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Novel screening tool for secondary headache in acute care—A pilot study

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1. Introduction

Headache is one of the most frequent symptoms presenting to acute-care services and constitutes 4% of general practice and emergency consultations and, 30% of neurology outpatients appointments.[1,2] The prevalence of secondary headache is unknown. Primary headaches constitute at least 98% of all headaches.[3] However, it is the secondary headaches which garner disproportionate attention by virtue of potential mortality.

A secondary headache arises as a result of another pathology often intracranial, thus bears the brunt of the headache *and* the precipitating pathology. Imaging gives cross-sectional information, thus, at a single time-point. A presumption of causality of any abnormality is based upon whether the rate of development of the abnormality is paralleled with that of the headache. Primary headaches are benign, albeit disabling. There is increasing evidence for a genetic predisposition to the primary headaches.[4] However, even in secondary headaches, the headache occurs more often in those who are prone, those with a past or family history of headache. Moreover, the headache can continue with varying severity once the offending secondary precipitant has been addressed.[5,6] Headache alone has not been shown to be a reliable indicator for ongoing or re-emergent pathology.

It has been consistently shown that imaging patients with isolated headache and a normal examination is as likely to reveal an abnormality as incidental lesions in an asymptomatic population.[3] Less than 1% of patients presenting with migraine with or without typical aura, or tension-type headache, have an actionable abnormality on imaging.[7] This is similar to that observed in an asymptomatic population. Nevertheless, the need to intervene often prevails over conservative management. The International Classification of Headache Disorders has an ever-increasing list of secondary headaches, each based on precipitating pathology.[8] Yet, to date there is little evidence that each pathology carries a signature headache which is helpful either diagnostically or therapeutically. Given that most headaches remain a lifelong tendency, there is no rationale for screening isolated headache for an underlying sinister pathology.

Most guidelines adopt a red-flag system to identify secondary headaches. The lack of consistency of red flags is often driven by endorsement of the expert opinion in lieu of a comprehensive literature search and development of an evidence-based framework. Historically, a causative association has been made without comparison to an asymptomatic control population, thus adding further bias to red-flag recommendations.

The majority of secondary headaches present to the acute-care services.[2] Comparative data in patients with and without a pathology, addressing urgent intervention, suggests that the most sensitive indictors (red-flags) for secondary headache include sudden-onset (thunderclap) headache, focal neurological symptoms, focal neurological signs or systemic features. In these groups, the ages most affected are those $\geq$ 50 years.[9] In the specific case of thunderclap headache, whilst risk scoring systems have been produced to differentiate between primary and secondary thunderclap headache, none do so reliably or equivalent to current practice. The latter comprises CT head scan within 6 h and cerebrospinal fluid examination in CT-negative cases or those presenting later than 6 h after symptom onset.

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Table 1
Five key questions to determine which patients need investigation for secondary headache (non-traumatic).

1. Is there true thunderclap headache i.e. severe headache going from zero to maximum intensity at onset within 30 min? (If yes, do CT head, if normal CSF examination including photospectrometry at 12 h.)
2. Any headache + *Neurological symptoms
3. Any headache + *Neurological signs including papilloedema

* Motor/ sensory/ visual/ cerebellar/ alteration of consciousness/ seizure/ behavioural change

4. Any headache + systemic features (e.g. fever, meningism, weight loss, abnormal observations)
5. New onset headache aged >50?

If answer to above five questions is no, manage as primary headache. If any clinical uncertainty, please discuss with senior colleague.

Clinicians naturally seek to exclude important differentials of secondary headache. Yet even where such guidance does exist, adoption in clinical practice is compounded by embedded practices and the personal resources required to maintain professional development.[10,11]

Pooling this literature, we derived five key questions (Table 1) to field test whether one or a combination of questions can provide an effective succinct clinical tool, which can safely reduce admission rates and unnecessary investigation. These included thunderclap-onset headache, presence of neurological symptoms, signs or systemic features and age 50 years or greater.

The study is reported based upon the Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0).

2. Methods

This is an observational study of adult patients (age >18 years) presenting to acute-care services with non-traumatic headache to a university hospital in central London. The observation was carried out on selected days over a 5-month period and included patients attending via accident and emergency, ambulatory care and acute medicine. A proforma was provided to the admitting medical staff to record data contemporaneously to ensure inclusion of the five key questions (Full details Table 1)

1. Is there true thunderclap headache i.e. severe headache going from zero to maximum intensity at onset within 30 min?
2. Any headache + Neurological symptoms
3. Any headache + Neurological signs including papilloedema
4. Any headache + systemic features
5. New onset headache aged >50?

