Red and orange flags for secondary headaches in clinical practice

SNNOOP10 list

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Neurology® 2019;92:134-144. doi:10.1212/WNL.0000000000006697

Abstract

A minority of headache patients have a secondary headache disorder. The medical literature presents and promotes red flags to increase the likelihood of identifying a secondary etiology. In this review, we aim to discuss the incidence and prevalence of secondary headaches as well as the data on sensitivity, specificity, and predictive value of red flags for secondary headaches. We review the following red flags: (1) systemic symptoms including fever; (2) neoplasm history; (3) neurologic deficit (including decreased consciousness); (4) sudden or abrupt onset; (5) older age (onset after 65 years); (6) pattern change or recent onset of new headache; (7) positional headache; (8) precipitated by sneezing, coughing, or exercise; (9) papilledema; (10) progressive headache and atypical presentations; (11) pregnancy or puerperium; (12) painful eye with autonomic features; (13) posttraumatic onset of headache; (14) pathology of the immune system such as HIV; (15) painkiller overuse or new drug at onset of headache. Using the systematic SNNOOP10 list to screen new headache patients will presumably increase the likelihood of detecting a secondary cause. The lack of prospective epidemiologic studies on red flags and the low incidence of many secondary headaches leave many questions unanswered and call for large prospective studies. A validated screening tool could reduce unneeded neuroimaging and costs.

Introduction

A minority of headache patients have a secondary headache disorder. There are many possible laboratory tests available for a suspected secondary headache.[1] However, running a standard test battery including brain imaging and blood tests in every headache patient is costly[2] and entails the risk of false-positive test results and incidental findings.[3] Furthermore, it is not possible to detect every secondary headache with standard neuroimaging or laboratory tests.

The medical literature promotes red flags to direct the clinician to initiate a workup plan.[4–12] The absence of red flags may suggest that no workup is needed. Clinical experience and large case series of patients with a specific secondary headache form the basis for many red flags. This only allows for the sensitivity of red flags to be known. The specificity and predictive value of a red flag are also necessary to determine whether further testing is necessary.

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Glossary

ICHD-3 = International Classification of Headache Disorders 3; **MOH** = medication overuse headache; **SAH** = subarachnoid hemorrhage; **TAC** = trigeminal autonomic cephalalgia; **TBI** = traumatic brain injury; **TCH** = thunderclap headache.

In this review, we aim to discuss the incidence and prevalence of secondary headaches as well as the data on sensitivity, specificity, and predictive value of red flags for secondary headaches.

Epidemiology of secondary headaches

Neurologists worldwide estimate that 18% of patients with a headache have a secondary headache disorder.[13] The International Classification of Headache Disorders 3 (ICHD-3) provides a list of 8 categories and 46 subcategories of potential secondary causes.[14]

In a Norwegian population study, the 1-year prevalence of chronic secondary headaches was 2.1% and the majority of these patients had medication overuse headache (MOH).[15]

Regarding studies conducted at tertiary treatment sites, an epidemiologic study identified a secondary cause in 12.9% of their headache patients.[16] The most common cause was MOH, accounting for 7.4%. Other secondary causes were identified in ≤1.5% of patients. Another study at a tertiary treatment site also reported similar findings, with one-fifth of the headache patients having a secondary cause identified.[17]

There appears to be a large risk of selection bias in the above-mentioned studies as one-third of patients with chronic secondary headaches do not have their headache investigated.[18]

The chance of encountering a secondary headache disorder is high in the emergency department, where headache is often the primary neurologic complaint.[19–21]

The studies show a high prevalence of secondary headaches. The prevalence variates depending on the setting, i.e., primary care, emergency department, or tertiary headache centers. This must be kept in mind when applying knowledge from the literature into clinical practice.

The evidence for using red and orange flags

We define red flags as symptoms or other pieces of information that encourage testing or observation of the patient. We define orange flags as information that is only alarming when it occurs with other orange or red flags.

A secondary headache disorder is more often suspected than detected. Many headache patients undergo neuroimaging without detecting anything of clinical relevance. A prospective study conducted over 5 years at a tertiary headache service included 3,655 nonacute headache patients.[22] The authors used red flags[23] to determine whether a patient should undergo imaging or not. After screening, 530 (14.5%) patients underwent imaging. Only 11 had an abnormality (2.1% of patients scanned and 0.3% of the total study population).[22] A retrospective study reviewed 360 patients referred for MRI evaluation of a chronic or a recurrent headache.[24] Only 0.7% of the patients had relevant findings on MRI.[24] In a review of 328 patients with a nonfocal headache, only 1.5% had clinically relevant results.[2] A review of 402 chronic headache cases identified abnormalities in 3.7%.[25]

These studies reveal that even with the use of red flags, most scans still return no findings. Thus, there is a need for assessing the predictive value of red flags.

