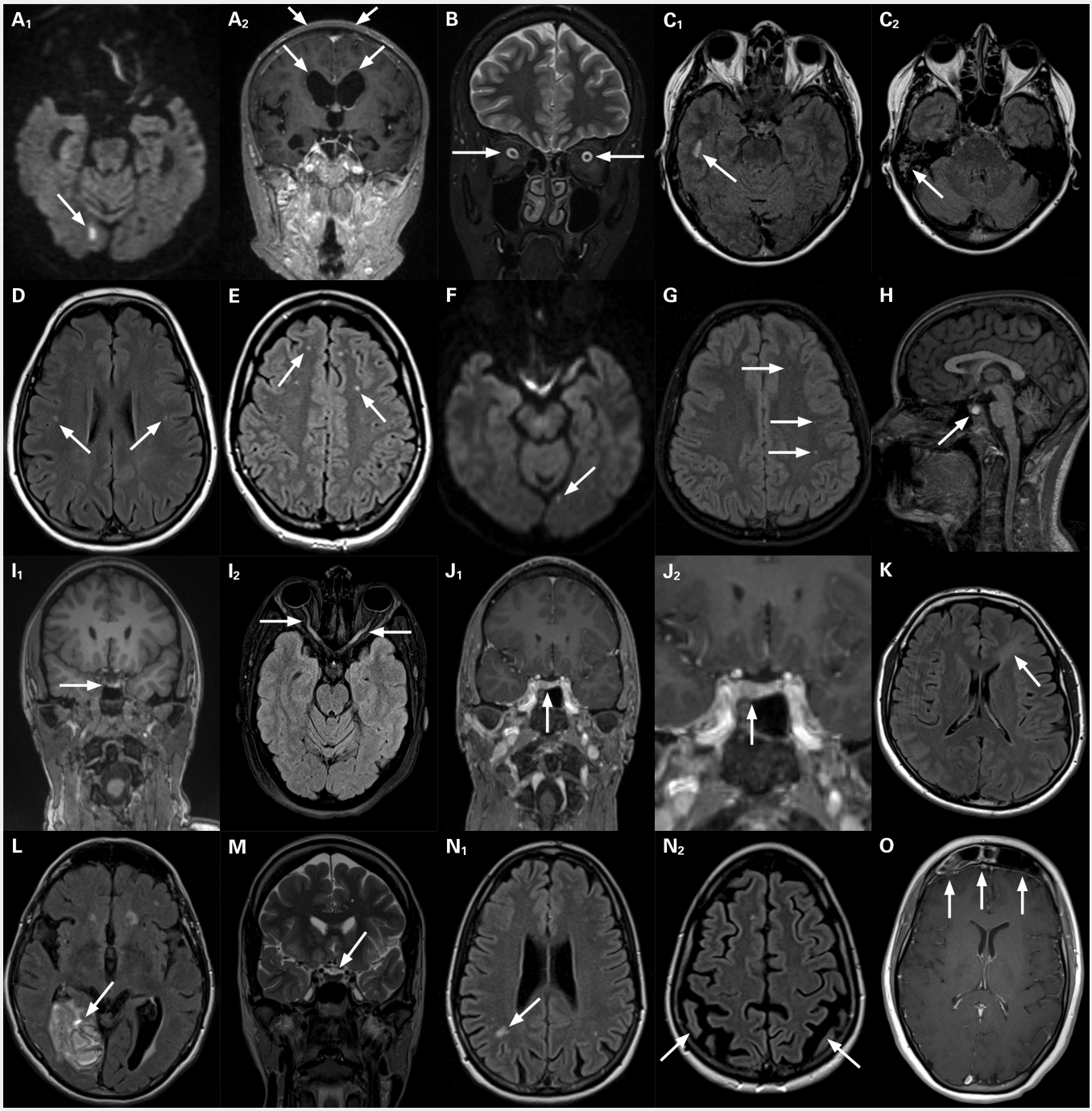

Figure 2

Magnetic resonance imaging (MRI) of acute headache patients from a medical walk-in clinic display a variety of significant findings. MRI scans indicating the significant findings in our study are displayed. White arrows indicate the main pathological finding(s). Diagnoses are listed in the figure.

A HDS 1, acute ischemia occipital right (A_1), normal pressure, hydrocephalus (A_2)
B HDS 4, suspected pseudotumor cerebri
C HDS 13, meningitis (C_1) complicating mastoiditis (C_2)
D HDS 14, suspected vasculitis
E HDS 41, suspected vasculitis
F HDS 44, acute ischemia occipital left
G HDS 45, multiple subcortical white matter lesions
H HDS 48, bleeding pituitary gland
I HDS 51, suspected pseudotumor cerebri ($I_{1,2}$)
J HDS 60, microadenoma of the pituitary gland ($J_{1,2}$)
K HDS 64, suspected low grade glioma
L HDS 69, hemorrhagic infarction
M HDS 74, suspected pseudotumor cerebri
N HDS 78, multiple subcortical white matter lesions (e.g. N_1), cortical atrophy (N_2)
O HDS 81, complicated sinusitis with meningitis

A

Variable	Odds Ratio	95% CI
Female Gender	3.08	(0.69 - 13.68)
Ophthalmologic symptoms	3.93	(0.99 - 15.63)
Syncope	31.38	(1.73 - 569.86)
Vomiting	7.45	(1.20 - 46.41)

B

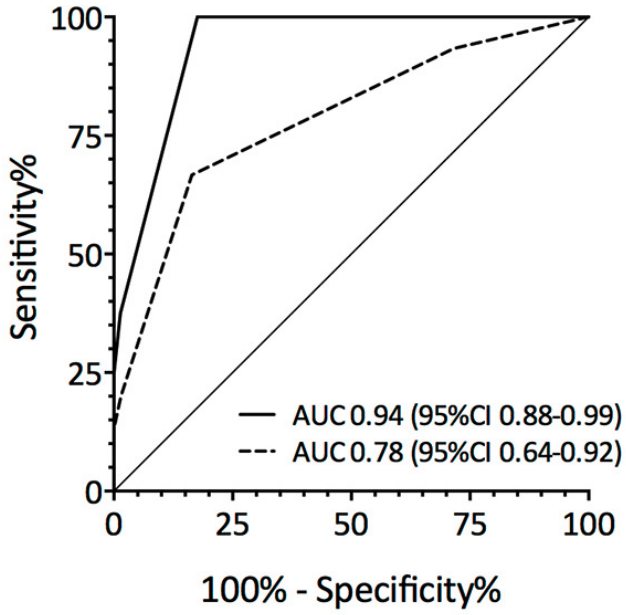

Figure 3
Statistical modelling and data visualisation using a ROC analysis of factors associated with significant magnetic resonance imaging (MRI) findings in headache patients. **(A)** Factors identified in binary, stepwise logistic regression analysis to be associated with significant MRI findings. **(B)** ROC analysis of a clinical score based on syncope (2 points), vomiting (1 point), ophthalmological symptoms (1 point), and female gender (1 point). Visualisation of a score cut-off of 2 points is displayed. Line indicates ROC analysis for “all significant findings that potentially caused headache”. Dotted line indicates ROC analysis for ‘all significant findings’. Score point distribution in the groups is indicated in figure S2 (appendix). AUC = area under the curve; ROC = receiver operating characteristic