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# Approaching Headaches—A Guide to Differential-Diagnostic Considerations and Causal Claims

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**Abstract:** Headaches can be nociplastic, neuropathic, and nociceptive. Pain related to the latter two categories occurs in the presence of nerve lesions and nociceptive stimuli; attributing pain to the last category requires a list of potential causes and arguments supporting the causal claim. Taking a history and examining patients serves to assess diagnostic criteria and screen for disorders whose diagnosis requires additional examinations. Screening information occurs in two types: one indicates that patients have a headache due to another condition; the other suggests they are at risk. Aspiring to make causal claims for a headache is reasonable because if underlying disorders appear independently and randomly, it is probable that there is only one cause. Thus, having found a cause often implies having found the cause. The prerequisites for causal claims are temporal sequencing, correlation, and elimination of alternate causes. Mechanistic, manipulative, and probabilistic evidence supports the second criterion. The importance of headaches lies in their frequent appearance as an early symptom of an incipient disorder ("sentinel symptom"). Hence, they provide the opportunity to diagnose early diseases with potentially deleterious consequences. Thus, it is sensible to assess each attack carefully and systematically.

**Keywords:** differential diagnosis; red flags; primary headache; secondary headache



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## 1. Introduction

Shortly after Carl von Linné proposed his botanic and zoological classifications in the 18th century, in 1763, Boissier du Sauvage published his attempt to classify diseases entitled "*Nosologia methodica*" [1]. Over the years, accruing knowledge of microbiology, histopathology, and physiology allowed refining their approaches. Today, classifications are an indispensable and widely used tool in medicine. They enable decisions on the next appropriate therapeutic steps and their urgency and help estimate a patient's prognosis.

After several less well-known attempts at classifying headaches [2], the ad hoc classification was published in 1962, and the International Headache Classification, now available in its third edition (ICHD-3, published in 2018), followed in 1988 [3–5]. Still, doctors confronted with the symptom "headache" and charged with its classification often find themselves in trouble. Studies assessing the inter-rater agreement and the number of requested imaging studies document their hardship [6–8].

Various factors contribute to the challenge of diagnosing headaches. One is that pain does not quantify bodily dysfunction and carries little information regarding its origin and cause [9]. Additionally, the history is important, but patients may struggle to recall relevant symptoms. Likewise, physicians may struggle to gather and integrate the information [7]. Furthermore, the validity of the collected data is uncertain, and language may be generally unsuited to communicate the highly individual experience of pain.

Nevertheless, it makes sense to take headaches seriously because they are often among the earliest symptoms of an incipient disorder ("sentinel symptom") [10,11]. Hence, considering differential diagnoses allows the early detection and treatment of diseases with potentially grave implications.

This narrative review aims to discuss the thought process behind diagnosing headaches.

## 2. Identification of Potential Causes of Headache

Current conceptualisation views pain as nociceptive, neuropathic, or nociplastic. Nociceptive pain is due to the activation of nociceptors by an adequate stimulus, and neuropathic pain is "caused by a lesion or disease of the somatosensory nervous system" [12]. Nociplastic pain is due to neither a sufficient stimulus nor a lesion; some authors hypothesise a central sensitisation [13,14].

The pain experienced during headaches can fall into all three categories [13]: (i) neuropathic pain presents, for example, as neuralgia and neuropathy and rarely as central post-stroke pain or central pain due to multiple sclerosis [15]; (ii) nociplastic headaches are referred to as primary headaches (e.g., migraine, cluster headache, and tension-type headache) and (iii) nociceptive headaches as secondary headaches.

Many patients with nociplastic, i.e., primary, headaches recall that specific factors flared their pain [16–18]. However, these factors—generally called triggers—do not activate nociceptors sufficiently to cause pain. Instead, at least some seem to modulate the pain threshold. Examples are sleep deprivation [19,20], oestrogen withdrawal [21], and fasting [22]. Furthermore, alcohol likely increases the pain threshold, suggesting that withdrawal could lower it [23].