In 2003, the mnemonic SNOOP (systemic symptoms/signs and disease, neurologic symptoms or signs, onset sudden or onset after the age of 40 years, and change of headache pattern) was proposed as a red flag detection tool for secondary headaches.[7] National and regional guidelines[8–11] have since provided more items to screen for potential secondary causes leading to the current SNNOOP10 (table 1). We review these items in the following paragraphs.

Systemic symptoms including fever

The combination of headache and fever prompts the clinician to rule out a systemic or neurologic infection or vasculitis, rheumatic disease, or any other inflammatory disease. Neuroinfections include bacterial meningitis, viral meningitis, encephalitis, and brain abscesses. Bacterial meningitis has an annual incidence ranging 0.7–1.38 per 100,000,[26,27] with higher incidences reported in specific countries.[28] Viral meningitis has an annual incidence of 4.7–7.6 per 100,000 in adults,[29,30] higher in children aged <14 years at 27.8 per 100,000[30] and infants <1 year old at 219 per 100,000.[30] Acute encephalitis has an annual incidence of 6.43–7.4 per 100,000.[31] Brain abscesses are rare in developed countries, with an annual incidence of 1.3 per 100,000.[32]

Fever accounted for 4.8% of all emergency department consultations in the United States in 2007.[33] Only a minority of patients with fever have a neurologic infection.[34] In a cohort of 213 patients with fever, pneumonia accounted for 27.2%

Table 1 SNNOOP10 list of red and orange flags

	Sign or symptom	Related secondary headaches (most relevant ICHD-3b categories)	Flag color
1	Systemic symptoms including fever	Headache attributed to infection or nonvascular intracranial disorders, carcinoid or pheochromocytoma	Red (orange for isolated fever)
2	Neoplasm in history	Neoplasms of the brain; metastasis	Red
3	Neurologic deficit or dysfunction (including decreased consciousness)	Headaches attributed to vascular, nonvascular intracranial disorders; brain abscess and other infections	Red
4	Onset of headache is sudden or abrupt	Subarachnoid hemorrhage and other headaches attributed to cranial or cervical vascular disorders	Red
5	Older age (after 50 years)	Giant cell arteritis and other headache attributed to cranial or cervical vascular disorders; neoplasms and other nonvascular intracranial disorders	Red
6	Pattern change or recent onset of headache	Neoplasms, headaches attributed to vascular, nonvascular intracranial disorders	Red
7	Positional headache	Intracranial hypertension or hypotension	Red
8	Precipitated by sneezing, coughing, or exercise	Posterior fossa malformations; Chiari malformation	Red
9	Papilledema	Neoplasms and other nonvascular intracranial disorders; intracranial hypertension	Red
10	Progressive headache and atypical presentations	Neoplasms and other nonvascular intracranial disorders	Red
11	Pregnancy or puerperium	Headaches attributed to cranial or cervical vascular disorders; postdural puncture headache; hypertension-related disorders (e.g., preeclampsia); cerebral sinus thrombosis; hypothyroidism; anemia; diabetes	Red
12	Painful eye with autonomic features	Pathology in posterior fossa, pituitary region, or cavernous sinus; Tolosa-Hunt syndrome; ophthalmic causes	Red
13	Posttraumatic onset of headache	Acute and chronic posttraumatic headache; subdural hematoma and other headache attributed to vascular disorders	Red
14	Pathology of the immune system such as HIV	Opportunistic infections	Red
15	Painkiller overuse or new drug at onset of headache	Medication overuse headache; drug incompatibility	Red

Abbreviation: ICHD-3b = International Classification of Headache Disorders 3b.
An overview of signs and symptoms, their related secondary headache, and distribution in red and orange flags.

and urinary tract infections for 21.1%; one patient, 0.5%, was diagnosed with meningitis.[34]

In bacterial meningitis (table 2), the triad of fever, neck stiffness, and decreased consciousness was present in 21.4% to two-thirds of confirmed episodes.[28,35–37] Headache was present in 51.7%–87%,[35,37,38] fever in 77%–97%,[28,35–38] and neck stiffness in 50%–88% of the cases.[28,35–38]

