Review article

Secondary headaches - red and green flags and their significance for diagnostics

Tissa Wijeratne [a,b,c,*], Chanith Wijeratne [d,e], Nadja Korajkic [b], Stefanie Bird [b,e], Carmela Sales [b], Franz Riederer [f,g]

[a] School of Psychology and Public Health, La Trobe University, Melbourne, Australia
[b] Department of Neurology, Western Health & University Melbourne, AIMSS, Level Three, WHCRE, Sunshine Hospital, St Albans 3021, Australia
[c] Department of Medicine, Faculty of Medicine, University of Rajarata, Saliyapura, Anuradhapura, Sri Lanka
[d] Monash Medical School, Clayton, Victoria, Australia
[e] Migraine Foundation & Australian Institute of Migraine, 522, Bell Street, Pascoe Vale South, Victoria, Australia
[f] Department of Neurology, Clinic Hietzing and Karl Landsteiner Institute for Clinical Epilepsy Research and Cognitive Neurology, Vienna, Austria
[g] Faculty of Medicine, University of Zurich, Switzerland

A B S T R A C T

A small percentage of patients suffer from a secondary headache syndrome. It is imperative that clinicians are able to differentiate primary headache syndromes from secondary headache syndromes, as failure to do so significantly worsens morbidity and mortality. Recent advances in our understanding of pathobiological mechanisms offer useful information on these enigmatic disorders. We now understand that the causes of secondary headache syndromes can vary significantly – these may be infectious, inflammatory, vascular, traumatic or structural in origin.

A well-taken history and targeted physical examination coupled with appropriate investigations can enable these syndromes to be recognized consistently and thus allow their timely and appropriate treatment. Along with their epidemiology, some of their key characteristics shall thus be discussed in this review so as to aid the busy clinician at the bedside. Red flags including sudden onset, high pain intensity, pattern of change of a preexisting headache, focal neurological signs or seizure, systemic signs and precipitation by physical activity can guide the clinician to suspect a secondary headache. Importantly a preexisting headache is not an exclusion of a secondary headache – it might even be a predisposition in certain cases.

1. Introduction

Headaches are generally divided into primary and secondary headache disorders, where primary headaches such as migraine or cluster headaches are the disease itself, whereas secondary headaches are the expression of an underlying disease. The epidemiology of secondary headaches may vary depending on the clinical setting or the population sampled. For example, emergency-based studies yielded a prevalence rate of 2% to 7% [1,2] while the numbers documented in community-based research ranges from 2% to 23% [3,4]. Age-related variability may also be observed, with elderly patients having a higher likelihood of secondary headaches compared to their younger counterparts [5]. The International Classification of Headache Disorders (ICHD)-3 attributes secondary headaches to a causative disorder such as vascular, inflammatory, traumatic, and neoplastic aetiologias [6]. However, other causes such as medication-overuse headache should also be recognized as one study has shown that it outnumbers all other causes and can result in significant morbidity if inadequately treated [7]. Early recognition of secondary headaches is critical, as in many cases, early treatment proves lifesaving.

A secondary headache may have the characteristics of a primary headache but still fulfil criteria for causation by another disorder [6]. The ICHD-3 defines secondary headaches as:

- Headache attributed to trauma or injury to the head and/or neck
- Headache attributed to cranial or cervical vascular disorder

- Headache attributed to non-vascular intracranial disorder
- Headache attributed to a substance or its withdrawal
- Headache attributed to infection
- Headache attributed to disorder of homoeostasis
- Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
- Headache attributed to psychiatric disorder

Only a selected group of secondary headache syndromes will be reviewed in this paper. So-called "red-flags" have been defined to guide the clinician when to consider a secondary headache that may be a symptom of potentially life-threatening disorder. These red flags are rarely based on evidence and will be briefly discussed at the end of the manuscript. Recently, "green flags" have been suggested to help the clinician to recognize frequently "benign" primary headaches, a concept that needs further study.

2. Post- Traumatic Headaches (PTH)

The ICHD-3 defines Post Traumatic Headaches (PTH) related to trauma to the head and/or neck as traumatic, whiplash or related to craniotomy [6]. It is classified as acute if it occurs within one week following the inciting event or after reemergence of consciousness or after cessation of medications that would impair discernment or reporting of headache, while persistent PTH is considered if it lasts more than three months [6,8]. While most headaches resolved within this time frame, various reports document an incidence of persistence up to one year from 21 to 54% [9]. Factors associated with PTH include the number of post-traumatic symptoms, young age and female sex [10]. Among patients who developed PTH following war combats, other factors which may be contributory to persistence include various socio-economic factors, insomnia, post-traumatic stress disorder and history of loss of consciousness [11].

It is thought that PTH is likely due to traumatic brain injury (TBI)-induced diffused axonal damage, which culminates in the structural remodeling of various regions involved in pain modulation (somatosensory cortical and subcortical regions, the insular cortex and fiber tracts from relevant cortical and subcortical regions to brainstem nuclei) [12,13]. TBI may also cause PTH by altering brain metabolism. Neuronal injury leads to increased glutamate release along with ion and calcium concentration changes (and associated metabolic abnormalities and oxidative stress). Secondary axonal damage similar to stroke and brain involvement in COVID-19 then ensues [14–17].

PTH is one of the most common secondary headache disorders, yet there are still significant unmet needs regarding this. Pharmacologic therapies are nonspecific and may have significant adverse effects – further investigation is needed to support these interventions. Regardless of whether the phenotype of PTH is tension-like, migraine-like or akin to other cephalalgias, the use of paracetamol, NSAIDs, caffeine and sometimes triptans or any of these combinations may be acceptable [18,19]. Preventative treatment according to phenotype consisting of antidepressants, antihypertensives, Onabotulinum toxin injections and CGRP inhibitors are also considered acceptable with the occurrence of more than eight disabling headache days per month [18,20]. Non-pharmacologic interventions such as non-invasive brain stimulation and cognitive behavioral therapy are considered to have the most robust studies with a trend to benefit in the management of PTH [8]. Other interventions such as progressive muscle relaxation, acupuncture and physical therapy are not only useful for headache alleviation but may also be useful in the management of their concomitant psychiatric comorbidities [21]. Over-all, the management of PTH is complex and requires a multifaceted approach.

3. Headache attributed to cranial or cervical vascular disorder

These headaches may arise from stroke (ischemic and hemorrhagic), arterial dissection, arteritis, cerebral venous sinus thrombosis (CVST), reversible cerebral vasoconstriction syndrome (RCVS), genetic vasculopathies or other post-procedural headaches [6]. In many of these cases, diagnosis of the headache and its causal link is relatively simple. These headaches tend to present acutely with neurological signs and remit rapidly. A close temporal relationship between a headache and these neurological signs heavily suggests causation.

In some cases (e.g. ischemic or hemorrhagic stroke), the presence of the headache is overshadowed by focal signs and/or disorders of consciousness, which are important red flags. In others (e.g. subarachnoid hemorrhage) headache is often a prominent symptom. Additionally, in some conditions that can induce stroke (e.g. dissections, CVST, giant cell arteritis, central nervous system angiitis) headache may be an initial warning sign. Recognizing the association of a headache with these disorders is therefore critical to allow early diagnosis and treatment of the underlying vascular disease and thus prevent potentially devastating neurological consequences.

