Pathophysiology and Therapy of Associated Features of Migraine

Subjects: Neurosciences

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Migraine is a complex and debilitating disorder that is broadly recognised by its characteristic headache. The associated symptoms to migraine, apart from the painful component, are frequent, under-recognised and can be more deleterious than the headache itself. The clinical anamnesis of a headache patient should enquire about the associated symptoms, and treatment should be considered and individualised.

Keywords: migraine pathophysiology ; nausea ; osmophobia ; phonophobia ; vertigo ; allodynia

1. Introduction

Migraine has been traditionally associated with the core symptom, headache [1]. Photophobia and vomiting, two of the canonical symptoms associated with migraine [2], are also widely accepted features of the typical migraine attack, as understood classically by patients and physicians [3]. However, reducing the understanding of migraine to a few symptoms would be as simplistic, perhaps, as reducing Parkinson's disease to tremors.

The way that migraineurs deal with their attacks provides valuable information about hypersensitivity to sensorial stimulation, including avoiding movement, light, sounds, touch or smells [4]. These are usually subjective, unpleasant experiences, unshared by family, friends or colleagues. Consequently, migraine patients presenting associated symptoms as prominent features can usually be labelled as sensitive. The Greek translation for sensitive, Ευαίσθητος "evahistos", can be separated into the following two parts: the prefix meaning good or well, and the rest meaning sense or perception. However, any positive connotation of the term has nowadays dissipated. Many of these "evahistic" manifestations can actually be the main symptom of the clinical picture in a patient with migraine, and imply a higher disability [5]. Migraine patients with sensory hypersensitivity may have more attention difficulties during daily activities [6], or more cranial autonomic symptoms associated to the headache [7], and the response to preventive treatments may vary [8]. Exogenous factors, such as stress, obesity, intestinal microbiota and even parental behaviour, have been speculated to play a role in the chronification and sensitization process [9][10][11][12].

2. Nausea and Vomiting

2.1. Nausea in Migraine and Conditions Related to Migraine

Nausea is one of the symptoms associated with migraine that is considered canonical, according to the International Classification of Headache Disorders, 3rd Edition (ICHD-3) [2]. Ictal and interictal nausea has a high impact on quality of life and economic cost [13][14], and is the second most bothersome migraine symptom, reported in 28% of patients, exceeded only by photophobia [15].

Up to half of the people with episodic migraine suffer from nausea in more than half of their headache episodes, and the attacks were accompanied by more headache symptoms and a higher impact, compared to patients with less frequency of nausea. The majority of those reporting high-frequency nausea were women [16] and had an increased risk of developing chronic migraine in 2 years [17].

Having migrainous biology could result in patients having more disability when presenting with other disorders that are generally associated with nausea and vomiting.

2.2. Neuroanatomy and Neuropharmacology

There is a matrix of neuro-anatomical structures involved in the onset and control of nausea, as well as several neurotransmitters that have been the main targets of antiemetic and acute treatment schemes.

Dopamine has been the main compound implicated in the pathophysiology of nausea associated with migraine, at least since the 1970s [18]. Patients with migraine are sensitive to dopaminergic pharmacological agents [19][20][21] and develop nausea and other classically considered dopaminergic symptoms, such as yawning, not necessarily accompanied by headache [19][21]. This propensity may entail a genetic predisposition, and a particular allelic distribution was found to be significantly different for the D_2 dopamine receptor in a subpopulation of migraineurs with prominent dopaminergic symptoms [22]. Among the dopaminergic symptoms, nausea, unlike yawning, is considered post-synaptic, and is triggered by apomorphine and inhibited by domperidone, which targets D_2 receptors [21]. Dopamine may also regulate headache pain, as dopaminergic neurons play a role in nociceptive control by modulating trigemino-vascular neurons [23].

Serotonin also has a major role in nausea, with the receptor 5-hydroxytryptamine- 5-HT_3 as the main target not only of modern antiemetic pharmacological compounds, but also of natural antiemetics used for centuries, such as the gingerol compounds contained in ginger [24].

Hyporexia during headaches may be explained by the loss of appetite that can be observed during noxious dural stimulation, which activates the nucleus parabrachial and the ventromedial of the hypothalamus, and may be mediated by cholecystokinin [25]. However, nausea can also appear before the headache, during the premonitory phase, in almost a quarter of spontaneous attacks [26]. This percentage was doubled when headache attacks were triggered in a controlled environment [27].