Regarding viral meningitis, the triad of fever, neck stiffness, and decreased consciousness never occurred in a 10-year cohort of viral meningitis cases.[37] Headache was present in 72.2%, fever in 61.1%, and neck stiffness in 50% of the cases. In a pediatric emergency department, 5.2% of cases with headache as the primary complaint had viral meningitis.[39] In a review of patients who underwent lumbar puncture for investigation of putative meningitis and headache with fever as main complaints, 15% had viral meningitis.[40]

Encephalitis is most commonly caused by herpes simplex virus. In a study of 113 patients with herpes simplex encephalitis, headache was present in 79% and fever in 87% of the episodes.[41]

In brain abscesses, the frequency of headache at presentation ranges from 49% to 81%, while the frequency of fever ranges from 29% to 57%.[42–45] Isolated fever was recorded in 29% of 21 episodes of brain abscesses caused by streptococcus pneumonia.[44]

Based on the above-mentioned studies, concurrent fever and headache has a relatively high sensitivity for neuroinfections. The specificity cannot be determined from these studies, but presumably it is low as these 2 symptoms occur in a variety of infections. The presentation of the triad of fever, neck stiffness, and decreased consciousness is variable and a lack of this does not rule out a neuroinfection. Headache with systemic symptoms is categorized as a red flag or orange flag in the case of isolated fever.

Table 2 The frequency of headache, fever, neck stiffness, and decreased consciousness in bacterial meningitis, viral meningitis, encephalitis, and brain abscesses

Author (year)	Population	Headache, %	Fever, %	Neck stiffness, %	Decreased consciousness, %	Triad of fever, neck stiffness, and decreased consciousness, %
Bacterial meningitis						
Van de Beek et al. (2004)[35]	696 Episodes	87	77	83	69	44
Durand et al. (1993)[36]	493 Episodes	Not reported	85	88	78	Two-thirds (exact distribution not reported)
Hussein and Shafran (2000)[39]	103 Episodes	66	97	87	51	Not reported
Sigurdardóttir et al. (1997)[28]	132 Episodes	Not reported	97	82	66	51
Wiberg et al. (2008)[37]	17 Episodes	51.7	78.6	50.0	57.1	21.4
Viral meningitis						
Wiberg et al. (2008)[37]	18 Episodes	72.2	61.1	50.0	27.8	0
Encephalitis						
Whitley et al. (1982)[41]	113 Episodes of encephalitis caused by herpes simplex	79 In historical findings	84 In historical findings	Not reported	Not reported	Not reported
		Not reported at presentation	87 At presentation			
Brain abscess						
Carpenter et al. (2007)[42]	49 Episodes	49	43	4	45	Not reported
Chun et al. (1986)[43]	45 Episodes	72	42	5 Presented with a stiff neck as a symptom	83	Not reported
				49 Presented with nuchal rigidity during physical examination		
Grigoriadis and Gold (1997)[44]	21 Episodes of brain abscess caused by *Streptococcus pneumoniae*	81	29	Not reported	57	Not reported
Kao et al. (2003)[45]	53 Episodes	55	57	8	45	Not reported

Key points

- Headache with fever is primarily alarming when accompanied by relevant symptoms (e.g., neck stiffness, decreased consciousness, and neurologic deficit).
- However, the presentation of a triad of fever, neck stiffness, and decreased consciousness occurs in far from all episodes of neuroinfections.

Neoplasm in history

The worldwide annual incidence of brain tumors is estimated to be 3.4 per 100,000 with a 5-year prevalence of 6.6 per 100,000.[46]

The risk of finding a brain tumor in a headache patient without a history of any neoplasm is low. It is less than

0.1%,[22,47] of which the majority presents after the age of 50 years.[47] Lung cancer, breast cancer, and malignant melanoma have the highest risk of intracranial metastasis.[48]

The frequency of brain metastasis was 24% in a review of patients with breast cancer.[49] Headache was the most common symptom and was present in 35% of the cases. In a study of oncology patients, there were intracranial metastases in 32% of 68 patients presenting with a newly developed headache.[5] Other risk factors were emesis, headache duration of ≤10 weeks, and atypical headache pattern. In a similar study, 54% of 54 oncology patients with newly developed headache had brain metastasis.[6] The authors identified 4 independent predictors: pulsating quality and moderate to severe intensity, emesis, gait instability, and extensor plantar response.