Patients were hence identified from the electronic patient records each week and reviewed by a neurologist for the clinical presentation, examination, observations, blood tests and imaging results. The patients were reviewed after discharge by telephone appointment, in an ambulatory-care setting or in the outpatient clinic. Contact details of the clinic were provided if there was a recurrence of symptoms and appropriate ongoing review arranged accordingly. The clinical record was reviewed several months after presentation to address if the patient had re-attended. A final diagnosis was made of a primary or secondary headache, the headache syndrome in each group and the sensitivity and specificity of the five questions in diagnosing secondary headache.

In line with guidelines of the Health Research Authority (http://www.hra-decisiontools.org.uk/ research/) the work was registered as service evaluation and registered with the Information Governance department at the National Hospital for Neurology and Neurosurgery.

2.1. Statistical analysis

The statistical analyses were performed in R using tidyr, corrplot, pROC, SDMTools, and ROCR packages. Pearson's correlation coefficient (r) was assessed between each question in the screen and the dichotomised, secondary or primary headache, diagnosis and the results plotted as a heatmap.

Sensitivity and specificity were also calculated on the dichotomised data, and thus area under the curve (AUC) of receiver operating characteristic (ROC), 95% confidence interval for AUC-ROC, and the Nagelkerke R^2 were calculated.

3. Results

3.1. Demographics

During the study period, there were 732 patients who attended the emergency services with headache. Seventy-nine patients (10.8%) were admitted and enrolled into the study with 44 females and 35 males. Of the cases, 88.6% were primary headaches.

3.2. Primary headaches

Migraine was the most common headache and a trigeminal autonomic cephalgia (TAC) was the second largest group (Fig. 1).

The age distribution of migraine was greatest between the ages of 25–54 whilst tapering off at both ends (Table 2). Migraine affected men and women equally, which was unexpected since the true incidence is greater in females and there were more females enrolled in the study. Of the TACs detected, hemicrania continua was the most common representing half of all TACs. However, the sample size is too small to derive conclusions regarding age and sex distribution in this pilot study.

3.3. Secondary headaches

Nine cases out of 79 were identified with secondary headache. There was only one brain tumour and no case of subarachnoid haemorrhage (Table 3).

3.4. Five question tool

To assess the influence of each question on the outcome, primary or secondary headache, the correlation between each question and the binary outcome was studied (Fig. 2). The strongest correlation with outcome appears to be question 3, presence of headache with neurological signs. While question 2, any headache and neurological symptoms, triggered the pathway more so than question 3, the latter was far stronger in its correlation with outcome i.e. its discriminatory value. In turn this fits the clinical observation that the presence of neurological signs is more important than symptoms in identifying pathology. Question 2 and 5, new onset headache age > 50, seemed to have little effect though there was only one patient in group 5, who turned out to have migraine.

To determine if the efficacy of the tool could be increased, question 2 was removed and the correlation matrix and the AUC was recalculated (See Appendix Figures 1–4). This revealed the AUC increased to 78.4% from 69%. The higher AUC shows good prediction from the 'four questions triggered' variable with a Nagelkerke r^2 of 0.297. The 95% Confidence interval for AUC is 63.9–92.9%, comfortably outside of the 50% mark which is the 'by chance' prediction.

3.5. Follow-up

The majority of patients were followed up; 74/79 were seen and followed up in secondary-care or emergency-care settings, supporting the observation that a significant amount of headache presents to acute services. In the patients with primary headache there were no changes