All of these conditions may occur in patients who have previously suffered a primary headache of any type. For example, migraine has been linked with cervical artery dissection while migraine with aura is associated to stroke, particularly when other risk factors are present [22,23]. The emergence of new-onset headache which may be very strong is intensity (worst ever) unlike any headaches the patient has previously experienced is a key sign that an underlying vascular condition may be present. When this is seen one should urgently look for any of the vascular conditions previously mentioned.

Diagnostic criteria for such a headache include the following (when they can reasonably be derived)

1. Headache fulfilling criterion C
2. A cranial and/or cervical vascular disorder known to be able to cause headache has been demonstrated
3. Evidence of causation demonstrated by at least two of the following:
   - headache has developed in temporal relation to the onset of the cranial and/or cervical vascular disorder
   - either or both of the following:
     – headache has significantly worsened in parallel with worsening of the cranial and/or cervical vascular disorder
     – headache has significantly improved in parallel with improvement of the cranial and/or cervical vascular disorder
   - headache has characteristics typical for the cranial and/or cervical vascular disorder
   - other evidence exists of causation
   - Not better accounted for by another ICHD-3 diagnosis [4].

4. Arterial ischemic event

Headaches related to arterial ischemia may occur in the setting of transient ischemic attack or cerebrovascular infarction. A meta-analysis of >50 studies revealed that it can occur in 6% to 44% of ischemic stroke patients and usually associated with tension-type features [24]. Some of the risk factors identified include previous history of headache disorders, female, the presence of midbrain lesions and posterior circulation strokes [24–27]. Like PTH, persistent post-stroke headache occurs when the symptomatology lasts for more than three months and is usually associated with obstructive sleep apnea and other musculoskeletal abnormalities [28]. Atherosclerosis or embolism are both painless events and it is also known that intracerebral vasculature are insensate to nociceptive stimuli [29] However, it has been identified that cortical spreading depression (CSD) along with the release of pro-inflammatory substances such as serotonin and prostaglandin are central to its pathophysiology in the acute stage, while nociceptive processes in the

chronic stage are less understood but central sensitization has been identified as a potential mechanism [29]. In the acute period, it is essential to rule out malignant infarction resulting in increased intracranial pressure from mass effect as the etiology of headache. In this scenario, medical or surgical intervention may be warranted. In the setting of acute ischemic stroke, aspirin plays a dual role in the prevention of thrombogenesis and for acute pain control [30]. There are however limited well-designed studies on the use of analgesics for post ischemic stroke headaches. Management of persistent post-stroke headache requires a multi-pronged approach with the emphasis on non-pharmacologic interventions. As chronic headache post-stroke usually occurs in association with fatigue, depression and anxiety, treatment of these comorbidities is also essential along with strategies such as exercise, stretching, physiotherapy, CBT and biofeedback [31].

5. Non-traumatic ICH

Headaches associated with acute, non-traumatic intracerebral, subarachnoid and subdural hemorrhage are usually more common than an ischemic etiology. One study reported that it is the second most common presentation of all hemorrhagic strokes while another documented that it is the leading presentation among patients with cortical bleed [32,33]. Aneurysmal subarachnoid hemorrhage (SAH) is another common cause of secondary headache and is associated with thunderclap features which typically reaches maximum severity within 60 s. Signs and symptoms of SAH can be subtle prodromal events seen in up to 50% of patients of a sentinel bleed coupled with a transient and mild headache [34]). MacGrory and colleagues found that clinical features such as occipital location of the headache, presence of a prior headache, stabbing pain, a rapid peak of intensity within one second of headache onset and meningism generally suggested SAH [35]. A sudden increase in the intracranial pressure because of hematoma expansion is the main mechanism involved in ICH-related headaches. This results in the traction and distortion of pain sensitive structures such as the dura and the meninges [36]. There is also evidence to show that latent headaches associated with non-traumatic ICH may also be related to CSD, particularly with SAH [37].

The diagnosis of ICH is straightforward with all suspected patients to undergo an urgent non-contrast cranial CT in the emergency room. The sensitivity and specificity of this modality in SAH nearly reaches 100% especially if performed in the first six hours following the onset of symptoms [38,39]. Angiographic studies such as CT angiography or Digital Subtraction Angiography (DSA) are also useful in excluding other vascular causes of ICH as well as conditions which may present with thunderclap headache such as reversible cerebral vasoconstriction syndrome (RCVS). [39]. Lumbar puncture may also be useful to detect xanthochromia particularly for delayed presentation as this may persist in the CSF up to two weeks after [40,41].

Opioids are generally used in the acute setting following a SAH although alternative treatment must be explored due to the potential of opioid dependence [42,43]. More than one-third of patients with SAH have persistent headaches, hence the need to explore long-term analgesic options [44]. Some of the alternatives explored to reduce the need for opioid include magnesium and gabapentin as well as pterygopalatine blocks and cannabidiol [45–48].

6. Cranio-cervical arterial dissection and headaches

Dissection refers to a tear in the wall of an artery. These may be intracranial or extracranial and may involve the vertebral or the carotid artery circulation. The location of the headache among patients with anterior circulation dissection tends to be more temporal while those related to the vertebro-basilar circulation is typically associated with occipital neck pain [49]. Compared to ischemic stroke patients, headaches related to dissection tend to be more severe and associated with a throbbing and pulsating quality [50]. Other associated symptoms include ipsilateral facial or neck pain in 60–95% of cases while thunderclap features may also be observed in a minority [51–53]. Further case reports detail the varying phenotypes of headache that may be present in a dissection – these include a migraine-like (including aura [54] or hemicrania-like headache [55]. Primary headache disorders such as Trigeminal Autonomic Cephalalgias (TACs) are a possible differential diagnosis if the right clinical context is present.

Some of the identified factors associated with headache in craniocervical dissection include female sex, posterior circulation involvement, previous history of headache disorder and an low-density lipoprotein <1.8 mmol/L 9 [55,56]. It is speculated that the headache associated with arterial dissection is a sequela of the release of inflammatory neurotransmitters from the injured vessel [57]. Recommendations on the treatment of arterial dissection include intravenous thrombolysis for ischemic stroke complication in the hyperacute setting particularly for extracranial arterial dissection, endovascular and surgical interventions, and antiplatelet and anticoagulation for secondary stroke prevention [58] However, it is unclear whether these interventions have an impact on headache alleviation. The prognosis of headaches related to arterial dissection likewise remains debatable although one study reported that around 25% of patients were still symptomatic after six months [59].

7. Cerebral Venous Sinus Thrombosis (CVST) and headaches

COVID-19 vaccines created a renewed interest in CVST globally [60,61]. The incidence of CVST varies between studies but is generally estimated to be between 2 and 5 million per year, with a higher prevalence reported from Netherlands, Australia, and Asia in the recent past [62–64]. Up to 90% of CVST patients present with a non-specific headache that shows no specific clinical features directing the clinician towards CVST, the clinical presentation ranging from thunderclap headache to subacute headache [65]. Female gender, use of contraceptives containing estrogen, pregnancy and peripartum status are known risk factors for CVST. Delayed onset headache (particularly a week after vector based COVID-19 vaccination) has also been noted to be associated with CVST as per recent observation in a small cohort study, defining a new red flag [66]. CVST seems to be a rare complication of adenovirus-based COVID-19 vaccines and is associated with thrombocytopenia (vaccine-induced thrombotic thrombocytopenia) which is potentially treatable [67]. COVID-19 infection also seems associated with CVST.