A high proportion of patients with cancer with new onset of a headache have an intracranial metastasis especially if they have a cancer type prone to metastasis to the brain[48] or one of the above-mentioned clinical predictors.[5,6] Thus, every oncology patient with newly developed headache should undergo MRI. Consequently, neoplasm in history is categorized as a red flag.

Key points

- A newly developed headache in a patient with neoplasm is highly suspect for an intracranial metastasis.
- Relevant accompanying symptoms include emesis, headache duration ≤10 weeks, atypical headache pattern, pulsating quality and moderate to severe intensity, gait instability, and extensor plantar response.

Neurologic deficit (including decreased consciousness)

Neurologic deficits presenting with headache may have several causes. The most common cause is presumably migraine with aura (causing reversible deficits) followed by intracranial hemorrhage and ischemic stroke. Primary headache disorders with neurologic deficits[50–52] are often known by the patient and do not cause alarm. Other causes are infections, abscesses, tumors, and others. The annual incidence of stroke is approximately 300–500 per 100,000.[53]

In a review of headache in ischemic cerebrovascular disease, headache presented in 16%–65% of patients with TIA and nondisabling stroke.[54] Headache occurred in 3%–44% depending on stroke subtype in studies including both TIA and ischemic stroke. Headache occurred more often due to ischemia in the posterior than in the anterior circulation. In a prospective study of 240 patients with acute stroke, headache occurred in 64.5% of the cases with hemorrhagic stroke and 32% of the cases with ischemic stroke.[55] In the hemorrhagic stroke group, headache was present in all patients with subarachnoid hemorrhages and in 58% of intraparenchymal hemorrhages. Headache occurred in 59% of patients with a stroke caused by vertebrobasilar artery disease and 26% of patients with stroke caused by anterior circulation disease. In patients with cortical stroke, 56.5% had a headache, whereas only 26.5% of those with subcortical stroke reported a headache. Ten percent had a sentinel headache before the occurrence of the neurologic deficits. A study of headache at stroke onset included 2,196 patients with ischemic stroke or TIA.[56] A quarter of the patients presented with headache. Headache at stroke was associated with female sex, history of migraine, younger age, cerebellar stroke, and low blood pressure values on admission. This distribution is similar to a study of 238 patients.[57] This study also found that headache severity is not proportional to the size of ischemic stroke lesion. Another study of 876 patients reports equivalent findings.[58]

As headache with a neurologic deficit has a high sensitivity for stroke, this is categorized as a red flag. Unquestionably, neurologic deficits should always raise serious concern regardless if a headache is present or not.

Key points

- Headache occurs in one-fourth of episodes of acute stroke with a higher frequency in hemorrhagic than in ischemic stroke.
- The severity of headache is not related to the size of the lesion.

Onset of headache is sudden or abrupt (thunderclap headache)

The ICHD-3 defines thunderclap headache (TCH) as a high-intensity headache of abrupt onset.[14] The ICHD-3 defines abrupt onset as reaching maximum intensity in <1 minute. Besides the ICHD-3, there is no clear consensus of what sudden/abrupt onset constitutes, varying from <1 minute to 1 hour.[14,59] It should be kept in mind that not all acute headaches are thunderclap headaches as both the temporal aspect and high intensity need to be present. The annual incidence of acute severe headache was 43 per 100,000 in a Swedish cohort.[60] It is associated with serious intracranial disorders of vascular origin, in particular subarachnoid hemorrhage (SAH). Less common secondary causes are cerebral venous or sinus thrombosis and other stroke subtypes, intracranial hypotension, reversible cerebral vasoconstriction syndrome, and others.[61]

A large multicenter cohort study conducted at tertiary care emergency departments included a total of 2,131 patients with acute headache peaking within 1 hour and no neurologic deficits.[59] SAH was identified in 6.2%. The combination of age older than 40 years, neck pain or stiffness, loss of consciousness, or onset during exertion resulted in a sensitivity of 98.5% and specificity of 27.5% for SAH. The addition of thunderclap headache and limited neck flexion on examination increased sensitivity to 100% with

a reduction of specificity to 15.3%. The positive predictive value was 7.2% and the negative predictive value was 100%. A recent review on sudden and severe headache reported a cerebrovascular cause in 27% of the cases, an infectious origin in 7%, and nonvascular origin in 5%.[62] A prospective study identified SAH in 25% of 148 episodes of TCH.[63] It was the only symptom in half of the cases. The term sentinel headache defines a headache attack before the rupture of an aneurysm.[64] The incidence of a sentinel headache before SAH was 10%–43% in a systematic review.[65]

In 3 prospective studies,[59,60,63] 6.2%–25% of patients presenting with an acute headache had SAH. In addition, 12% of the included patients had another serious neurologic condition (e.g., meningoencephalitis).[63] Thus, TCH is categorized as a red flag.

