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REVIEW

Primary Headaches and Their Most Important Imagistic Features in Clinical Practice

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Abstract: *Background. Primary headaches are comprised of three big categories: migraines (with or without aura), the third most common and the 6th most disabling disease worldwide, tension-headaches, and trigeminal autonomic cephalalgias, each with different, complex, and not completely understood pathophysiological, clinical, and neuroimagistic characteristics. Structures like the brain stem, hippocampus, or hypothalamus have been depicted as being the main triggers of these types of headaches, which have a significant impact on the quality of life. Methods. We performed a broad literature review on primary headaches from January 2016 to June 2023, analyzing the latest scientific updates and emphasizing the pathophysiological and neuroimagistic characteristics. Results. We provide a concise review of the main neuroimaging studies that help in differential diagnosis between several types of primary headaches. Conclusions. It is difficult to approach the pathophysiology of these three primary headache categories. Keeping in mind that neuroimagistic methods are rapidly developing (especially in the MRI sphere), the most important endpoint of future studies will be to establish a reliable distinction system for all these types of cephalalgias, thus updating the protocols and guidelines. Currently, imaging studies are indicated only in certain circumstances.*

Keywords: *migraine; tension-type headache; pathophysiology; trigeminal autonomic cephalalgias; imaging studies; cluster headache; SUNCT; MRI; fMRI; SUNA*

INTRODUCTION

Headache is a recurrent and upsetting symptom in the neurological sphere, also being one of the most frequent ones, patients often present to the physician for it. Most of the studies suggested that more than 90% of the population has suffered from headaches at least once in their lives [1]. The diagnostic standard for headaches of any cause has been offered over the past two decades by ICHD since 2004 and today reaches the updated ICHD-3 [2]. This accounts for approximately 3% of emergency department admissions, but some authors have identified percentages as high as 8% [3,4]. It is important to emphasize that the repeated presentation of a patient to ED for the same symptoms significantly increases the costs associated with medical care. These recurrent presentations occur in approximately 10% of headache patients [3]. When a severe headache begins, patients present to the ED frightened by the thought of a serious condition. However, one study showed that of 3026 imaging studies of patients presenting to the emergency department, pathology was objectified by imaging in less than 3% of them [5].

Given the high prevalence of this type of neurologic symptomatology, clinicians must carefully consider the indication for imaging studies because they are expensive and usually do not provide the desired information to guide subsequent treatment. In addition, headaches can lead to absenteeism from school or work, increasing the indirect costs associated with pathology. In a recent study, workers with

headaches were observed to have low productivity or, more rarely, to be absent from work for up to 7.5 days/month [6].

Headaches of a primary cause are set apart by the presence of headache without any underlying pathology. These are far more common than secondary headaches. For example, the prevalence of TTH is as high as 70% during a person's lifetime [7]. In the past, categorization of these pathologies has been difficult because symptoms vary from person to person, but also in the same individual over time [8]. Standardization of primary cause headaches has been achieved by the ICHD-3 classification, which divides primary headaches into migraine, both with aura or without it, tension-type headache (TTH), and cephalalgias which belong to the trigeminal autonomic sphere [2,9]. The mechanism of action of these pathologies is not yet known, but research is ongoing. In this paper, we propose to present the situations in which imaging studies are indicated.

MATERIALS AND METHODS

We reviewed the literature related to primary cause headaches by searching the Google Scholar and Pubmed English databases between 2000 and 2023 with keywords such as "headache", "cephalalgia", "imaging", "MRI", "primary", "migraine", "tension-type", "cluster", "trigeminal", "autonomic", or any logical combination of these terms. In the first stage, the retrieved studies were filtered by a title check to exclude duplicates and assess their relevance. After this first step, the outstanding studies were distributed evenly and randomly to the authors of this study, in the first phase by reviewing the abstract to determine relevance and later by studying the entire text. We have extracted relevant, basic information from these articles, but also important news that may change the paradigm of primary headaches.