8. Headaches related to arteritis and related disorders

Giant cell arteritis (GCA) and primary and secondary angiitis of the central nervous system are examples of inflammatory headache disorders. One of the common secondary causes of headache particularly in the elderly is giant cell arteritis which is usually associated constitutional symptoms, jaw claudication, blindness, and pain in the temporal region [68]. Among patients with biopsy proven GCA, headache and visual disturbance usually occurs in 75% and 68.4%, respectively and these symptoms are usually responsive to a course of steroid treatment, which makes the latter also considered as a criterion for the diagnosis of GCA [3,69].

There is usually a rapid improvement in symptomatology following the initiation of steroids. The European Headache Federation recommends the use of 40–60 mg equivalent dose of oral prednisone per day while those who develop ischemic complications are commenced on 500–1000 mg of intravenous methylprednisolone [70]. Weekly doses of tocilizumab have also been show in clinical trials to be useful in inducing clinical remission and commenced in patients who are refractory to steroids [70–72]. Methotrexate 7.5 to 15 mg per week has also been reported to reduce steroid requirement and helpful in preventing first and second relapses [70]. The need for optimized immunosuppression is essential in achieving headache control and prevention of complications.

9. Reversible cerebral vasoconstriction syndrome (RCVS)

RCVS is another secondary headache disorder which is related to a reversible vascular cause (ICHD). It is characterized by recurrent thunderclap headaches and radiological demonstration of reversible vasoconstriction that resolves over three months [73]. Some of the identified triggers include sexual activity, pregnancy and the post-partum period, recreational agents, catecholamine-secreting tumors and other vasoactive drugs [73,74]. Some of the proposed mechanisms related to its occurrence include increased sympathetic response, endothelial dysfunction, and oxidative stress [74].

It is important to recognize this uncommon etiology for secondary headache as it may be precluded other neurovascular complications including ischemic strokes, ICH, SAH and PRES. Magnetic resonance angiography or CT angiography showing stenosis and arterial beading are the characteristic neuroimaging features [75]. The mainstay of treatment is the use of calcium-channel blockers such as nimodipine or verapamil while steroids have no role and have been associated with worse outcomes [76]. While it is expected that arteriolar vasoconstriction reverses within three months, headache may persist for one year in around 50% of patients and remain disabling in 10% [77], Some of the risk factors which result in headache persistence include prior history of depression, anxiety, and previous history of migraines [77,78]. The prognosis of RCVS is generally favorable with only 5–10% of patients having persistent deficits [77].

10. Hypertension and headaches

Among patients who present to the emergency room for elevated blood pressure, nearly 50% of them complain of headache [105]. ICHD-3 classified this group as 10.3 as follows - headache, often bilateral and pulsating, caused by arterial hypertension, usually during an acute rise in systolic (to ≥180 mmHg) and/or diastolic (to ≥120 mmHg) blood pressure. It remits after normalization of blood pressure [6].

10.1. Diagnostic criteria:

1. Any headache fulfilling criterion C
2. Hypertension, with systolic pressure ≥ 180 mmHg and/or diastolic pressure ≥ 120 mmHg, has been demonstrated
3. Evidence of causation demonstrated by either or both of the following:
4. headache has developed in temporal relation to the onset of hypertension
5. either or both of the following:
   a) headache has significantly worsened in parallel with worsening hypertension
   b) headache has significantly improved in parallel with improvement in hypertension
6. Not better accounted for by another ICHD-3 diagnosis.

Mild (140–159/90–99 mmHg) or moderate (160–179/100–109 mmHg) chronic arterial hypertension does not appear to *cause* headache. Whether moderate hypertension *predisposes* to headache remains controversial, but there is some evidence that it does [6]. Ambulatory blood pressure monitoring in patients with mild and moderate hypertension has shown no convincing relationship between blood pressure fluctuations over a 24-h period and presence or absence of headache. The clinical phenotype of the headache usually is bilateral or diffuse with pulsating quality. The headache tends to worsen with physical activity [6,39,79].Blood pressure measurement, examination of the optic discs and retinal photography is all of great value among patients presenting with headaches in this context [80].

11. Post Covid headache

Headache during and after COVID infection is a widely recognized occurrence. A meta-analysis revealed that nearly 50% of COVID survivors were diagnosed with post-COVID headache while 8.4% remain persistent after six months [81]. Headache can be an important prodromal or presenting symptom in COVID-19 and can have migraine or tension type like-features [82–89]. Three migraine-like yet distinct scenarios have been described as post-COVID Headache (PCH[[83]. These three different phenotypes may be categorized as migraine chronification, long-lasting COVID headache and delayed onset COVID headache [83]. Persistent maladapted low grade neuroinflammation is well described in Post-COVID Syndromes [84–87]. Headache may have a protective role in the context of survival and COVID-19 [88].

The treatment for persistent headache after COVID is limited. One study showed that amitriptyline may have beneficial effects especially those with tension-type features. [89]. Another retrospective, observational study revealed that for patients who are unresponsive to analgesics and triptans, indomethacin may have a therapeutic role [90]. Clearly, further COVID-19 and headache research is likely to unravel a great deal of useful information in the coming months globally.

12. Idiopathic intracranial hypertension (IIH) and headache

Headache is the most common symptom of IIH. Up to 93% of patients present with non-specific and potentially severe headaches with a significant threat to vision with misdiagnosis [91]. Previously used terms include benign intracranial hypertension (BIH), pseudotumor cerebri, meningeal hydrops and serous meningitis. The IHCD-3 diagnostic criteria for IIH are detailed below. [6].

12.1. Description

New headache, or a significant worsening of a pre-existing headache, caused by and accompanied by other symptoms and/or clinical and/or neuroimaging signs of idiopathic intracranial hypertension (IIH), with typical features suggestive of IIH.

12.1.1. Diagnostic criteria

1. New headache, or a significant worsening[1] of a pre-existing headache, fulfilling criterion C
2. Both of the following:
   - idiopathic intracranial hypertension (IIH) has been diagnosed[2]
   - cerebrospinal fluid (CSF) pressure exceeds 250 mm CSF (or 280 mm CSF in obese children)
3. Either or both of the following:
   - headache has developed or significantly worsened1 in temporal relation to the IIH, or led to its discovery
4. headache is accompanied by either or both of the following:
   A. pulsatile tinnitus
   B. papilloedema
5. Not better accounted for by another ICHD-3 diagnosis

One in twenty patients with IIH may not have papilloedema as 5.7% of patients with IIH have been noted to have normal optic discs [92]. MRI is critical in the diagnosis of IIH with findings such as empty sella turcica, optic nerve tortuosity, distension of the optic nerve sheath, posterior globe flattening, optic nerve protrusion and transverse sinus stenosis [93]. Neuroimaging findings are promising diagnostic markers for IIH [93]. However, negative MRI findings do not rule out the diagnosis of IIH. Most IIH patients are overweight young women in

childbearing age – however no age, sex or weight is exempt from the potential diagnosis. Pulsatile tinnitus, double vision and visual obscurations are well reported among patients with IIH. It is now recognized that IIH is not a benign pathology as it may cause blindness in 1–3% of cases [94].

Pharmacologic management of IIH include the use of acetazolamide and topiramate particularly for mild cases. Evidence from a randomized clinical trial revealed that up to 4 mg of acetazolamide resulted in improvement of papilledema and visual function [95,96]. Surgical interventions such VP shunt insertion, optic nerve fenestration and venous sinus stent insertion are usually reserved for severe cases which are refractory to medical therapy [97]. The benefit of weight loss should be emphasized to patients as this is the most effective strategy in reducing intracranial pressure which translates into meaningful clinical outcomes [98,99].