A significant challenge for differential diagnostic reasoning is that we identify nociplastic headaches by the absence of a nociceptive stimulus and a neuropathy. Thus, overlooking a nociceptive stimulus or a lesion of the somatosensory networks would result in the erroneous diagnosis of a primary headache with a different therapeutic approach. Therefore, searching thoroughly for nociceptive stimuli and nerve lesions is essential. (As a side note, we cannot diagnose contemporaneous primary and secondary headaches because of this strategy).

A stimulus qualifies as a cause of a nociceptive headache if it activates nociceptors. Evidence supporting such an attribution can be **probabilistic** and **mechanistic**. However, on its own, each type is insufficient [24].

Probabilistic evidence indicates the observed strength of an association but does not exclude that it is due to a common cause or random co-occurrence. Table 1 lists the proportion of patients who report headaches for various disorders.

Mechanistic evidence, on the other hand, suggests a causal relationship but not its strength.

Note that there are controversies about the nature of mechanistic evidence and the strength of the probabilistic evidence required to accept a stimulus as a potential cause of pain [25].

The proportions of patients with a specific disorder listed in Table 1 are imprecise correlation estimators. One reason is that the likelihood of getting a headache is high even without an underlying illness [26]. Particularly in chronic conditions, e.g., Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), the observed number of persons with headaches likely exceeds the number of persons with headaches due to the disorder. Hence, the occurrence of headaches is overdetermined [25].

**Table 1.** Prevalence of different disorders and proportions of affected persons reporting headaches; I—incidence, P—prevalence.

| Diagnosis | Epidemiology | Proportion with Headache |
|---|---|---|
| **Acute rhinosinusitis** | I: 17540 per 100,000 persons per year [27] | 29% [28] |
| **Bacterial meningitis** | I: 1.49 per 100,000 persons per year [29] | 84% to 90% [30–32] |
| **Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)** | P: 1.32 to 1.98 definite cases per 100,000 adults [33,34] | 45% to 55% [35,36] |
| **Cerebral ischaemic event** | I: 156 per 100,000 persons per year [37] | 7% to 34% [38] |

**Table 1.** *Cont.*

| Diagnosis | Epidemiology | Proportion with Headache |
|---|---|---|
| **Cerebral venous thrombosis** | I: 1.32 to 1.75 per 100,000 persons per year [39,40] | 76% to 77% [41,42] |
| **Cervical vertebral artery dissection** | I: 0.97 per 100,000 persons per year [43] | 69% [44] |
| **Chiari malformation type I** | P: 96 per 100,000 persons [45] | 43% to 81% [46–49] |
| **Giant cell arteritis** | P: 51.74 per 100,000 persons over 50 years [50] | 86% to 87% [51,52] |
| **Hypothyroidism** | I: 226.2 per 100,000 persons per year [53] | 30% to 34% [54,55] |
| **Idiopathic intracranial hypertension** | I: 0.9 per 100,000 persons per year [56,57] | 75% to 92% [56,58–60] |
| **Internal carotid artery dissection** | I: 1.72 per 100,000 persons per year [43] | 68% [44] |
| **Intracranial neoplasia** | I: 14.8 per 100,000 persons per year [61] | 48% to 60% [62–65] |
| **Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes (MELAS)** | P: 0.18 per 100,000 persons in Japan [66] | 69% to 86% [67,68] |
| **Moyamoya angiopathy** | P: 1.01, 16.1, and 6.03 per 100,000 in China [69] Korea [70], and Japan [71], respectively | 20% to 67% [72–75] |
| **Neurosarcoidosis** | I: 11.5 per 100,000 persons per year are affected by Sarcoidosis [76], 0.2 per 100,000 persons per year for isolated Neurosarcoidosis [77] | 32% [78] |
| **Non-traumatic intracranial haemorrhage** | I: 29.9 per 100,000 persons per year [79] | 26% [80] |
| **Pituitary apoplexy** | I: 4.0 per 100,000 persons per year [37] | 82% to 100% [81–83] |
| **Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations** | Unknown, probably exceedingly rare | 27% to 59% [84,85] |
| **Reversible cerebral vasoconstriction syndrome (RCVS)** | I: 0.3 per 100,000 persons per year [86] | 95% to 100% [87] |
| **Sleep apnoea** | P: 3420 per 100,000 persons [88] | 12% to 18% [89–91] |
| **Spontaneous intracranial hypotension** | I: 3.7 per 100,000 persons per year [92] | 90% to 100% [92,93] |
| **Transient ischemic attack** | I: 83 per 100,000 persons per year [94] | 26% to 36% [38] |
| **Unruptured vascular malformation** | P: 18 per 100,000 adults for arterio-venous malformations [95], 500 per 100,000 [96] for cavernous malformations | 49% to 54% [97] |
| **Viral meningitis** | I: 0.26 to 17 per 100,000 persons per year [98] | 99% [32] |