RESULTS

Migraine

Migraine is a disabling disease, being the most prevalent type of primary headache, with 12-15% of the general population suffering from it [10,11]. Prevalence is different between males and females, and also it varies by the age group: interestingly, in children, puberty, this pathology is more common in boys. In young adults, it differs, being more usual in females, probably due to the hormonal changes they undergo [12]. Throughout life, the prevalence is 12-17% for women and 4-6% for men [13]. It manifests as moderate to severe headache episodes, usually unilateral, with mild to moderate cognitive deficit and cortical hyper-excitability manifestations such as phonophobia or photophobia, nausea, and vomiting. Two phases of migraine are described: the ictal phase, which occurs during a migraine attack, and the interictal phase, which occurs between two migraine attacks.

Up to 30% of patients with headaches accuse migraine attacks, and their frequency also influences cognitive deficits [14,15]. The ratio of men to women is 1:3. According to the ICHD-3, the main types of migraine are those without aura, those with aura, chronic-type migraine, complications of migraine, probable migraine, and episodic syndromes associated with migraine [16]. Migraine appears as a result of electrical abnormalities occurring in the brainstem, and vascular abnormalities in the cerebrum, and when we talk about migraine with aura, the result of cortical spreading depolarization [17].

The aura manifests most often as a visual aura (80-90% of cases), characterized by flashes of light in the simplest situations to scotomas or complex hallucinations [18].

Four phases of migraine have been described: the prodromal phase, in which the first warning symptoms appear (depression, fatigue, hunger, food cravings), which are most likely associated with dopaminergic activation and precede the headache by 2-48 hours [19]; the aura (which occurs in one-third of migraine patients) represents reversible neurological symptomatology that usually lasts about one hour and it usually manifests as sensory, verbal or motor symptoms. However, the visual ones are the most common. These changes come before the start of the cephalalgia [16,20]; headache is commonly on only one side of the head, having a progressively aggravating pattern at the beginning, being linked with autonomic symptoms like photophobia or phonophobia, or with symptoms like nausea, sickness-like condition or vomiting [20]; the postdromal phase, which is associated with a localized headache that is aggravated by movement, fatigue, or dizziness.

Migraine can be clinically assessed by structural MR imaging. For example, we now know that both aura and headache are mainly associated with vasoconstrictive changes in cerebral arteries and veins. Hypersensitivity in the region innervated primarily by cranial nerve V, but also in extracranial regions, causes allodynia when a normally painless stimulus becomes painful, such as wearing glasses or a light touch to the face.

MRI examinations are not routinely recommended in migraine patients without aura when preventive treatment is not necessary, and some authors recommend imaging studies when three lines of preventive treatment fail [21]. Another recent study emphasizes that imaging examinations are not needed in migraine patients without red flags [22]. In migraine patients with aura, no examinations are recommended in typical cases, and in the remaining ones, MRI or MRA of the brain is recommended to rule out vascular anomalies [21]. Cerebral MRI is also recommended for vascular comorbidities

or headache onset after 50 years of age. MRI is not recommended for chronic migraine, especially if the history shows progressive worsening of headache with typical symptoms [21]. In patients with persistent aura, hospitalization, and diffusion-type imaging are mandatory to rule out cerebral ischemia.

Migraineurs are sensitive to olfactory stimuli. Up to 40% of them complain of headache exacerbation when exposed to strong, irritating, or sensitizing odors, even in the interictal phase, with studies demonstrating abnormal activation of the amygdala and insular cortex in the case of certain crises caused by odor stimuli [23,24]. On the other hand, other studies determining thermal stimulation showed unequal activation of certain areas between migraine patients and the control population, such as in the lentiform nucleus, parahippocampal gyrus, subthalamic nucleus, prefrontal cortex, or temporal lobe [25,26]. 40% of migraineurs report that their migraines are activated by strong light stimuli in the interictal phase, and 90% of them report that they suffer from photophobia in the ictal phase. Some studies demonstrate visual-nociceptive integration at the brainstem level [27].