13. Brain tumors and headaches

Headaches are more common in patients with a preexisting primary headache disorder coupled with a co-existing of brain tumor, as is true with many other common medical conditions [100]. Tumors in certain locations (e.g. posterior fossa tumor) cause headaches more often than a supratentorial tumor. Additionally, rapidly growing tumors are more likely to be associated with headaches [101]. These headaches are generally worse in the morning. Severity increases with laughing, coughing, and straining – note that this is also common among patients with migraine or cluster headaches. Note that headache associated with brain tumor is the only symptom only in rare cases, since seizures, focal neurological signs or neuropsychological abnormalities are frequently found [102].

14. SNNOOP10 list as red and orange flags for secondary headaches in clinical practice

Do et al. proposed the SNNOOP10 list as a useful checklist of features to look out for regarding secondary headache syndromes [103]. The absence of these red flags may support the notion that no further workup is necessary. They are as follows.

S = Systemic symptoms including fever suggestive of an infection or another systemic metabolic/vascular/endocrine disorder.

N = Neoplasm of the brain, primary or secondary.

N=Neurological symptoms or signs suggestive vascular,non-vascular or infectious brain disorder.

O=Onset of headache is sudden suggestive of SAH or vascular dissection intracranial/extracranial.

O = Older age after 50 years at headache presentation suggesting the possibility of giant cell arteritis, cranial or extra cranial vascular disorders, neoplasms, or non-vascular disorders.

P=Pattern change or recent onset headache suggesting neoplasm, vascular or non-vascular disorders.

P=Positional headaches suggesting intracranial hypertension or hypotension.

P=Precipitated by sneezing, coughing or exercise suggesting posterior cranial fossa pathology or Chiari malformation.

P=Papilloedema suggesting neoplasm, other vascular disorders or IIH.

P=Progressive headaches and atypical presentations suggesting neoplasms and other non-vascular intracranial disorders.

P=Pregnancy or puerperium suggesting headaches attributed cranial or cervical vascular disorders, postdural lumbar puncture headaches, hypertension related disorders (preeclampsia), CVST, hypothyroidism, anemia, diabetes).

P=Painful eye with autonomic features suggesting pathology in posterior fossa, pituitary region, or cavernous sinus,Tolosa -Hunt syndrome, ophthalmic causes.

P=Post traumatic onset of headaches suggesting acute and persistent PTH, subdural hematoma and other headaches attributable to vascular disorders.

P=Pathology of the immune system such as HIV suggesting opportunistic infections.

P=Painkiller overuse or new drug at onset of headaches suggesting medication overuse headache or drug incompatibility.

We propose adding further two Ps as follows.

P = Post Covid headaches suggesting persistent, maladapted neuroinflammation culminating in different phenotypes of headache syndromes as part of PCNS/Long Covid.

P = Post-Vaccinations headaches with delayed onset within a week to explore the possibility of CVST contributing to these headaches.

This would then become the SNOOP12 list, with further epidemiological studies needed to explore the sensitivity and specificity of these clinical features.

15. Green Flags

Recently green flags have been defined based on discussion rounds by headache experts, as detailed below [104].

1. The current headache has already been present during childhood.
2. The headache occurs in temporal relationship with the menstrual cycle.
3. The patient has headache-free days.
4. Close family members have the same headache phenotype"; and (v).
5. Headache occurred or stopped more than one week ago.

However, the expert panel recommended to search for red and green and further studies are needed to evaluate a potential benefit of the green flag concept. In summary, a preexisting primary headache disorder does not exclude a potentially dangerous secondary headache. Migraine is associated with diseases causing secondary headache such as stroke or cervical artery dissection. On the other hand, a pre-existing primary headache makes headache more likely to be symptom of a disease affecting the brain such as for instance stroke or brain tumor. Thus, careful history taking, and examination is mandatory to notice changes in the pattern or characteristics of a previous headache disorder or subtle clinical signs such as Horner's syndrome that could indicate an additional secondary cause.

CRediT authorship contribution statement

Tissa Wijeratne: Conceptualization, Writing – original draft, Writing – review & editing. **Chanith Wijeratne:** Writing – review & editing. **Nadja Korajkic:** Writing – review & editing. **Stefanie Bird:** Writing – review & editing. **Carmela Sales:** Writing – review & editing. **Franz Riederer:** Writing – review & editing.

References

[1] K.H. Chu, T.E. Howell, G. Keijzers, J.S. Furyk, R.M. Eley, F.B. Kinnear, O. Thom, I. Mahmoud, A.F. Brown, Acute headache presentations to the emergency department: a statewide cross-sectional study, Acad. Emerg. Med. 24 (1) (2017 Jan) 53–62, https://doi.org/10.1111/acem.13062 (PMID: 27473746).

[2] A.M. Kelly, W.S. Kuan, K.H. Chu, F.B. Kinnear, G. Keijzers, M.A. Karamercan, S. Klim, T. Wijeratne, S. Kamona, C.A. Graham, R. Body, T. Roberts, D. Horner, S. Laribi, the HEAD Study Group, Epidemiology, investigation, management, and outcome of headache in emergency departments (HEAD study)-a multinational observational study, Headache. 61 (10) (2021 Nov) 1539–1552, https://doi.org/10.1111/head.14230 (Epub 2021 Nov 2. PMID: 34726783).

[3] A.A. Silva Junior, M. Bigal, L.P. Vasconcelos, J. Rodrigues, R.S. Gomez, A. V. Krymchantowski, P. Moreira Filho, A.L. Teixeira, Prevalence and burden of headaches as assessed by the health family program, Headache 52 (3) (2012) 483–490, https://doi.org/10.1111/j.1526-4610.2012.02090.x. Epub 2012 Feb 21. Erratum in: Headache. 2012 May;52(5):861. PMID: 22352696.

[4] K. Aaseth, R.B. Grande, K.J. Kvaerner, P. Gulbrandsen, C. Lundqvist, M.B. Russell, Prevalence of secondary chronic headaches in a population-based sample of 30-44-year-old persons. The Akershus study of chronic headache, Cephalalgia. 28 (7) (2008) 705–713, https://doi.org/10.1111/j.1468-2982.2008.01577.x (Epub 2008 May 21. PMID: 18498398).

[5] P. Tanganelli, Secondary headaches in the elderly, Neurol. Sci. 31 (Suppl. 1) (2010) S73–S76, https://doi.org/10.1007/s10072-010-0277-6 (PMID: 20464588).

[6] Headache Classification Committee of the International Headache Society (IHS), The International Classification of Headache Disorders 3rd edition, vol. 38(1), Cephalalgia, 2018, pp. 1–211.

[7] Organization, W.H, Atlas of Headache Disorders and Resources in the World 2011, World Health Organisation, Geneva, 2011.

[8] A.A. Argyriou, et al., An updated brief overview on post-traumatic headache and a systematic review of the non-pharmacological interventions for its management, Expert. Rev. Neurother. 21 (4) (2021) 475–490.

[9] B. Theeler, et al., Post-traumatic headaches in civilians and military personnel: a comparative, clinical review, Headache 53 (6) (2013) 881–900.