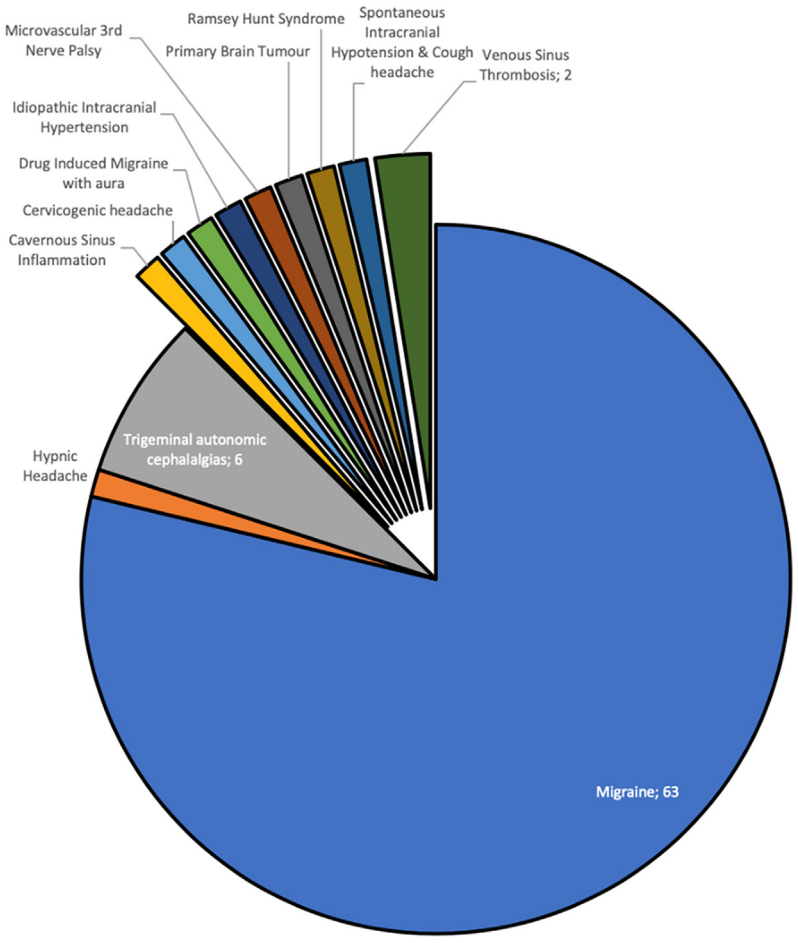

Fig. 1. Primary headaches accounted for 88.6% of all headaches. The expanded segments correspond to all secondary headache diagnoses.

Table 2
Primary headache diagnoses with age and sex breakdown. Primary headaches accounted for 69 of the 79 headaches in the study (88.6%). Of these, 90% were migraine. There were six cases of trigeminal autonomic cephalalgias: hemicrania continua (*), cluster headache (+) and paroxysmal hemicrania (•).

Final Diagnosis	Total No. of Patients	Age Range							Sex	
		18–24	25–34	35–44	45–54	55–64	65–74	75+	M	F
Migraine	62	5	12	15	16	5	5	3	32	30
Primary Sex Headache	1	0	0	0	0	1	0	0	1	0
Hypnic Headache	1	0	0	1	0	0	0	0	1	0
Trigeminal autonomic cephalalgias	6	0	2**	0	1+	2*•	0	1+	2	4

to a secondary headache diagnosis after follow-up. There was a 2-month observation period following admission of the last patient included in this pilot. Of the 653 patients not admitted, there were no reattendances to the hospital during this time.

4. Discussion

Following field testing with 79 patients, the five questions tool shows reasonable sensitivity and specificity for discriminating between primary and secondary headache. The presence of focal neurological signs on examination has the strongest correlation with predicting secondary headache, which is in keeping with clinical experience. Further refinement of the tool by removing the relatively insensitive question 2 (focal neurological symptoms), improves the area under the curve, with the confidence intervals comfortably outside the 'by chance' region. This is similarly in line with evolution of the guidelines for the National Institute of Clinical Excellence for the diagnosis of brain cancer. The revision encompasses all red flags within the remit of 'progressive, sub-acute loss of central neurological function[12] and with this, has improved its diagnostic capability compared to the multitude of proposed red-flags which had populated the 2005 guidance.[13] The revised 2019 guidelines of the British Association for the Study of Headache continues to adopt a similar approach.[14]

4.1. Limitations of study

The patient cohort was not enrolled over consecutive days and did not capture patients presenting overnight. However, patients were captured over consecutive weeks and those coming in overnight with suspected secondary headache are either usually admitted or sent to ambulatory care the next day, under medical colleagues, where they were picked up.

All patients were reviewed by a senior neurologist and although four out of the five questions do not require specialist neurological training to ask, the presence of a normal neurological examination including fundoscopy (three secondary care patients picked up because of papil-

Table 3
Secondary headache diagnoses. Secondary headaches accounted for nine of the 79 headaches in the study (11.4%).