Usually, imaging studies are not required in patients with a normal clinical examination who present with typical migraine symptoms according to the ICHD-3 definition [20,28]. To distinguish between patients who do not require additional imaging studies and patients with warning signs who do require imaging studies, the SNOOP algorithm is used successfully, as follows: S for systemic disease (e.g., infections, HIV), N for neurologic assessment (confusion, seizures, focal neurologic signs), O for onset (sudden onset, first episode after age of 50), O from other associated features (medications, toxins, trauma, association of headache with Valsalva maneuver), and P from previous episodes (or headache progression). The American College of Emergency Physicians 2019 (ACEP 2019) and American Academy of Neurology (AAN) guidelines recommend imaging studies only for warning signs that are not indicative of a common headache [29,30]. The American College of Radiology (ACR) emphasizes that clinical physicians should not perform repeated imaging studies when the headache is not complicated [31].

However, in migraine, deep white matter lesions (Figure 1A, T2, and FLAIR hyperintensities) are seen in 20-30% of MRI examinations, regardless of age or periventricular white matter lesions. Their exact pathophysiology is not known, but two theories have been mainly discussed: the theory of ischemia due to circulatory disturbances in the small perforating vessels together with inflammatory changes with consequent hypoperfusion, evidenced in MRI imaging by the appearance of small focal ischemic spots, mainly at the level of the frontal lobe (Figure 1B), but also in the corpus callosum, and the theory of neuroinflammation [32,33]. The latter emerged after the CAMERA study, which highlighted in females that deep WML takes place without a connection with ischemic lesions [32]. It is noteworthy that numerous subsequent studies have highlighted the fact that in migraine, the deep supratentorial white matter lesions are important but these do not correlate with the development of the disease, whereas the infratentorial lesions do not affect migraine attacks [30]. In addition, migraine patients appear to have a higher risk for cerebrovascular disease, but also doubling the risk of ischemic stroke [34,35].

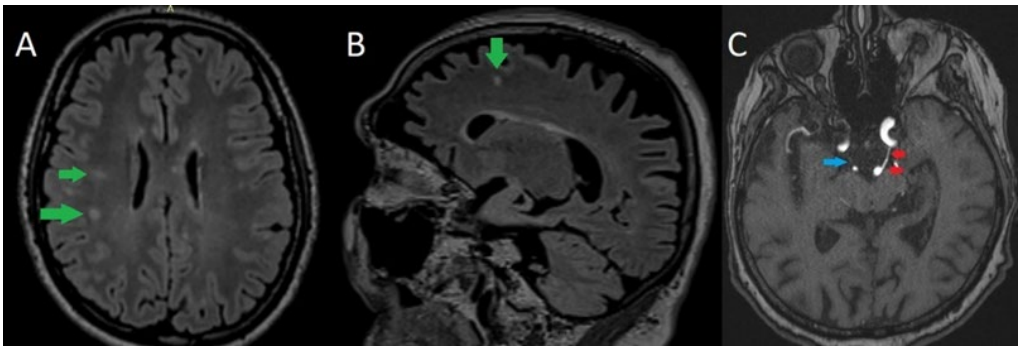

Figure 1: A: T2-weighted and FLAIR hyperintense lesions, in the centrum semiovale on the right side and deep white matter in a patient accusing repeated migraine attacks (green arrows). **B**: T2-weighted and FLAIR hyperintense lesion in the superior frontal gyrus (green arrow), the usual location for demyelinating lesions in migraine patients. **C**: asymmetry of the circle of Willis, showing a filiform right posterior communicating artery (blue arrow) compared to the contralateral one that shows significant blood flow (red arrows).

In migraine with aura, there may be transient restricted diffusion in the affected areas during the aura, in many studies taking place, especially in the corpus callosum [36].