[10] A.M. Andersen, H. Ashina, A. Iljazi, H.M. Al-Khazali, B. Chaudhry, M. Ashina, S. Ashina, H.W. Schytz, Risk factors for the development of post-traumatic headache attributed to traumatic brain injury: a systematic review, Headache. 60 (6) (2020) 1066–1075, https://doi.org/10.1111/head.13812. Epub 2020 Apr 22. PMID: 32320055.

[11] M.W. Waung, G.M. Abrams, Combat-related headache and traumatic brain injury, Curr. Pain Headache Rep. 16 (6) (2012) 533–538, https://doi.org/10.1007/s11916-012-0294-7 (PMID: 22956047).

[12] T.J. Schwedt, et al., Persistent post-traumatic headache vs. migraine: an MRI study demonstrating differences in brain structure, J, Headache Pain 18 (1) (2017) 87.

[13] C.D. Chong, et al., Less cortical thickness in patients with persistent post-traumatic headache compared with healthy controls: an MRI study, Headache 58 (1) (2018) 53–61.

[14] G. Barkhoudarian, D.A. Hovda, C.C. Giza, The molecular pathophysiology of concussive brain injury - an update, Phys. Med. Rehabil. Clin. N. Am. 27 (2) (2016) 373–393.

[15] T. Wijeratne, et al., COVID-19 pathophysiology predicts that ischemic stroke occurrence is an expectation, not an exception—a systematic review, Front. Neurol. 11 (1759) (2021).

[16] T. Wijeratne, S. Crewther, Post-COVID 19 neurological syndrome (PCNS); a novel syndrome with challenges for the global neurology community, J. Neurol. Sci. 419 (2020), 117179.

[17] T. Wijeratne, et al., First Australian case of good recovery of a COVID-19 patient with severe neurological symptoms post prolonged hospitalization, Cureus 12 (9) (2020), e10366.

[18] H. Ashina, A.K. Eigenbrodt, T. Seifert, A.J. Sinclair, A.I. Scher, H.W. Schytz, M. J. Lee, R. De Icco, A.G. Finkel, M. Ashina, Post-traumatic headache attributed to traumatic brain injury: classification, clinical characteristics, and treatment, Lancet Neurol. 20 (6) (2021) 460–469, https://doi.org/10.1016/S1474-4422(21)00094-6 (PMID: 34022171).

[19] S.F. Kothari, et al., Characterization of persistent post-traumatic headache and management strategies in adolescents and young adults following mild traumatic brain injury, Sci. Rep. 12 (1) (2022) 2209.

[20] P. Zeeberg, J. Olesen, R. Jensen, Efficacy of multidisciplinary treatment in a tertiary referral headache Centre, Cephalalgia 25 (12) (2005) 1159–1167.

[21] F. Fraser, Y. Matsuzawa, Y.S.C. Lee, M. Minen, Behavioral treatments for post-traumatic headache, Curr. Pain Headache Rep. 21 (5) (2017) 22, https://doi.org/10.1007/s11916-017-0624-x (PMID: 28283812).

[22] V. De Giuli, et al., Association between migraine and cervical artery dissection: the Italian project on stroke in young adults, JAMA Neurol. 74 (5) (2017) 512–518.

[23] C.Y.H. Ng, et al., Myocardial infarction, stroke and cardiovascular mortality among migraine patients: a systematic review and meta-analysis, J. Neurol. 269 (5) (2022) 2346–2358, https://doi.org/10.1007/s00415-021-10930-x.

[24] A.M. Harriott, F. Karakaya, C. Ayata, Headache after ischemic stroke: a systematic review and meta-analysis, Neurology. 94 (1) (2020) e75–e86, https://doi.org/10.1212/WNL.0000000000008591 (Epub 2019 Nov 6. PMID: 31694924; PMCID: PMC7011689).

[25] Q. Xie, Y. Wu, J. Pei, Q. Gao, Q. Guo, X. Wang, J. Zhong, Y. Su, J. Zhao, L. Zhang, X. Dou, Prevalence and risk factors of ischemic stroke-related headache in China: a systematic review and meta-analysis, BMC Public Health 22 (1) (2022) 1533, https://doi.org/10.1186/s12889-022-13917-z. PMID: 35953857; PMCID: PMC9367127.

[26] S. Tentschert, et al., Headache at stroke onset in 2196 patients with ischemic stroke otransient ischemic attack, Stroke 36 (2) (2005) e1–e3.

[27] F. Assarzadegan, et al., Secondary headaches attributed to arterial hypertension, Iran. J. Neurol. 12 (3) (2013) 106–110.

[28] J. Lai, R.A. Harrison, A. Plecash, T.S. Field, A narrative review of persistent post-stroke headache - a new entry in the international classification of headache disorders, 3rd Edition, Headache 58 (9) (2018) 1442–1453, https://doi.org/10.1111/head.13382 (Epub 2018 Aug 27. PMID: 30152015).

[29] F.A.A. Oliveira, P.A. Sampaio Rocha-Filho, Headaches attributed to ischemic stroke and transient ischemic attack, Headache. 59 (3) (2019) 469–476, https://doi.org/10.1111/head.13478. Epub 2019 Jan 22. PMID: 30667047.

[30] V. Limmroth, Z. Katsarava, H.C. Diener, Acetylsalicylic acid in the treatment of headache, Cephalalgia. 19 (6) (1999) 545–551, https://doi.org/10.1046/j.1468-2982.1999.019006545.x (PMID: 10448540).

[31] A.R. Plecash, A. Chebini, A. Ip, J.J. Lai, A.A. Mattar, J. Randhawa, T.S. Field, Updates in the treatment of post-stroke pain, Curr. Neurol. Neurosci. Rep. 19 (11) (2019) 86, https://doi.org/10.1007/s11910-019-1003-2 (PMID: 31720885).

[32] M. Bahrami, M. Keyhanifard, M. Afzali, Spontaneous intracerebral hemorrhage, initial computed tomography (CT) scan findings, clinical manifestations and possible risk factors, Am. J. Nucl. Med. Mol. Imag. 12 (3) (2022) 106–112 (PMID: 35874296; PMCID: PMC9301088).

[33] Y.Z. Hu, J.W. Wang, B.Y. Luo, Epidemiological and clinical characteristics of 266 cases of intracerebral hemorrhage in Hangzhou, China J. Zhejiang Univ. Sci. B 14 (6) (2013) 496–504, https://doi.org/10.1631/jzus.B1200332. PMID: 23733426; PMCID: PMC3682165.

[34] J.A. Edlow, L.R. Caplan, Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage, N. Engl. J. Med. 342 (1) (2000) 29–36.

[35] B. Mac Grory, et al., Distinguishing characteristics of headache in nontraumatic subarachnoid hemorrhage, Headache 58 (3) (2018) 364–370.

[36] R. Leira, M. Castellanos, J. Alvarez-Sabín, E. Diez-Tejedor, A. Dávalos, J. Castillo, Stroke Project, Cerebrovascular Diseases Group of the Spanish Neurological Society, Headache in cerebral hemorrhage is associated with inflammatory markers and higher residual cavity, Headache. 45 (9) (2005) 1236–1243, https://doi.org/10.1111/j.1526-4610.2005.00248.x (PMID: 16178955).

[37] K. Sugimoto, D.Y. Chung, Spreading depolarizations and subarachnoid hemorrhage, Neurotherapeutics. 17 (2) (2020) 497–510, https://doi.org/10.1007/s13311-020-00850-5. PMID: 32323204; PMCID: PMC7283429.