The mechanisms through which specific disorders activate nociceptors are not always well known. Furthermore, even when they are known, it is uncertain if they are the only mechanisms. There are hypotheses about the mechanisms of pain for several types of headaches:

- Several secondary headaches, including traumatic injuries to the head, whiplash, and craniotomy, likely result from the activation of nociceptors by tissue damage or distension. A similar mechanism may apply to the reversible cerebral vasoconstriction syndrome and subarachnoid haemorrhage. The latter could also lead to pain through a mechanism such as that of mass lesions (see below).
- Inflammatory disorders are likely to share a common mechanism. Research on COVID-19 infections suggested that cytokine release—Interleukin 10 in particular—might be associated with headaches [99,100].

- Mass lesions, e.g., brain tumours, might cause pain through pressure-induced traction of pain-sensitive structures due to their size, accompanying oedema, or hydrocephalus. Subsequently, sensitisation could increase the pain intensity [101].
- Similarly, strokes could lead to pain by exerting pressure on pain-sensitive structures. However, pain also occurs in smaller ischemia suggesting additional mechanisms. The release of pro-inflammatory substances and perhaps the occurrence of a cortical spreading depression could contribute to the pain [38,102].
- Different hypotheses attempt to explain headaches in patients affected by CADASIL. One is that they are more prone to pain induced by cortical spreading depression. Hypoperfusion might also be a mediating factor [103]. Another hypothesis is that damage to the periaqueductal grey could increase the likelihood of headaches [103].
- Milhorat and co-workers suggest that the cause of headaches in patients with Chiari Type 1 malformation may be a reduced CSF volume that results in difficulty mitigating pressure changes [46,104]. Additionally, Williams observed a "craniospinal pressure dissociation" that comprised a steeply increased pressure in the cranial but not the spinal CSF [105]. In addition to the elevated pressure distending the meninges, the pressure gradient might result in a further herniation of the tonsils with subsequent straining of pain-sensitive structures, which might contribute to the pain [104].
- Headache due to pituitary gland apoplexy may result from increased intrasellar pressure, which activates nociceptors [106].
- The pathophysiology of morning headaches due to sleep apnoea is incompletely understood. While hypoxia is a relevant factor, elevated intracranial pressure is also involved [90,107].
- Headache due to hypothyroidism could be linked to an increased pituitary gland volume, which leads to the activation of intrasellar nociceptors [55,106]. Another hypothesis postulates that thyroxine has antinociceptive properties [55,106].
- Focal demyelination of the trigeminal nerve leads to hyperexcitable afferents, which can result in synchronised after-discharge activity [108]. The latter results in pain perception in trigeminal neuralgia.

Overall, the presence of both mechanistic and probabilistic evidence suggests that a disorder is a potential cause of headaches. Equipped with this list, the next step is to develop a search strategy for these disorders in patients with headaches.

## 3. Searching for Potential Causes of Headaches

Central assumptions of disease classifications are that different entities are distinguishable and that identical disorders are listed as one entity (principle of unambiguousness) [1,109]. Consequently, if a patient suffers from a specific disorder, we should be able to detect symptoms or signs indicative of that underlying disorder. However, a crucial restriction complicates the diagnostic process.

Because of the high prevalence of headaches [110], additional examinations cannot be ordered for everyone. Yet, several diagnoses require more than a history and a physical examination. Thus, preselection and targeted testing are necessary. Consequently, one aspect of data collection is screening for underlying disorders whose diagnosis requires further investigations [111].

There are two types of information (provided by the history and clinical examination) that support the detection of a potential cause of a headache. These are information with diagnostic value and information with screening value.