Key points

- TCH can be the only initial symptom of SAH.
- A high sensitivity for SAH can be achieved with a combination of TCH and age older than 40 years, neck pain or stiffness, loss of consciousness, onset during exertion, or limited neck flexion on examination.
- TCH also occurs in other neurologic conditions.

Older age (onset after 65 years)

A prospective study from a tertiary headache center showed a higher frequency of secondary headache in patients aged >65 years compared to a younger population (11.2% vs 8.0%).[66] Infection was the most common cause of secondary headache, accounting for 29.4% of the episodes. A prospective study included 262 headache patients ≥65 years old.[67] The authors identified a secondary cause in 16%. This is in line with findings from a population-based study.[68] A study reviewed the records of 193 patients ≥65 years old with headache as their initial and primary symptom.[69] While the likelihood of a patient seeking care at a general hospital for headache decreased with age, the risk of a serious underlying cause increased 10-fold at age ≥65 years compared to a younger population. A serious secondary cause (e.g., stroke, temporal arteritis, and others) was identified in 15% of the elderly patients vs 1.6% in a group of patients <65 years old.

Older age is categorized as a red flag; the odds are higher for identifying a secondary cause of alarming etiology in this age group.

Key point

- Headache patients ≥65 years old have a higher frequency of serious secondary cause than younger patients.

Pattern change or recent onset of new headache

It is unknown how often pattern change in headache occurs. Presumably, the odds of encountering a secondary etiology are higher in patients with pattern change or recent onset (<3 months) compared to patients with chronic symptoms (>3 months).

Twelve of 30 (40%) patients diagnosed with cerebral venous thrombosis had headache as the only symptom.[70] The diagnosis was delayed in the group with isolated headache (9 ± 6.7 days vs 4.5 ± 4.2 days). A prospective study investigated the incidence of isolated headache in patients with intracranial tumors.[71] Fifteen of 183 (8.2%) patients had recent onset of headache as their only symptom. Recent onset of headache was an independent predictor for intracranial metastasis in oncology patients.[5] A prospective population-based study investigated 100 adult patients with recent onset of a new headache or pattern change of an existing headache.[72] There were intracranial lesions in 21% of the patients and normal neurologic examinations in 62% of these patients. The mean duration of headache was shorter in the secondary headache group (2.9 vs 8.2 months).

While there are a limited amount of data regarding this red flag, it has been suggested that recent change of pattern or a newly developed headache (<3 months) can be the only signs of a serious underlying etiology. These are accordingly red flags.

Key points

- A recent change of pattern or a newly developed headache can be the only signs of a serious underlying etiology. A correct diagnosis is often delayed in these cases.

Positional headache

Headache occurring immediately or within seconds of assuming an upright position and resolving quickly after lying horizontally is suggestive for low CSF pressure.[50] It is commonly recognized in patients who have recently undergone a lumbar puncture or neurosurgical operation. Positional headaches occur spontaneously, with an annual incidence of 5 per 100,000.[73]

Spontaneous intracranial hypotension differs widely in onset and presentation. In a case series of 5 patients, the onset varied from sudden to gradually over 3 months.[74] Four of the patients had orthostatic headache as the presenting complaint. Common accompanying symptoms are nausea, visual disturbances, neck stiffness, vertigo, tinnitus, and cognitive abnormalities.[74–76] Spontaneous intracranial hypotension is commonly caused by CSF leaks at the spinal level.[76] The orthostatic features may disappear in the chronic patient.[76]

Many migraine patients report an increase of their headache during physical activity,[77] which may mimic positional headache, but is not expected to resolve after lying horizontally.

Positional headache is a red flag as it is a common symptom of intracranial hypotension. The symptoms of intracranial hypotension can be masked by other headache disorders.

Key points

- Positional headache is the trademark of intracranial hypotension and the most common cause is CSF leak at the spinal level.
- The orthostatic features may diminish over time and they can be masked by other headache disorders.