[38] N.M. Dubosh, M.F. Bellolio, A.A. Rabinstein, J.A. Edlow, Sensitivity of early brain computed tomography to exclude aneurysmal subarachnoid hemorrhage: a systematic review and Meta-analysis, Stroke. 47 (3) (2016) 750–755, https://doi.org/10.1161/STROKEAHA.115.011386. Epub 2016 Jan 21. PMID: 26797666.

[39] R. Yeung, T. Ahmad, R.I. Aviv, L.N. de Tilly, A.J. Fox, S.P. Symons, Comparison of CTA to DSA in determining the etiology of spontaneous ICH, Can. J. Neurol. Sci. 36 (2) (2009) 176–180, https://doi.org/10.1017/s0317167100006533 (PMID: 19378710).

[40] T. Hashiyama, N. Mori, Y. Tsuruyama, Xanthochromia: yellow color is a red flag, Qjm 114 (7) (2021) 521–522.

[41] A. Williams, Xanthochromia in the cerebrospinal fluid, Pract. Neurol. 4 (3) (2004) 174–175.

[42] A. Mahta, M.N. Anderson, A.I. Azher, L.N. Mahmoud, K. Dakay, H. Abdulrazeq, A. Abud, S. Moody, M.E. Reznik, S. Yaghi, B.B. Thompson, L.C. Wendell, S.S. Rao, N.S. Potter, S. Cutting, B. Mac Grory, C. Stretz, C.E. Doberstein, K.L. Furie, Short-and long-term opioid use in survivors of subarachnoid hemorrhage, Clin. Neurol. Neurosurg. 207 (2021), 106770, https://doi.org/10.1016/j.clineuro.2021.106770. Epub 2021 Jun 22. PMID: 34182238.

[43] V. Viswanathan, B. Lucke-Wold, C. Jones, G. Aiello, Y. Li, A. Ayala, W.C. Fox, C. B. Maciel, K.M. Busl, Change in opioid and analgesic use for headaches after aneurysmal subarachnoid hemorrhage over time, Neurochirurgie. 67 (5) (2021) 427–432, https://doi.org/10.1016/j.neuchi.2021.03.006. Epub 2021 Mar 23. PMID: 33771620.

[44] T. Huckhagel, R. Klinger, N.O. Schmidt, J. Regelsberger, M. Westphal, P. Czorlich, The burden of headache following aneurysmal subarachnoid hemorrhage: a prospective single-center cross-sectional analysis, Acta Neurochir. 162 (4) (2020 Apr) 893–903, https://doi.org/10.1007/s00701-020-04235-7. Epub 2020 Feb 4. PMID: 32016589; PMCID: PMC7066282.

[45] L.P. Dhakal, D.O. Hodge, J. Nagel, M. Mayes, A. Richie, L.K. Ng, W.D. Freeman, Safety and tolerability of gabapentin for aneurysmal subarachnoid hemorrhage (sah) headache and meningismus, Neurocrit. Care. 22 (3) (2015) 414–421, https://doi.org/10.1007/s12028-014-0086-5 (Erratum in: Neurocrit Care. 2015 Jun;22(3):422. Nagal, Jay [Corrected to Nagel, Jay]. PMID: 25403765).

[46] S.M. Dorhout Mees, D. Bertens, H.B. van der Worp, G.J. Rinkel, W.M. van den Bergh, Magnesium and headache after aneurysmal subarachnoid haemorrhage, J. Neurol. Neurosurg. Psychiatry 81 (5) (2010) 490–493, https://doi.org/10.1136/jnnp.2009.181404. Epub 2009 Oct 13. PMID: 19828484.

[47] N. Henry, J.F. Fraser, J. Chappell, T. Langley, J.M. Roberts, Cannabidiol's multifactorial mechanisms has therapeutic potential for aneurysmal subarachnoid hemorrhage: a review, Transl. Stroke Res. (2022), https://doi.org/10.1007/s12975-022-01080-x (Epub ahead of print. PMID: 36109476).

[48] C.R. Smith, W.C. Fox, C.P. Robinson, C. Garvan, M.A. Babi, M.A. Pizzi, E. Lobmeyer, A. Bursian, C.B. Maciel, K.M. Busl, Pterygopalatine Fossa Blockade as Novel, Narcotic-Sparing Treatment for Headache in Patients with Spontaneous Subarachnoid Hemorrhage, 2023.

[49] Y. Wang, W. Cheng, Y. Lian, The headache and neck pain in ischemic stroke patients caused by Cervicocerebral artery dissection. A case-control study, J. Stroke Cerebrovasc. Dis. 28 (3) (2019) 557–561, https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.10.034 (Epub 2018 Nov 16. PMID: 30455101).

[50] Y. Wang, W. Cheng, Y. Lian, The headache and neck pain in ischemic stroke patients caused by Cervicocerebral artery dissection. A case-control study, J. Stroke Cerebrovasc. Dis. 28 (3) (2019) 557–561, https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.10.034 (Epub 2018 Nov 16. PMID: 30455101).

[51] Y.E. Ju, T.J. Schwedt, Abrupt-onset severe headaches, Semin. Neurol. 30 (2) (2010 Apr) 192–200, https://doi.org/10.1055/s-0030-1249229. Epub 2010 Mar 29. PMID: 20352589; PMCID: PMC3558726.

[52] P.L. Silbert, B. Mokri, W.I. Schievink, Headache and neck pain in spontaneous internal carotid and vertebral artery dissections, Neurology 45 (8) (1995) 1517–1522.

[53] V. Biousse, et al., Head pain in non-traumatic carotid artery dissection: a series of 65 patients, Cephalalgia 14 (1) (1994) 33–36.

[54] N. Morelli, et al., Vertebral artery dissection onset mimics migraine with aura in a graphic designer, Headache 48 (4) (2008) 621–624.

[55] Y. Wang, W. Cheng, Y. Lian, J. Zhang, Y. Zheng, Y. Hu, Y. Chen, S. Wu, Z. Huang, Y. Shi, Characteristics and relative factors of headache caused by cervicocerebral artery dissection, J. Neurol. 266 (2) (2019 Feb) 298–305, https://doi.org/10.1007/s00415-018-9111-5. Epub 2018 Dec 12. PMID: 30542949.

[56] V. De Giuli, et al., Association between migraine and cervical artery dissection: the Italian project on stroke in young adults, JAMA Neurol. 74 (5) (2017) 512–518.

[57] S. Vidale, Headache in cervicocerebral artery dissection, Neurol. Sci. 41 (Suppl. 2) (2020 Dec) 395–399, https://doi.org/10.1007/s10072-020-04651-8 (PMID: 32852688).

[58] S. Debette, M. Mazighi, P. Bijlenga, A. Pezzini, M. Koga, A. Bersano, J. Kõrv, J. Haemmerli, I. Canavero, P. Tekiela, K. Miwa, D. Seiffge, S. Schilling, A. Lal, M. Arnold, H.S. Markus, S.T. Engelter, J.J. Majersik, ESO guideline for the management of extracranial and intracranial artery dissection, Eur. Stroke J. 6 (3) (2021 Sep), https://doi.org/10.1177/23969873211046475. XXXIX-LXXXVIII. Epub 2021 Oct 13. PMID: 34746432; PMCID: PMC8564160.