- **Information with diagnostic value** comprises all diagnostic criteria that patients may be aware of, i.e., phenotypes and several specific causes of headaches.
- Phenotypes are relevant for the diagnosis of primary headaches. The causes that patients can be inquired about are trauma to the head, whiplash, craniotomy, medication overuse, exposure to a substance (nitric oxide [NO] donor, phosphodiesterase [PDE] inhibitor, alcohol, and cocaine), withdrawal (pain killers in the case of medication overuse headache and caffeine), high altitude, aeroplane travel, diving, dialysis, and

fasting [5]. Moreover, many patients will know if they have a systemic or localised inflammation.

- There are two types of **information with screening value**: One comprises symptoms and signs typical of a headache, whose diagnosis requires additional examinations [111]. The other includes *risk factors* indicating an increased likelihood of a secondary headache.
- The difference between these two types lies in the provided temporal information: A risk factor implies that the patient may develop a specific headache *eventually*; however, it allows no conclusions about the pathophysiology of the *current* headache. On the other hand, a symptom of another disorder suggests that the patient is *currently* diseased [111]. The former does not provide temporal information; the latter does.

The following two subsections discuss these two types of information with screening value in further detail.

### *3.1. Screening Factors with Temporal Information*

Screening factors that provide temporal information can be likened to screening tests [111]. Thus, they suggest but do not prove the presence of a specific disease. Screening factors for secondary headaches are called red flags [111,112].

Since secondary headaches often require more urgent measures than primary headaches, they should not be missed. Consequently, red flags need high sensitivity (i.e., few false negatives). However, specificity is important, too. If it is too low, the number of false positives will be high; the more unspecific red flags are being used, the more unnecessary additional tests will result (cf. multiple comparison problem) [111]. Thus, it makes sense to maximise specificity of individual red flags and aim for high specificity of their entirety. A recent study shows that the strategy can be successful, as a set of red flags had high sensitivity despite fairly low sensitivity of the individual red flags [113].

Table 2 provides an overview of red flags with temporal information. In addition to them, the Ottawa rule may help to screen for a subarachnoid haemorrhage [114]. Furthermore, trauma to the head, which itself may lead to pain, also indicates an increased risk of a traumatic haemorrhage that can cause headaches, too.

**Table 2.** Overview of red flags with temporal information screening for secondary headaches.

| Red Flag | Associated Condition |
|---|---|
| **Abnormal neurologic examination** | Headaches with different aetiologies including mass lesion, hydrocephalus, and dural fistula [115] |
| **Arterial hypertension** | Pheochromocytoma, hypertensive crisis, pre-eclampsia and eclampsia, acute pressure response to an exogenous agent, and acute increase in intracranial pressure (Cushing response) [116] |
| **Cough headache** | Chiari malformation type 1 [117] and posterior fossa lesion [118] |
| **Delayed headache after COVID-19 vaccination** | Sinus thrombosis [119] |
| **Exertional headache** | Subarachnoid haemorrhage, sinusitis, and brain metastases [117] |
| **Fever** | Systemic infection, meningitis, and encephalitis |
| **Headache associated with sexual activity** | Subarachnoid haemorrhage [117] |
| **Jaw claudication** | Temporal arteritis, temporomandibular joint dysfunction, and myofascial pain [120] |
| **Morning headache** | Brain tumour [101], medication overuse headache [121], and sleep apnoea [89] |
| **Neck stiffness** | Meningitis [122] and intracranial haemorrhage [123] |
| **Numb chin** | Metastatic tumour (infrequently associated with pain) [124] |
| **Papilledema** | Raised intracranial pressure [125] |