Following some recent studies using MRI angiography (MRA), a new theory arises, advocating that there are asymmetries pointed out in the circle of Willis in a bigger population of

migraine patients, particularly with aura (Figure 1C) [37,38].

In summary, in migraine patients without aura, imaging studies are not recommended for usual symptomatology that does not require treatment. For treatment-emergent migraine episodes, some authors recommend cerebral MRI or MRA when three lines of therapy have failed. In migraine patients with aura, an MRI of the brain is almost always recommended, or MRA if posterior fossa symptoms are present. In chronic migraine patients, additional imaging studies are not recommended as long as the symptomatology is not progressing, as long as the symptoms do not progress, but fundoscopy should be an integral part of the clinical examination in all patients with headaches [2,21].

Tension-type headache (TTH)

Tension-type headache represents a mild to moderate cephalalgia with a pressure-like character and usually occurs bilaterally, sometimes with anterior or posterior topography and sometimes it is longitudinal, lasting from minutes to days or even weeks. In contrast to migraine, it does not go along with autonomic manifestations or nausea and vomiting, and the presence of the above features precludes the diagnosis of tension-type headache. ICHD-3 classified TTH into four broad categories: infrequent epi-sodic TTH lasting < 1 day/month, frequent episodic TTH lasting 1-14 days/month throughout> 3 months, chronic TTH with a duration of > 14 days over > 3 months, and probable TTH [16]. The best diagnostic tool for tension-type headaches is the creation of a diary in which the patient records the frequency of painful episodes, their intensity, and their characteristics [39]. Considering the lower pain intensity, a lower proportion of patients with TTH consult a physician compared with migraine patients. One study has shown that the number of physician visits for TTH is 3 times lower than for migraine patients [40].

TTH is the second leading cause of chronic disease worldwide and is a socioeconomic burden, with 820 days missed from work or school per 1000 patients [41,42]. The most common differential diagnosis is migraine, as migraine patients often overlap with tension-type headaches.

The reported prevalence is 70% of the population, although 59% of patients report only episodic TTH [7,43]. Prevalence peaks in the 30-to-39-year-old age group and then decreases slightly [44]. Several studies have observed that sleep deprivation in combination with a disorganized lifestyle contributes to the occurrence of TTH [42,45].

Central factors are particularly important in tension-type headaches. While the pain threshold is normal in patients with eTTH, this threshold is somehow lower in tension-type headache patients with a chronic form [46,47]. Negative states, like depression or anxiety, and also chronic stress in TTH patients can increase the risk of headaches by lowering the nociceptive threshold [48,49].

In a study from Taiwan, it was suggested that the risk factors for TTH were more than 7 days of headache and female gender [50].

To date, although we use more and more advanced imaging techniques, the TTH pathophysiology is still not completely elucidated. Myofascial factors are incriminated to have a crucial role in episodic TTH along with pericranial muscle contractures, whereas sensitization of nociceptive sensory pathways by repetitive headaches leads to chronic TTH [51-53].

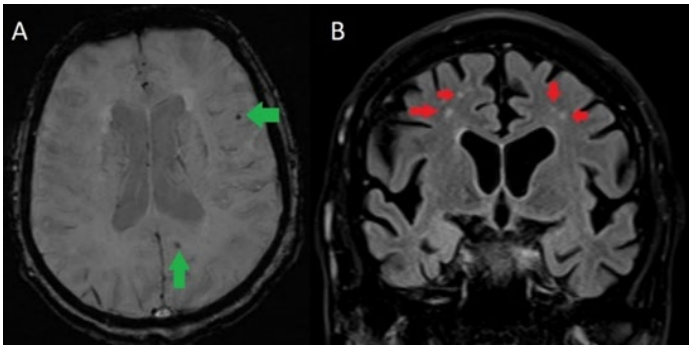

Figure 2: A. Magnetic susceptibility sequence in the axial plane. Changes in the magnetic susceptibility sequence with a suggestive appearance for microhemorrhages in the deep white matter and cortico-subcortical junction. **B**. Lesions in T2 and FLAIR hypersig-nal at the level of the bilateral corona radiata, in TTH patients without being specifically associated with some deep localizations such as in migraineurs.