[59] H.W. Schytz, M. Ashina, M. Magyari, V.A. Larsen, J. Olesen, H.K. Iversen, Acute headache and persistent headache attributed to cervical artery dissection: Field testing of ICHD-III beta, Cephalalgia 34 (9) (2014) 712–716, https://doi.org/10.1177/0333102414520767. Epub 2014 Feb 5. PMID: 24500814.

[60] A. Tiede, et al., Prothrombotic immune thrombocytopenia after COVID-19 vaccine, Blood 138 (4) (2021) 350–353, https://doi.org/10.1182/blood.2021011958.

[61] M. Sharifian-Dorche, et al., Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review, J. Neurol. Sci. 428 (2021), 117607.

[62] F.M. Siddiqui, A.K. Kamal, Incidence and epidemiology of cerebral venous thrombosis, Pak. Med. Assoc. 56 (11) (2006) 485–487.

[63] S. Devasagayam, et al., Cerebral venous sinus thrombosis incidence is higher than previously thought, Stroke 47 (9) (2016) 2180–2182.

[64] J.M. Coutinho, et al., The incidence of cerebral venous thrombosis, Stroke 43 (12) (2012) 3375–3377.

[65] R. Cumurciuc, et al., Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases, J. Neurol. Neurosurg. Psychiatry 76 (8) (2005) 1084–1087.

[66] D. García-Azorín, et al., Delayed headache after COVID-19 vaccination: a red flag for vaccine induced cerebral venous thrombosis, J, Headache Pain 22 (1) (2021) 108.

[67] B. Bikdeli, et al., Venous thrombosis within 30 days after vaccination against SARS-CoV-2 in a multinational venous thromboembolism registry, Viruses 14 (2) (2022).

[68] S.J. Nahas, Headache and temporal arteritis: when to suspect and how to manage, Curr. Pain Headache Rep. 16 (4) (2012) 371–378, https://doi.org/10.1007/s11916-012-0265-z (PMID: 22552735).

[69] E. Dunstan, S.L. Lester, M. Rischmueller, T. Dodd, R. Black, M. Ahern, L. G. Cleland, P. Roberts-Thomson, C.L. Hill, Epidemiology of biopsy-proven giant cell arteritis in South Australia, Intern. Med. J. 44 (1) (2014) 32–39, https://doi.org/10.1111/imj.12293 (PMID: 24118799).

[70] S.P. Mollan, K. Paemeleire, J. Versijpt, R. Luqmani, A.J. Sinclair, European headache federation recommendations for neurologists managing giant cell arteritis, J, Headache Pain 21 (1) (2020) 28, https://doi.org/10.1186/s10194-020-01093-7. PMID: 32183689; PMCID: PMC7079499.

[71] J. Loricera, R. Blanco, J.L. Hernández, S. Castañeda, A. Mera, E. Pérez-Pampín, E. Peiró, A. Humbría, J. Calvo-Alén, E. Aurrecoechea, J. Narváez, A. Sánchez-Andrade, P. Vela, E. Díez, C. Mata, P. Lluch, C. Moll, Í. Hernández, V. Calvo-Río, F. Ortiz-Sanjuán, C. González-Vela, T. Pina, M.Á. González-Gay, Tocilizumab in giant cell arteritis: multicenter open-label study of 22 patients, Semin. Arthritis Rheum. 44 (6) (2015) 717–723, https://doi.org/10.1016/j.semarthrit.2014.12.005. Epub 2014 Dec 27. PMID: 25697557.

[72] M. Calderón-Goercke, J. Loricera, V. Aldasoro, S. Castañeda, I. Villa, A. Humbría, C. Moriano, S. Romero-Yuste, J. Narváez, C. Gómez-Arango, E. Pérez-Pampín, R. Melero, E. Becerra-Fernández, M. Revenga, N. Álvarez-Rivas, C. Galisteo, F. Sivera, A. Olivé-Marqués, M. Álvarez Del Buergo, L. Marena-Rojas, C. Fernández-López, F. Navarro, E. Raya, E. Galindez-Agirregoikoa, B. Arca, R. Solans-Laqué, A. Conesa, C. Hidalgo, C. Vázquez, J.A. Román-Ivorra, P. Lluch, S. Manrique-Arija, P. Vela, E. De Miguel, C. Torres-Martín, J.C. Nieto, C. Ordas-Calvo, E. Salgado-Pérez, C. Luna-Gomez, F.J. Toyos-Sáenz de Miera, N. Fernández-Llanio, A. García, C. Larena, N. Palmou-Fontana, V. Calvo-Río, D. Prieto-Peña, C. González-Vela, A. Corrales, M. Varela-García, E. Aurrecoechea, R. Dos Santos, Á. García-Manzanares, N. Ortego, S. Fernández, F. Ortiz-Sanjuán, M. Corteguera, J.L. Hernández, M.Á. González-Gay, R. Blanco, Tocilizumab in giant cell arteritis. Observational, open-label multicenter study of 134 patients in clinical practice, Semin. Arthritis Rheum. 49 (1) (2019) 126–135, https://doi.org/10.1016/j.semarthrit.2019.01.003 (Epub 2019 Jan 5. PMID: 30655091).

[73] S.-P. Chen, J.-L. Fuh, S.-J. Wang, Reversible cerebral vasoconstriction syndrome: an under-recognized clinical emergency, Ther. Adv. Neurol. Disord. 3 (3) (2010) 161–171.

[74] S.P. Chen, S.J. Wang, Pathophysiology of reversible cerebral vasoconstriction syndrome, J. Biomed. Sci. 29 (1) (2022) 72, https://doi.org/10.1186/s12929-022-00857-4. PMID: 36127720; PMCID: PMC9489486.

[75] T.J. Song, K.H. Lee, H. Li, J.Y. Kim, K. Chang, S.H. Kim, K.H. Han, B.Y. Kim, A. Kronbichler, A. Ducros, A. Koyanagi, L. Jacob, M.S. Kim, D.K. Yon, S.W. Lee, J. M. Yang, S.H. Hong, R.A. Ghayda, J.W. Kang, J.I. Shin, L. Smith, Reversible cerebral vasoconstriction syndrome: a comprehensive systematic review, Eur. Rev. Med. Pharmacol. Sci. 25 (9) (2021) 3519–3529, https://doi.org/10.26355/eurrev_202105_25834 (PMID: 34002826).

[76] C. Cappelen-Smith, Z. Calic, D. Cordato, Reversible cerebral vasoconstriction syndrome: recognition and treatment, Curr. Treat. Options Neurol. 19 (6) (2017) 21, https://doi.org/10.1007/s11940-017-0460-7 (PMID: 28456915).

[77] Y.H. Ling, Y.F. Wang, J.F. Lirng, J.L. Fuh, S.J. Wang, S.P. Chen, Post-reversible cerebral vasoconstriction syndrome headache, J, Headache Pain 22 (1) (2021) 14, https://doi.org/10.1186/s10194-021-01223-9. PMID: 33765906; PMCID: PMC7992969.

[78] S. John, A.B. Singhal, L. Calabrese, K. Uchino, T. Hammad, S. Tepper, M. Stillman, B. Mills, T. Thankachan, R.A. Hajj-Ali, Long-term outcomes after reversible cerebral vasoconstriction syndrome, Cephalalgia 36 (4) (2016) 387–394, https://doi.org/10.1177/0333102415591507. Epub 2015 Jun 18. PMID: 26088331.