**Table 2.** *Cont.*

| Red Flag | Associated Condition |
|---|---|
| **Positional headache** | Intracranial hypertension and intracranial hypotension [126] |
| **Pulsatile tinnitus** | Intracranial hypertension, arterio-venous malformation, and arterio-venous fistula [127] |
| **Recent unwanted weight loss, night sweat** | Systemic disorders including infection, malignancy (e.g., lymphoma), autoimmune (e.g., polymyalgia rheumatica), and endocrinologic disorders (e.g., carcinoid syndrome) [128] |
| **Reddening of one eye** | Glaucoma [129], carotid-cavernous fistula [130], and cavernous sinus thrombosis [131] |
| **Reduced range of motion in the flexion-rotation test** | Cervicogenic headache [132] |
| **Skin rash** | Systemic infection, meningitis, meningoencephalitis due to, e.g., measles, Mediterranean spotted fever, Syphilis, Neisseria meningitides, varicella zoster virus, and West Nile virus [133,134] |
| **Tenderness upon palpation of the temporal and masseter muscles** | Temporal-mandibular dysfunction and temporal arteritis [120] |
| **Thunderclap headache** | Subarachnoid haemorrhage [10], reversible cerebral vascular constriction syndrome (RCVS) [135,136], cervical artery dissection, cerebral venous sinus thrombosis, spontaneous intracranial hypotension [137], and pituitary apoplexy [138] |
| **Tongue Scalloping** | Bruxism [139] and sleep apnoea [140] |
| **Transient visual obscuration** | Intracranial hypertension [141] |

### *3.2. Screening Factors without Temporal Information (Risk Factors)*

Several authors recommend including screening factors without temporal information, i.e., risk factors, in clinical reasoning [142]. However, basing decisions on data that does not provide temporal information may seem unreasonable, given that there is screening information that does (see Table 2). On the other hand, it is unknown if screening with temporal information alone allows for identifying every patient with a secondary headache at every stage of the underlying disorder. Hence, it makes sense to consider risk factors.

We distinguish two types of risk factors. One is a disease that can eventually lead to pain; the other is a disease that predisposes for another that can lead to pain. The latter can serve as the starting point for a hypothesis about the origin of the pain that can be corroborated.

- **Type 1 risk factors** are chronic conditions that increase the long-term risk of a secondary headache. Examples listed in the ICHD-3 are MELAS, CADASIL, Chiari malformation type 1, vascular malformation, temporomandibular dysfunction, and Moyamoya disease [5].
- **Type 2 risk factors** indicate an increased risk of developing or having a disorder that might lead to a secondary headache or neuralgia.
- Examples are pregnancy (increased risk of hypertensive disorders, e.g., eclampsia) [143] and extracranial solid tumours (increased risk of headaches due to metastases) [144]. Furthermore, overweight females have an increased risk of idiopathic intracranial hypertension [145], and multiple sclerosis increases the risk of trigeminal neuralgia [146]. Moreover, polymyalgia rheumatica increases the risk of giant cell arteritis [147].
- In addition, AV malformations, dural fistula, and Moyamoya disease that may lead to headaches themselves also predispose patients to a haemorrhage [148,149].
- Additionally, exposure to several substances is a type 2 risk factor. Several chemotherapeutic agents, CHOP/R-CHOP regimens in particular, increase the risk of a posterior reversible encephalopathy syndrome (PRES) [150]. Cannabis and perhaps co-

caine consumption could precipitate a reversible cerebral vasoconstriction syndrome (RCVS) [151]. Treatment with doxycycline and retinoids can increase intracranial pressure [152]; and eculizumab treatment predisposes meningitis [153]. Furthermore, treatment with oral contraception increases the risk of cerebral thromboses [154].

The disadvantage of Type 1 risk factors is that they could be blamed for every headache the patient has—irrespective of a "true" connection. The reason is that a causal relationship between an individual headache attack and these risk factors cannot be shown (see next section). An exception is Chiari malformation type 1, as it leads to headaches of a specific phenotype.

Conversely, the advantage of type 2 risk factors is that they provide a hypothesis about the origin of a headache that screening factors with temporal information and further diagnostic tests can corroborate. For example, papilledema provides temporal information and supports a causal claim in a patient treated with retinoids and complaining about headaches.

Figure 1 provides an overview of the different types of information discussed in the last section.