As we already found out in the migraines chapter, imaging studies should not be carried out with typical-ly-described symptoms. More specifically, in patients with infrequent tension-type headaches, imaging is not recommended. In patients with frequent or chronic TTH, similar to migraine, some authors recommend an imaging examination when three lines of preventive treatment have failed [21]. Patients with chronic tension-type headaches should undergo one

single imaging examination, either MR or CT, at the initial admission in the ED to exclude other differential diagnosis pathologies. The same applies to the TTH patients. The latter ones will generally have small foci of hemorrhage defined as hypodensities on susceptibility-weighted sequences deep in the white matter (Figure 2A) and deep WML, having the same physiopathological substrate as the migraineurs, increasing the risk of dementia or stroke later in life [54-56]. TTH and migraine patients generally have a similar number and amplitude of deep WML, but contrary to migraineurs, the TTH-associated WML does not show a preferred topography (Figure 2B). However, studies have shown that imaging examinations are not recommended because they do not improve the diagnosis and treatment, but they can cause and increase anxiety related to health status [57,58]. Acetaminophen and aspirin are thought to be efficient in cutting down acute symptomatology of hypertensive headaches. Opioids or triptans should be avoided. Ibuprofen and ketoprofen are the most effective NSAIDs for pain relief. Most patients benefit from lifestyle changes that promote a healthy lifestyle by quitting smoking and eating foods rich in antioxidants, and nonpharmacologic and behavioral therapies such as relaxation, biofeedback, or acupuncture can be helpful in most cases.

Trigeminal autonomic cephalalgias (TAC)

Cluster headache

Cluster headache is not a common headache, but is the most prevalent one in the group of TAC cephalalgias, having a prevalence of about 0,1% in the general population, affecting males and females differently, in a 6:1 manner. Many of the patients affected are older than 20 years of age [14,59]. Its most characteristics are severe pain with spontaneous remission, recurrent (usually circadian), unilateral, lasting 15-180 minutes, associated with autonomic ipsilateral cranial clinical signs such as lacrimation, conjunctival injection, or nasal congestion, the latter often leading to the misdiagnosis of sinus pain, with a completely different treatment from cluster headache [16,60]. In rare cases, cluster headaches may occur without autonomic symptoms [61].

80-90% of patients have episodic cluster headaches that occur apart from circadian development related to season (especially spring and autumn), number of daily light hours, and sleep stage, being more frequent during REM sleep [62]. Moreover, the relationship between sleep and cluster headache is very close. Many studies have shown that approximately 80% of patients who have manifestations of cluster headache will present cephalalgia attacks in the middle of the night, disturbing their sleep, but only 30% of them will show cephalalgias when they are napping during the day [63]. However, most of the patients complain of disturbed sleep quality, whether it occurs during or outside the headache period, and as a compensatory measure, some patients forget nightly sleep to avoid developing cephalalgic episodes [64]. An association between cluster headaches and sleep apnea has also been noted [63]. 10-20% of patients suffer from chronic cluster headaches, which have a very short period of remission, generally of the order of days.

The physiopathologic mechanism of this pain is not fully known. Both neurovascular causes and central mechanisms are suspected [65,66]. Given the predominant development with circadian recurrences, it has been suggested that the hypothalamus is of central importance for the development of pain, and also the trigeminovascular system and the parasympathetic systems being incriminated for starting and maintaining the symptomatology, those being involved in the autonomic trigeminal reflex [67]. Even though the V1 division of the 5th cranial nerve plays an important role in the development of algic symptoms, the autonomic ones are developed by the parasympathetic fibers of the facial nerve [68]. Since the 1990s, but also in more recent research, a genetic substrate is suspected, as there is a familial predisposition [69-71].