Precipitated by sneezing, coughing (Valsalva), or exercise

Secondary cough headache is associated with Chiari malformation type 1 (a herniation of the cerebellar tonsils) in 40%.[78] In an MRI study of 2,000 healthy volunteers aged ≥45 years, 0.9% had a Chiari malformation.[3] Other studies estimate the prevalence of Chiari malformation at 0.24%–3.6% of the general population.[79] The prevalence of symptomatic Chiari malformation is different from the prevalence of image-defined Chiari malformation.[79] Only one-third of detected cases were symptomatic at the time of diagnosis of MRI-positive Chiari malformations.[80] Besides Chiari malformations, posterior fossa lesions account for approximately 15% of cases with cough headache.[78] Other less common causes were arachnoid cysts,[81] dermoid tumors,[81] meningiomas,[81] os odontoideum,[81] subdural hematoma,[83] brain metastases,[82] acute sphenoid sinusitis,[82] CSF pressure related,[83–86] infection,[87] hydrocephalus,[88] and vascular diseases.[89–91] Other triggers for headache in patients with primary cough headache could be laughing,[81,92] lifting heavy objects,[82,92] postural changes,[81,92] and defecation.[81,82]

Cough headache is categorized as a red flag as it can be a sign of serious underlying pathology such as Chiari malformations and posterior fossa lesions.

Key points

- Cough headache can be a sign of serious underlying pathology.

Papilledema

Papilledema was a predictor of intracranial abnormalities in an MRI study.[4] Papilledema should thus always lead to further investigation. However, in a prospective study of 34 pediatric patients initially suspected of having papilledema, the majority had pseudo-papilledema or a normal variant.[93] Only 2 patients had real papilledema. This type of misinterpretation has also been described in a case report of an adult patient who sustained a head injury after tripping and was suspected to have raised intracranial pressure.[94] An ophthalmologist later identified bilateral optic nerve head drusen. Even with these studies in mind, one should still be wary of a potential intracranial tumor. In a retrospective study of 74 pediatric patients diagnosed with primary brain tumors, 38% presented with papilledema and 31% had a triad of headache, vomiting, and papilledema.[95]

As there is a high prevalence of patients with papilledema who have serious pathology, papilledema is categorized as a red flag.

Key point

- A high prevalence of patients with papilledema have a serious underlying pathology.

Progressive headache and atypical presentations

New or recent onset of daily or continuous headache should be alarming, especially if the pain or associated symptoms are progressive. In a series of 17 cases of cerebral venous thrombosis with headache as the only presenting symptom, 65% had a progressive course of their headache.[96]

An atypical presentation of headache is associated with increased likelihood of abnormality. A study used MRI to evaluate 402 patients for the primary complaint of chronic headache.[25] Relevant abnormalities were identified in 15 patients (3.7%). Two-thirds of the patients retrospectively presented with an atypical headache pattern defined as not fulfilling the criteria for any of the primary disorders.

Progressive headache and atypical headache presentation are not commonly described and defined in detail in the literature but given that they may be associated with serious underlying pathology they are thus considered to be red flags.

Key point

- Progressive headache and atypical headache presentation can be the only signs of serious underlying pathology.

Pregnancy or puerperium

The risk of secondary headache is higher during pregnancy and puerperium due to physiologic changes (e.g., hypercoagulability, hormonal changes, or intervention, such as epidural anesthesia).[97]

In a review of de novo headache during pregnancy, the incidence of new onset of headache during pregnancy is estimated to be at 5% of all pregnant women.[97] The prevalence of secondary causes for headache is believed to be higher during the third trimester. In a retrospective study of 140 pregnant women presenting to acute care with headache, a secondary cause was identified in one-third.[98] The majority presented during the third trimester (56.4%). The authors identified additional risk factors that should prompt a more thorough investigation: the absence of a headache history and the presence of seizures, hypertension, or fever. The most common secondary causes

were hypertensive disorders, accounting for approximately half of the cases of secondary headache, followed by pituitary adenoma or apoplexy (20.1%). A secondary cause was identified in 27 of 63 (42.8%) consecutive cases of pregnant women with new onset of headache.[99] A nationwide cohort investigating the incidence of stroke during pregnancy found an incidence of 1.5 per 100,000 women.[100] This occurred predominantly during the third trimester and puerperium (85% of the cases). A multicenter prospective observational study found that 17% of the cases of venous stroke in women occurred either during pregnancy or puerperium.[101] Immediate postpartum headache affects 40% of women.[102] Accidental post–dural puncture headache accounts for the majority in those receiving epidural or spinal anesthesia.[102,103]

One should also keep non-neurologic disorders in mind when a pregnant woman presents with headache.[97] Hypertension seems to be the most common, with potential severe consequences such as preeclampsia, but other non-neurologic pathology such as hypothyroidism, anemia, electrolyte imbalance, and diabetes should also be suspected.[97,98]

As headache during pregnancy can be related to severe pathology, it is categorized as a red flag. Further concern should be raised if there is a presence of additional risk factors.