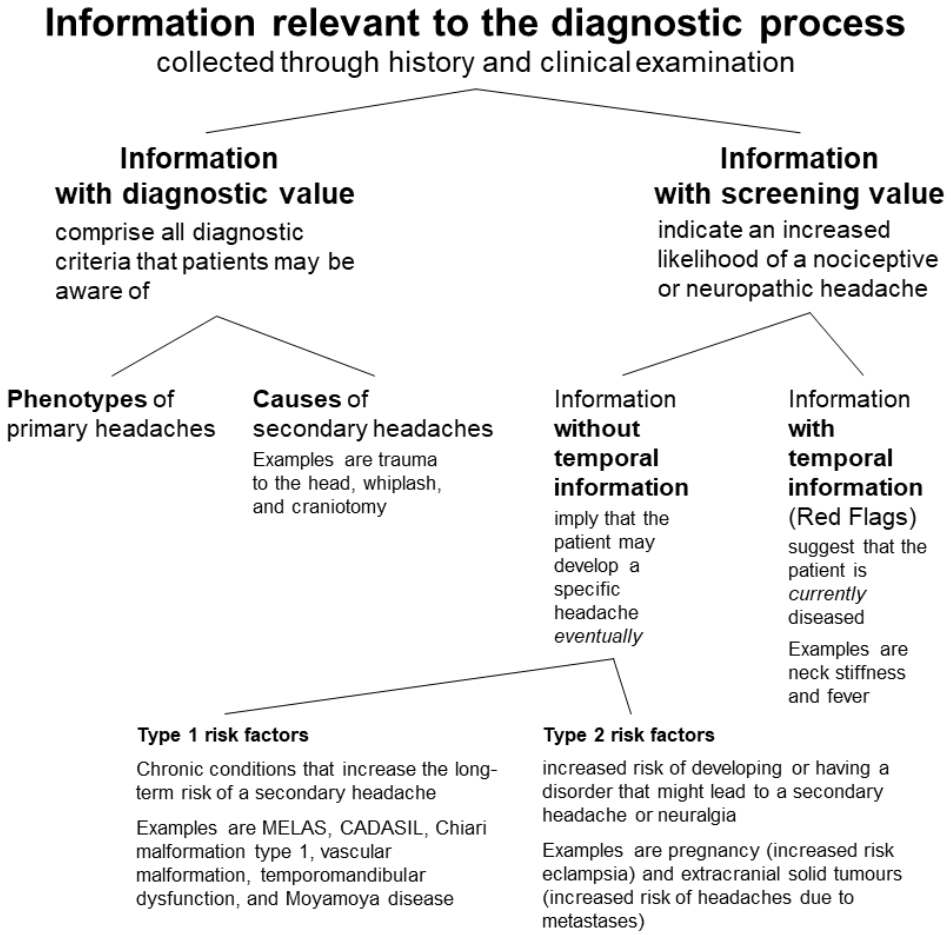


**Figure 1.** Overview of the pieces of information obtained through history and physical examination that are relevant to differential diagnostic reasoning; MELAS—Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes, CADASIL—Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy.

Should the information collected, as outlined above, indicate the presence of a secondary headache, further diagnostic tests should be ordered to confirm the suspicion. The pertinent examination depends on the suspected disorder.

- Cerebral imaging is helpful when a haematoma, haemorrhage, ischemia, blood vessel malformation, tumour, hydrocephalus, and other causes of increased intracranial pressure or inflammation are suspected [155].
- A spinal tap allows measuring the intracranial pressure and searching for inflammation, haemorrhage, and tumour cells.
- An ophthalmic examination may help detect signs of raised intracranial or intraocular pressure, inflammation, including keratitis, and refractive errors [156].
- An ear, nose, and throat specialist should be consulted when local inflammation (e.g., otitis or mastoiditis) and craniomandibular dysfunction are suspected [157].
- Monitoring the blood oxygen levels during sleep can detect sleep apnoea.
- Occasionally, myelography can help to detect a cerebrospinal fluid leak [158].

However, the presence of a potential cause of a headache does not prove it *is* the cause because most nociceptive stimuli and many lesions of the somatosensory system do *not necessarily* cause pain. Hence, strategies are required to support the assumption of causality on an individual level.

## 4. Causal Claims

Headaches are unspecific: they can be due to many different causes, and most potential causes do not always lead to pain (see Table 1). Thus, identifying a patient's *potential* source of pain does not mean identifying *the* source. However, once *a* source of pain is identified, *the* (sole) source of pain is likely found.