An association between cluster headaches and smoking has been confirmed. A recent study showed that 88% of the participating patients were active smokers or had smoked in the past [72]. When partial Horner syndrome occurs, cerebral MRI scans and targeted imaging studies at the level of the lung apex must be performed to identify lesions of the recurrent laryngeal nerve. Polysomnography may also be performed in cluster headache patients, as it is often associated with restless legs syndrome and helps to identify and treat this pathology [21].

In all types of TAC, cerebral MRI with high-resolution sequences of the cranial nerves is required at baseline to evaluate the parasellar structures. Similar to migraine, MRA is recommended if the first three lines of preventive treatment fail [21]. Changes in some brain structures were observed on imaging, particularly at the level of the thalamus, nucleus cinguli, prefrontal, parietal, and insular cortex [73,74]. Some older studies showed structural changes in the hypothalamus by MRI scans when headache was active, whereas other studies did not find these changes [75-77]. Some authors suggested that a decrease in grey matter volume in the visual cortex can occur, but it is non-specific [78,79].

Treatment of cluster headaches is divided into acute episode treatment and prophylactic treatment [80]. It includes drug treatment as well as patient education and lifestyle modification. As lifestyle changes, we can mention the

avoidance of alcohol consumption, daytime sleep, or excessive physical activity. Treatment of the acute episode is initially by administering 100% oxygen by mask, up to 10 L/minute, for 15-20 minutes, which can relieve the cephalalgic episode in up to 15 minutes. Other therapeutic options include sumatriptan, a serotonin receptor agonist known to be the most effective therapeutic option and effective within 15 minutes when administered intravenously; dihydroergotamine, effective within 10 minutes when administered intravenously; zolmitriptan, effective within 30 minutes when administered orally; and local anesthetics [81]. Prophylactic treatment consists mainly of prednisone, dexamethasone, and ergotamine derivatives.

SUNCT and SUNA

SUNCT and SUNA are the other two types of TAC. Together, they are referred to as SUNHA [82]. The etiology and pathophysiology are not fully known. The association between these pathologies and posterior fossa lesions is well known, and recently the association between pituitary adenomas and these headaches has been discussed [83]. The pain generally occurs in the trigeminal area, more specifically in the V1 division and there is a high difficulty in differentiating between SUNHA and trigeminal neuralgia. These headaches have a sharp or burning character, last for a minimum of 5 seconds to a maximum of 10 minutes, and have a "sawtooth" development. A minimum of 20 pain attacks correlating with autonomic symptoms is required for clinical diagnosis, criteria defined by ICHD-3 [16,84]. The incidence is 0.1 per 10,000 population and the prevalence is 0.6 per 10,000 population [85].

The physiopathologic mechanism incriminated is represented by the activation of the trigeminal reflex and, similar to cluster headache, by triggering the hypothalamus [86]. Some recent studies have shown that trigeminal neurovascular conflict is important in the etiology of SUNCT and probably SUNA, with neuroimaging highlighting the similarity of changes in both pathologies, even assuming that the distinction between these two entities can be discarded [87,88]. High-resolution MRI imaging revealed neurovascular conflicts in more than 85% of patients with SUNCT or SUNA [87]. In addition, a recent study demonstrated ischemic changes in the left ventricular septal defect in approximately 15% of patients, leukoaraiosis in 5% of patients, and brainstem infarction in 5%. 88% of all patients had a vasculonervous conflict between the trigeminal nerve and certain vascular branches [85].