[79] D.E. Chou, Secondary headache syndromes, CONTINUUM: Lifelong Learn. Neurol. 24 (4) (2018) 1179–1191.

[80] B.B. Bruce, Nonmydriatic ocular fundus photography in the emergency department: how it can benefit neurologists, Semin. Neurol. 35 (5) (2015) 491–495.

[81] C. Fernández-de-Las-Peñas, M. Navarro-Santana, V. Gómez-Mayordomo, M. L. Cuadrado, D. García-Azorín, L. Arendt-Nielsen, G. Plaza-Manzano, Headache as an acute and post-COVID-19 symptom in COVID-19 survivors: A meta-analysis of the current literature, Eur. J. Neurol. 28 (11) (2021 Nov) 3820–3825, https://doi.org/10.1111/ene.15040. Epub 2021 Aug 8. PMID: 34327787; PMCID: PMC8444899.

[82] E. Caronna, et al., Headache: a striking prodromal and persistent symptom, predictive of COVID-19 clinical evolution, Cephalalgia 40 (13) (2020) 1410–1421.

[83] E. Caronna, et al., Toward a better understanding of persistent headache after mild COVID 19: three migraine-like yet distinct scenarios, Headache: J. Head Face Pain 61 (8) (2021) 1277–1280.

[84] T. Wijeratne, et al., Case report: posterior reversible leukoencephalopathy syndrome (PRES) as a biologically predictable neurological Association in Severe COVID-19. First reported case from Australia and Review of Internationally Published Cases, Front. Neurol. 11 (2020), 600544.

[85] T. Wijeratne, et al., COVID-19 pathophysiology predicts that ischemic stroke occurrence is an expectation, not an exception-a systematic review, Front. Neurol. 11 (2020), 607221.

[86] T. Wijeratne, C. Wijeratne, Clinical utility of serial systemic immune inflammation indices (SSIIi) in the context of post covid-19 neurological syndrome (PCNS), J. Neurol. Sci. 423 (2021), 117356.

[87] T. Wijeratne, S. Crewther, COVID-19 and long-term neurological problems: challenges ahead with post-COVID-19 neurological syndrome, Aust. J. Gen. Pract. (2021) 50.

[88] R.E. Shapiro, et al., The impact of headache disorders on COVID-19 survival: a world population-based analysis. medRxiv, 2021, 2021.03.10.21253280.

[89] A. Gonzalez-Martinez, Á.L. Guerrero-Peral, S. Arias-Rivas, L. Silva, Á. Sierra, A. B. Gago-Veiga, D. García-Azorín, Amitriptyline for post-COVID headache: effectiveness, tolerability, and response predictors, J. Neurol. 269 (11) (2022 Nov) 5702–5709, https://doi.org/10.1007/s00415-022-11225-5. Epub 2022 Jul 12. PMID: 35829760; PMCID: PMC9553757.

[90] A.V. Krymchantowski, R.P. Silva-Néto, C. Jevoux, A.G. Krymchantowski, Indomethacin for refractory COVID or post-COVID headache: a retrospective study, Acta Neurol. Belg. 122 (2) (2022 Apr) 465–469, https://doi.org/10.1007/s13760-021-01790-3. Epub 2021 Sep 21. PMID: 34546559; PMCID: PMC8453033.

[91] D.I. Friedman, Headaches in idiopathic intracranial hypertension, J. Neuroophthalmol. 39 (1) (2019).

[92] K.B. Digre, et al., A comparison of idiopathic intracranial hypertension with and without papilledema, Headache 49 (2) (2009) 185–193.

[93] A.F. Barkatullah, L. Leishangthem, H.E. Moss, MRI findings as markers of idiopathic intracranial hypertension, Curr. Opin. Neurol. 34 (1) (2021) 75–83.

[94] J. Best, et al., The incidence of blindness due to idiopathic intracranial hypertension in the UK, Open Ophthalmol. J. 7 (2013) 26–29.

[95] NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee, M. Wall, M. McDermott MP, K.D. Kieburtz, J.J. Corbett, S.E. Feldon, D.I. Friedman, D.M. Katz, J.L. Keltner, E.B. Schron, M.J. Kupersmith, Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial, JAMA 311 (16) (2014 Apr 23–30) 1641–1651, https://doi.org/10.1001/jama.2014.3312. PMID: 24756514; PMCID: PMC4362615.

[96] M.W. ten Hove, D.I. Friedman, A.D. Patel, I. Irrcher, M. Wall, M.P. McDermott, NORDIC idiopathic intracranial hypertension study group. Safety and tolerability of acetazolamide in the idiopathic intracranial hypertension treatment trial, J. Neuroophthalmol. 36 (1) (2016) 13–19, https://doi.org/10.1097/WNO.0000000000000322 (PMID: 26587993).

[97] A. Kalyvas, E. Neromyliotis, C. Koutsarnakis, S. Komaitis, E. Drosos, G. P. Skandalakis, M. Pantazi, Y.P. Gobin, G. Stranjalis, A. Patsalides, A systematic review of surgical treatments of idiopathic intracranial hypertension (IIH),

Neurosurg. Rev. 44 (2) (2021 Apr) 773–792, https://doi.org/10.1007/s10143-020-01288-1. Epub 2020 Apr 25. PMID: 32335853.

[98] S.P. Mollan, J.L. Mitchell, A. Yiangou, R.S. Ottridge, Z. Alimajstorovic, D. M. Cartwright, S.J. Hickman, K.A. Markey, R. Singhal, A.A. Tahrani, E. Frew, K. Brock, A.J. Sinclair, Association of amount of weight lost after bariatric surgery with intracranial pressure in women with idiopathic intracranial hypertension, Neurology 99 (11) (2022 Sep 13) e1090–e1099, https://doi.org/10.1212/WNL.0000000000200839. Epub 2022 Jul 5. PMID: 35790425; PMCID: PMC9536743.

[99] L.N. Johnson, G.B. Krohel, R.W. Madsen, G.A. March Jr., The role of weight loss and acetazolamide in the treatment of idiopathic intracranial hypertension (pseudotumor cerebri), Ophthalmology. 105 (12) (1998) 2313–2317, https://doi.org/10.1016/S0161-6420(98)91234-9 (PMID: 9855165).

[100] M.W. Green, Secondary headaches, Continuum (Minneap Minn) 18 (4) (2012) 783–795.

[101] R.A. Purdy, S. Kirby, Headaches and brain tumors, Neurol. Clin. 22 (1) (2004) 39–53.

[102] C.J. Schankin, et al., Characteristics of brain tumour-associated headache, Cephalalgia 27 (8) (2007) 904–911.

[103] T.P. Do, et al., Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list, Neurology 92 (3) (2019) 134–144.

[104] H. Pohl, et al., Green flags and headache: a concept study using the Delphi method, Headache 61 (2) (2021) 300–309.

[105] C. Fragoulis, K. Dimitriadis, E. Siafi, P. Iliakis, A. Kasiakogias, T. Kalos, I. Leontsinis, I. Andrikou, D. Konstantinidis, P. Nihoyannopoulos, G. Tsivgoulis, C. Thomopoulos, D. Tousoulis, M.L. Muiesan, K.P. Tsioufis, Profile and management of hypertensive urgencies and emergencies in the emergency cardiology department of a tertiary hospital: a 12-month registry, Eur. J. Prev. Cardiol. 29 (1) (2022) 194–201, https://doi.org/10.1093/eurjpc/zwab159 (PMID: 34718521).