As pain-causing disorders generally appear randomly, co-occurrence of two or more of them is unlikely—except if they are not independent events. Examples of headache diagnoses that increase the likelihood of another diagnosis that could lead to headaches, are headaches due to trauma to the head, AV malformations, dural fistula, and Moyamoya disease [148,149].

Identifying a disorder as the source of a patient's pain implies making causal claims. Doing so is justified when the three conditions of causality are satisfied—temporal sequencing, correlation/non-spurious association, and elimination of alternate causes [159].

- **Temporal sequence**: An essential requirement is that a cause must appear before its effect. However, in practice, that sequence may be difficult to evidence. Accordingly, the ICHD-3 relaxes that criterion for headaches due to acute disorders. It stipulates merely that the condition "has been diagnosed" [5]. Nevertheless, for every symptom supposedly due to an underlying disease, one should attempt to clarify the temporal sequence and note the onset time of each symptom.
- For non-acute disorders that permanently increase the likelihood of a headache (see above, type 1 risk factors), it is sufficient to make it plausible that the disorder was present before the headaches.
- **Correlation**: A spurious relationship seems unlikely when a disorder known to cause pain appears in close temporal association with pain. However, given how unspecific and prevalent headaches are, it is reasonable to consider the possibility of a random co-occurrence, especially when dealing with stimuli that weakly correlate with pain (see Table 1).
- Evidence supporting the assumption of a non-spurious relationship can be mechanistic, manipulative, and probabilistic (see below).
- **Elimination of alternate causes**: It is impossible to unequivocally eliminate all alternate causes of a headache, as there are no diagnostic tests for primary headaches, and the process of collecting information, as outlined above, does not necessarily detect all underlying conditions. Yet, for practical reasons, it makes sense to assume that this prerequisite is satisfied if clinical evidence does not suggest a yet-to-be-discovered secondary headache or neuralgia—provided that data were collected meticulously.

The following subsections discuss the different types of evidence for a non-spurious relationship between a nociceptive stimulus and a neuropathy in further detail. Note

that all kinds of evidence are only relevant for stimuli identified as potential causes of headaches, as discussed in Section 1.

In *primary headaches*, there are no causes whose association with the pain could be shown. In that case, headaches must have an appropriate phenotype, and alternate reasons must be eliminated as much as possible.

### *4.1. Mechanistic Evidence*

A high degree of certainty can be reached if the mechanism through which the stimulus causes pain is substantiated directly or indirectly.

Direct evidence is evidence of the underlying pathophysiologic mechanism. For example, in a patient in whom a brain tumour caused pain by increasing the intracranial pressure, the confirmation of increased intracranial pressure is direct mechanistic evidence.

On the other hand, indirect evidence comprises further (and potentially less specific) consequences of the suspected pathophysiology. For example, indirect mechanistic evidence in said patient would be another effect of intracranial pressure, such as papilledema and vomiting—Table 3 lists additional suggestions for evidencing the mechanism of pain.

**Table 3.** Examples of evidence of the mechanisms through which certain stimuli cause headache; IIH—idiopathic intracranial hypertension; SAH—subarachnoid haemorrhage; RCVS—reversible cerebral vascular constriction syndrome.

| Mechanism | Associated Conditions | Direct Mechanistic Evidence | Indirect Mechanistic Evidence |
|---|---|---|---|
| **Craniospinal pressure dissociation** | Chiari malformation type 1 | Measurement of the pressure gradient [105] | Headache attacks from coughing [47] |
| **Decreased intracranial pressure** | Spontaneous CSF leakage and postdural headache | Invasive evidence of a pressure gradient | MRI signs of reduced intracranial pressure [160] and positional headaches [126] |
| **Focal demyelination of the trigeminal nerve** | Neuralgia | - | MR evidence of nerve vessel conflict with thinning, grooving, or distortion of the nerve [161], presence of a trigger point or a trigger zone, or pain restricted to a skin area innervated by a specific sensory nerve [5,162] |
| **Inflammation** | Systemic or localised inflammation | - | Elevated inflammatory parameters, skin rash |
| **Medication overuse** | Medication overuse headache | - | Medication overuse and presence of morning headaches [121] |
| **Raised intracranial pressure** | IIH and brain tumour | Measurement of the pressure | Papilledema in fundoscopy, MRI signs of raised intracranial pressure, vomiting, impaired consciousness, bradycardia, hypertension (Cushing response) [116], and positional headaches [101] |
| **Sleep-related hypoxia** | Sleep apnoea | Reduced oxygen saturation during sleep | Morning headaches [89] |
| **Stimulation of arterial nociceptors** | SAH and RCVS | - | Thunderclap headache [10,135,136] and imaging evidence of a bleeding or vasospasm |
| **Traumatic stimulation of nociceptors** | Trauma to the head, whiplash, and craniotomy | Witness of the impact | Traces of the trauma, e.g., scars |