Therapeutically, the administration of many drugs used in other primary headaches has been tried, but with rather poor results. In this respect, SUNCT and SUNA differ from the other primary headaches. They respond mainly to the treatments used to treat neuropathic pain. Lamotrigine is effective in a large percentage of patients with the first pathology and less effective in the latter and is administrated at a dose of 100 to 300 mg daily. Topiramate isn't as effective as lamotrigine, and a smaller percentage of patients report symptomatology improvement. Carbamazepine is extensively studied and given in the treatment of these two pathologies, although with some poor results for the improvement of symptomatology in the SUNA group of patients. It is generally administrated in the standard dose of 200-1600 mg. Lidocaine is administered in an intravenous infusion of 1-4 mg/kg/hour to relieve severe headache attacks. Attempts may also be made to damage the trigeminal nerve or Gasser's ganglion by stereotactic surgery, radiofrequency stimulation, glycerol gangliolysis, or mechanical compression [89]. It is important to note that SUNCT and SUNA may also occur secondary to lesions at the level of the posterior fossa: damage to the cerebellum or brainstem by ischemic, tumoral, or vascular mechanisms. It is important to note that high-resolution MRI imaging studies can provide details about neurovascular compression, but these are not essential [2,21].

Hemicrania continua (HC)

Hemicrania continua is another primary headache that presents as a unilateral headache of moderate intensity with development over several months and belongs to the group of TACs according to ICHD-3 [2]. As the name implies, the pain is continuous and constant, but sometimes exacerbations associated with autonomic symptoms may occur. The response to indomethacin is pathognomonic [90]. It is estimated that the incidence of pathology is 1.0% and that continuous hemicrania accounts for approximately 1.5% of all primary headache cases [90]. Cases of continuous bilateral hemicrania were rarely presented [91]. According to ICHD-3, a clinical diagnosis requires a unilateral headache with pain duration of more than 3 months, ipsilateral autonomic symptoms, restlessness associated with the symptoms, and response to indomethacin treatment. Exacerbations may occur as a result of stress, alcohol consumption, or, in women, menstruation [90]. If HC is clinically suspected, cerebral MRI is recommended in all patients, and MRA or CT angiography of the head and neck should be indicated if an aneurysm or vascular pathology is suspected. Response to treatment with indomethacin is pathognomonic. Start with a dose of 25 mg three times daily, and if the patient does not respond to this treatment within 2-3 days, the dose is gradually increased up to a maximum of 300 mg per day [92].

Other primary headaches

Primary cough headache (PCH) represents a rare disorder in which bilateral cephalgia starts suddenly during coughing and

may last up to two hours. According to ICHD3, the clinical diagnosis of primary-type headache is made by at least two episodes of pain that occur only after coughing or the Valsalva maneuver and last between one second and two hours, with no other associated intracranial pathology. However, up to 50% of patients hospitalized for this type of pain may have underlying lesions, such as Chiari malformation type 1, obstructive hydrocephalus, or tumors. Therefore, it is strongly recommended that imaging studies of the brain be performed, such as MRI or MRA [2,21,93]. Indomethacin is the treatment of choice for this type of headache [2].

Primary exercise headache (PEH) is a rare pathology similar to PCH, characterized by a bilateral pulsating headache that occurs only in the context of prolonged physical activity, lasting 45 minutes or less [2]. According to ICHD-3, when the patient first presents to the hospital with symptoms, it is mandatory to perform imaging studies to rule out "subarachnoid hemorrhage, arterial dissection, or vasoconstriction syndrome." Indomethacin is the treatment of choice for this pathology, in a dose of 25-150 mg before starting physical activity [94].

Primary headache associated with sexual activity is a diffuse bilateral headache that begins during sexual activity and lasts from 1 minute to 24 hours, accompanied by nausea or vomiting but without autonomic symptoms. These may present as progressive or sudden headaches, most often beginning at the moment of climax. Although it is generally not a serious medical problem, brain imaging is recommended to rule out other pathologies, such as subarachnoid hemorrhage or aneurysm [95]. It is difficult to quantify the epidemiology of this pathology because patients are reluctant to go to the doctor to be examined due to shame or ethical reasons. Some authors recommend prophylaxis with beta-blockers and symptomatic treatment with indomethacin [96,101].