Final Diagnosis	Number of Patients	Age (s)	Sex
Cavernous Sinus Inflammation	1	56	F
Cervicogenic headache	1	74	F
Idiopathic Intracranial Hypertension	1	30	F
Microvascular 3rd Nerve Palsy	1	75	M
Primary Brain Tumour	1	46	F
Ramsey Hunt Syndrome	1	23	M
Spontaneous Intracranial Hypotension & Cough headache	1	40	F
Venous Sinus Thrombosis	2	21, 27	M, F

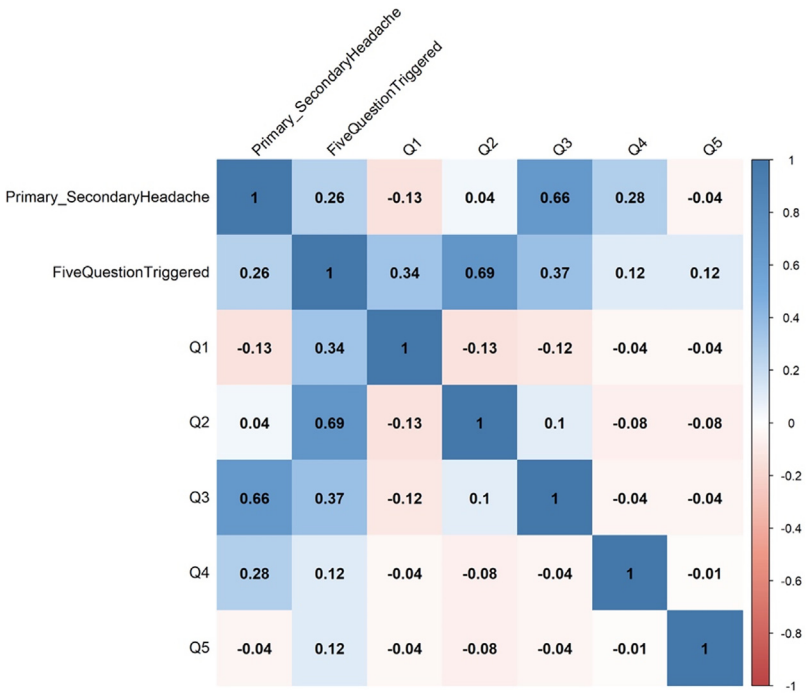

Fig. 2. Correlation plot of five questions tool and outcome. Primary or secondary headache with deep blue and deep red representing positive and negative correlations respectively. Question three appears to have the strongest correlation with the outcome.

loedema) is evidently central to the efficacy of the tool. Therefore, establishing the reliability of this specific part of the tool in the hands of acute medical and emergency colleagues would be useful. The advent also of acute neurology as a sub-speciality of its own, and validation of new methods of visualising the fundus rapidly, could evidently have considerable impact at all points of the patient pathway.[15]

Of those patients who were not admitted for investigation, there remains the concern of missing a secondary precipitant. The definitive study would be to investigate all headache presentations. However, the current evidence does not support developing a pilot study to screen all headache presentations. There were no reattendances to the hospital during the 2-month observation period following the last patient admitted to the cohort. From the literature, the onset of secondary headache is rapid. Therefore, if a secondary headache had been missed the expectation is that representation would have occurred within the 2-month period. If there had been readmissions after this time, one would have to consider whether any abnormality identified may be incidental to the headache. However, what cannot be accounted for is patients who may have had a secondary headache reattending through emergency services at another hospital. There were no thunderclap headaches. Given the prevalence of thunderclap headache is 43 per 100,000 person years, a much larger cohort would be required to address the value of question 1.

This present work suggests that the proposed tool could be a useful means of differentiating secondary from primary headache using a parameter which incorporates all red-flags. Larger numbers would show this definitively and encompass the breadth of disease that comprises secondary headache.

4.2. Future work

A multi-centre or dual centre study in two sufficiently busy accident emergency departments with access to neurologists, would have the potential to provide the numbers of secondary headaches required to establish the long-term viability of the tool. The alternative would be a single centre study over a longer period of time.

Author statements

Dr Salman Haider, Neurologist – Methodology, investigation, project administration, original draft preparation, review and editing.

Dr Maryam Shoai, Postdoctoral Statistical Geneticist – Formal analysis.

Dr Runil Shah, Foundation Year Trainee – Investigation.

Dr Chris Turner, Neurologist – Review and editing.

Dr Anish Bahra, Neurologist – Conceptualisation, methodology, supervision, reviewing and editing.

Declaration of competing interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinme.2023.100005.

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