If the mechanism cannot be observed or is unknown, another, albeit weaker, mechanistic approach to finding a causal relationship may be to search for other symptoms of the suspected stimulus. For example, a tumour responsible for a focal-neurological deficit may be more likely to cause headaches than a completely asymptomatic lesion. The rationale

for this strategy is that headaches are often among the first symptoms of an underlying disorder [10,11]. Thus, if a condition can produce symptoms, headaches are likely one of them.

### 4.2. Manipulative Evidence

If the most likely mechanism of pain is known, interventions may impede it. Observing changes in a symptom by manipulating its alleged cause provides manipulative evidence for a causal relationship [163].

There are two types of manipulative evidence concerning headaches. The first type comprises the treatment of the underlying cause. Examples are the removal of a tumour, treatment of hypothyroidism, withdrawal in medication overuse, and closing of a CSF leakage in intracranial hypotension.

The second type modifies the mechanism without attempting to abolish it. For example, relieving pain in a patient with increased intracranial pressure due to communicating hydrocephalus by lowering the pressure supports a causal claim [164]. A further example would be to relieve pain by reducing the inflammatory response without treating the cause of the inflammation.

However, some debate surrounds the value of this evidence type [163]. For example, if an intervention fails to provide mechanical evidence by relieving pain, a causal relationship is still not excluded because other mechanisms might sustain the pain. For instance, the pain of idiopathic intracranial hypertension may exacerbate following lumbar puncture despite a decrease in intracranial pressure [165]. In addition, pain caused by inflammation occasionally persists for long periods despite the end of detectable inflammatory activity [166].

### 4.3. Probabilistic Evidence

The assumption that a specific cause and a headache are associated can be supported when their occurrence is highly correlated (see Table 1 for correlation estimates). However, an exception is type 1 risk factors. They are unreliable even if there is a high correlation, as they indicate a generally increased likelihood of pain; their relationship with the current headache cannot be shown. (As discussed above, Chiari malformation type 1 is an exception, as it leads to a specific kind of pain.)

Occasionally, it may be acceptable to consider probabilistic evidence collected individually: patients who report regularly responding with a headache to a specific stimulus provide an inductive argument for a causal relationship. Note that these stimuli must satisfy the criteria for potential causes of pain, as discussed in Section 1.

Whenever possible, probabilistic evidence should be complemented by mechanistic or interventional evidence. The reason is that no cut-off value indicates when the correlation between disease and the symptom of pain is sufficiently strong to support the hypothesis of a causal connection.

## 5. Conclusions

Headaches are unspecific, and classifying them correctly is challenging. However, attempting to make a correct diagnosis makes sense, as causes, treatments, and prognoses differ vastly among different entities.

When approaching a patient with a headache, disposing of a list of potential causes is essential. These are characterised by the presence of both mechanistic and probabilistic evidence of their capability to cause pain.

In the next step, we collect information that helps to identify these disorders. However, as we cannot order additional examinations for every patient, but some diagnoses cannot be made without them, the collected information serves two purposes: besides making a diagnosis, it helps to decide about ordering additional tests.

Once an underlying disorder is identified, we must show that the co-occurrence of the headache and the condition was not due to chance. Ideally, there is mechanistic

or manipulative evidence supporting that assumption. Should there be no underlying disorder, we may assume the presence of a primary headache.

In summary, diagnosing a headache requires theoretical knowledge and the systematic collection of relevant information.

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