Because of the rarity of these pathologies, there are no large, homogeneous studies quantifying the imagistic changes specific to each of these three pathologies, but rather small studies and case reports. For this reason, it is important to undergo a CT scan, especially in cases of sudden onset headache, to rule out secondary causes such as rupture of an aneurysm or subarachnoid hemorrhage, and subsequent vascular studies such as CT angiography or MRA are recommended in specific cases.

DISCUSSION

Despite the use of increasingly advanced imaging examination methods that have improved the understanding of the pathophysiology and mechanisms of development of primary headaches, the medical community still cannot fully understand and fully, optimally treat primary headaches. Structural MR imaging has demonstrated the presence of T2 and FLAIR hypersignal lesions that can be correlated with different pathologies that mimic the primary types of headache, although those appear especially with aura migraine. MR Perfusion imaging has shown several abnormalities in blood circulation and neuronal activity during cephalalgia exacerbations in every type of primary headache, demonstrating a lowering of pain threshold and, compared with the general population, deficient activation of many different areas in the brain responsible for interpreting pain, and in the case of migraineurs in particular, there is both a supernumerary activation of the areas as well as a more important or intense activation of them. Many authors have demonstrated that the autonomic nervous system takes part in the mechanism of headache development, due to age-related development and the decrease in headache amplitude in the case of noninvasive stimulation of the vagal endings for cluster headache prevention. These suspicions, especially in migraine, are not confirmed by imaging studies, either structural or functional. The use of imaging studies, regardless of their type, to diagnose migraine or tension-type headaches is not recommended because of the lack of specificity of the studies. Because these are debilitating diseases that affect both individual lives and society, sufferers search for answers and go from one physician to another in search of them. Repeated imaging studies in these cases represent a significant waste of resources, and each pseudonormal imaging result leads to even greater concern and anxiety about health status. The correlation of the new, recently discovered data with the clinical evolution of the patient can improve the selection and treatment of patients at risk for primary headache development, sometimes even from childhood. Today we know that primary headaches begin around the age of 5 years and the highest prevalence is found in the age group between 20 and 40 years, decreasing with age. The phenotypes and treatments of each pathology are different, even if they belong to the same class of pathologies. Currently, we can summarize that there are ischemic lesions, circulatory disturbances, vascular conflicts, 5th cranial nerve activation, and a lower pain threshold, all having their role in the development of these pathologies. Current studies include far too small and inhomogeneous groups of patients to be able to present convincing results regarding structural changes in the brain parenchyma or the various neuronal circuits.

CONCLUSIONS

In recent years, significant progress has been made in understanding the pathophysiologic mechanisms, both central and peripheral, of the primary cause of headaches, by using highly advanced technologies like structural high-resolution

MR, both of these imaging studies of cerebral structures allow the detection of cerebral parenchyma lesions with greater precision.

Pharmacologic interventions may help alleviate headaches, and recently several minimally invasive interventions have been tried, mainly targeting the physiopathologic mechanism that occurs via the cranial V nerve, obtaining promising results. However, there are still physiopathologic and imaging ambiguities related to these primary pathologies.

There is still an unmet need for studies in all fields, in large groups of homogeneous patients, to answer these questions.

Conflicts of interest and sources of funding

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Authors' contribution

Conceptualization, RID, FAA, AMR, and CAS; methodology, AFN, FAA, AMS, and CAP; software, RID, AFN, OV, and AMR; validation, AMR, OV, CAS, and CAP; formal analysis, RID, AFN, AMR and FAA; investigation, RID, AMR, OV, AMS, and CAS; resources, AFN, FAA, and OV; data curation, RID, AMR, AMS, CAS, and CAP; writing—original draft preparation, RID, AMR and CAP; writing—review and editing, AFN and AMS; visualization, RID; FAA, AMR, and CAS; project administration, FAA. RID and AMR contributed equally to this paper. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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