Key points

- Headache during pregnancy and puerperium has a higher risk of severe pathology due to physiologic changes and interventions.
- Other risk factors are absence of headache history, occurring during third trimester, seizures, hypertension, and fever.

Painful eye with autonomic features

Eye problems constitute 2%–3% of all primary care consultations.[104,105] Orbital pain with redness of the eye occurs also in primary headache disorders and is typical for cluster headache and other trigeminal autonomic cephalalgias (TAC).[106] The 1-year prevalence of cluster headache is 53 per 100,000 persons and the lifetime prevalence is 124 per 100,000 persons.[107] The annual incidence ranges between 2 and 10 per 100,000.[108] Population studies on the epidemiology of TAC are sparse. One study found that 5.3% of all headache referrals in a general neurology setting had a form of TAC.[109] The proportion of TAC that is secondary is unknown. Thus, it is recommended that patients presenting with TAC or similar clinical features should always undergo MRI[1,110] as they can be secondary to pathology in the posterior fossa, pituitary region, or cavernous sinus.[110–113] While atypical presentations are more often associated with secondary findings,[110–113] even typical presentations of cluster headache can be due to a structural lesion.[114] There are many other diagnoses to consider, both of neurologic and ophthalmic etiology, such as glaucoma, inflammation, and corneal disorders.

Even though secondary etiology is rare, painful eye with autonomic features is categorized as a red flag because even typical presentations can be due to a structural lesion.

Key point

- Patients with presentations of painful eye with autonomic features should undergo neuroimaging as it can be due to a structural lesion.

Posttraumatic onset of headache

The annual incidence of traumatic brain injury (TBI) is 235–556 per 100,000[114] and accounts for 4.8% of all emergency department visits in the United States.[115] The prevalence of people living with long-term disabilities due to TBI is estimated to be 1.1%–1.7% of the US population.[116] The main causes of TBI are traffic accidents, assaults, and falls.[117]

In a prospective study of 212 patients with mild TBI, the cumulative incidence of headache 1 year after injury was 91%.[118] The majority met the criteria for migraine and probable migraine. A smaller proportion was found in a Lithuanian study of patients with concussion.[119] Only 11.5% reported headache after 3 months, and after 1 year, the prevalence was similar to controls. The authors suggest that the difference might be related to sociodemographic difference such as a lack of a third-party insurance scheme. A prospective observational study of acute and chronic posttraumatic headache after TBI included 628 patients with momentary loss of consciousness.[120] At 2 weeks, 51% had acute posttraumatic headache. At 3 months, 23% had developed chronic posttraumatic headache. Risk factors for acute posttraumatic headache were female sex, younger age, headache present in the emergency department, and CT scan abnormalities. Risk factors for chronic development were female sex and headache present at the emergency department. Patients with posttraumatic headache more often reported anxiety and depression after trauma.

The ICHD-3 guidelines state that posttraumatic headache must develop within 7 days of trauma.[14] A 7-day interval yields a higher specificity at the cost of sensitivity.[14] To our knowledge, there are no studies on the long-term outcome of patients with persistent headache attributed to traumatic injury to the head. Most experts try to treat this secondary headache based on the phenotype, e.g., if the headache is migraine-like, it is treated with prophylactic drugs with proven efficacy in migraine. However, no clinical trials have investigated which prophylactic or acute medication is effective in posttraumatic headache.

Depending on the time factor, this is categorized as either an orange or red flag. If the duration of the headache is chronic, it

is an orange flag. If headache occurs directly in relation to the trauma, it is a red flag.

Key point

- Posttraumatic headache is an unspecific marker depending sociodemographic factors. Nonetheless, headache related to trauma should always be explored.

Pathology of the immune system such as HIV

Approximately 1% of the global adult population is infected with HIV.[121] The majority of these cases are in sub-Saharan Africa, where it is estimated that 5.2% of the population is infected.[121] About 2.7 million people are infected with HIV every year worldwide.[121]

Headache is the most common pain problem in patients with HIV,[122,123] affecting up to 34%–61% of patients.[124] The incidence of opportunistic infections increases if the CD4 count is ≤ 200 cells/μL.[124] The most common etiologies of CNS lesions in advanced HIV are cerebral toxoplasmosis, primary CNS lymphoma, and progressive multifocal leukoencephalopathy.[125] Besides infections, one should be wary of inappropriate immune reactions such as aseptic meningitis.[125]

Pathology of the immune system is a red flag due to risk of opportunistic infections.

Key points

- Headache is the most common pain problem in patients with HIV.
- The risk of severe pathology is dependent on the degree of immunosuppression.

Painkiller overuse (MOH) or new drug at onset of headache

The prevalence of MOH among the adult population is 0.5%–7.2% and is the most common secondary headache disorder.[16,17,126] Several studies have shown that withdrawal of medication can revert chronic headache to episodic headache in up to 70% of patients.[127–129] Furthermore, abrupt withdrawal or tapering down of overused medication is recommended according to the European Federation of Neurologic Societies.[130] Yet the approach to treatment and the underlying pathophysiology behind MOH are still highly debated among headache experts. It is more common in women aged 40–50 years.[126] While MOH is not a fatal condition, it affects a large proportion of headache patients and should thus always be screened for.

The introduction of any drug can be associated with new onset of headache. In particular, nitric oxide donors, phosphodiesterase inhibitors, carbon monoxide intoxication, histamine intoxication from food sources, cocaine use, exogenous hormones, and acute pressor agents can cause secondary headaches.[50] The phenotype of some medication-induced headaches can be identical to primary headache disorders,[131] especially migraine, requiring an exact history of the temporal relationship between the onset of headache and medication intake. Furthermore, one should be aware of headache related to substance withdrawal, for instance due to caffeine, opioids, and estrogen.[50]

Medication headache is categorized as a red flag and it is critical to consider the temporal aspect. We emphasize that it is important to screen for MOH as it is a relatively straightforward treatable secondary headache, even though the course of the headache may be relatively harmless. On the other hand, onset of headache due to a new drug can be a sign of incompatibility with the given drug.

Key points

- Medication overuse is the most common cause of secondary headache.
- Onset of headache due to a new drug can be a sign of incompatibility with the given drug.

Discussion

An approximation of the sensitivity of a red flag is often possible while the specificity is more difficult to assess as most studies on the occurrence of clinical symptoms are based on retrospective studies of patients with a known secondary headache disorder.

New headache patients should be screened using the list to increase the likelihood of detecting a secondary cause. A combination of red flags might increase the chances of predicting the underlying etiology of a secondary headache. Much remains unclear since there is a lack of prospective epidemiologic studies. Furthermore, some red flags such as pattern change are poorly elucidated. Large-scale studies are necessary given the low incidence of many secondary causes. A validated screening tool for secondary headaches using red flags would be helpful, like the assessment for mild TBI, to minimize the amount of unnecessary testing and patient anxiety. Finally, a validated screening tool will lead to increased awareness of secondary headaches.

Author contributions

T.P. Do: drafting the original manuscript. A. Remmers: drafting the original manuscript. S. Henrik Winther: conceptualization and revising the manuscript for intellectual content. C. Schankin: conceptualization and revising the manuscript for intellectual content. S.E. Nelson: conceptualization and revising the manuscript for intellectual content. M. Obermann: conceptualization and revising the manuscript for intellectual content. J. Møller Hansen: conceptualization and revising the manuscript for intellectual content. A.J. Sinclair: conceptualization and revising the manuscript for intellectual content. A.R. Gantenbein: conceptualization and revising the manuscript for intellectual content. G.G. Schoonman: conceptualization and revising the manuscript for intellectual content.

Study funding

Thien Phu Do was funded by a grant from Candys Foundation. Christoph Schankin was funded by grants from German Migraine and Headache Society, Eye on Vision Foundation, and Baasch-Medicus-Stiftung.

Disclosure

T. Do, A. Remmers, H. Schytz, C. Schankin, and S. Nelson report no disclosures relevant to the manuscript. M. Obermann has received scientific support, travel support, and/or honoraria from Biogen Idec, Novartis, Sanofi/Genzyme, Pfizer, Teva, Lilly, Schwarz, and Heel; and received research grants from Allergan, Electrocore, Heel, and the German Ministry for Education and Research (BMBF). J. Hansen, A. Sinclair, A. Gantenbein, and G. Schoonman report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* April 15, 2018. Accepted in final form August 27, 2018.

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