Another intriguing component in migrainous nausea is substance P. Neurokinin 1 (NK-1) receptor antagonists can inhibit vomit produced by central or peripheral stimuli [28], and its central action may be mediated by inhibiting the substance P emetic effect [29], which may take place predominantly in the locus coeruleus [30].

Early pre-clinical experiments are good examples of the extent of anatomical structures that could be involved in the process of vomiting. Monkeys presented vomiting following the electrical stimulation of the olfactory tubercle, amygdala, septum, fornix and the thalamic ventral anterior nucleus [31]. In cats, lesions in the medulla abolished the characteristic pattern of respiratory motor nerve discharge, observed in vomiting [32], induced by emetic drugs and electrical vagal stimulation of abdominal afferents. This study suggested that the regions that control vomiting were localised between the obex and the retrofacial nucleus [33], both localized in the medulla.

In human neuroimaging studies, some brainstem areas showed significant activation with a $H_2{}^{15}O$ positron emission tomography (PET) scan in the premonitory phase of migraine participants with nausea, including the periaqueductal grey, dorsal motor nucleus of the vagus, nucleus ambiguous and nucleus tractus solitarius [34], as shown in the following paragraphs. Following a rostral-caudal approach, among them, the mesencephalic periaqueductal grey (PAG) deserves a special mention [34].

PAG has an important role in the descending modulation of the trigeminovascular processes [35]. PAG has been related to other autonomic sympathetic activity [36][37], emotional perception of pain and aversive behaviours [38][39] cough [40] and breathing control [41]. It is involved in modulating the descending pain pathways [42][43][44]. This modulation has recently been shown to be activated by mu opioids by means of presynaptic disinhibition and reducing GABAergic postsynaptic currents [45]. It is yet unknown whether this area is related to the chronification observed in migraineurs with frequent use of opioids, as commented on below.

More caudal areas in the rostral dorsal medulla were involved, including the dorsal motor nucleus of the vagus [34], which may relax the lower esophageal sphincter [46].

The nucleus tractus solitarius has connections with hypothalamic areas that play a role in autonomic control [47]. Both the nucleus tractus solitarius and dorsal motor nucleus of the vagus conform, along with the area postrema, the dorsal vagal complex, which is one of the main termination sites of the afferent fibres of the vagal nerve [48] and has a high distribution of dopamine D_{2-4} receptors [49]. The area postrema is one of the sensory circumventricular organs with a possible chemoreceptive function, situated outside the blood–brain barrier and connected to the hypothalamus, which is thought to be essential in controlling neuroendocrine functions [50], is rich in type D_2 dopamine receptors [51] and is the brain area with the higher estimates of substance P [52].

2.3. Treatment of Nausea

The treatment of nausea during migraine attacks must be considered in every patient presenting with that symptom. When nausea does not respond to analgesic treatment, specific antiemetic treatment should focus on the pathways of the neurotransmitters described above (dopamine, serotonin, substance P) as main targets for treatment. Nevertheless, acute

treatment can be essential in the management of nausea associated with migraine. NSAIDs could be effective in alleviating nausea in patients who have not taken any triptans [53] and there is a recent meta-analysis that supports gepants as an effective treatment for nausea in patients with episodic migraine [54]. Special attention must be paid to patients consuming opioids. Nausea is a recognised side effect following opioid use [55]. Patients with episodic migraines who are exposed to opioids have a twofold risk of migraine chronification [56], a likely reduction in the efficacy of triptans for acute treatment [57] and the issue of developing gastro-intestinal adverse events after long-term consumption [58].

3. Osmophobia

The perception of odour is certainly an extremely subjective experience, or we would all be wearing the same perfume. Being perhaps the less studied of the senses, the mechanisms behind the way a fragrance is perceived is not yet fully understood. A brief mention here is appropriate for two interesting theories that were proposed in the twentieth century, involving a lock-and-key system and vibrational wavelengths [59], which have not yet been fully developed.

There are several substances whose consumption or inhalation has been popularly related to headaches [60][61][62][63]. Remarkably, *Umbellularia californica* is a type of tree, commonly known as “the headache tree” [64], which contains umbellulone, a ketone that was reported of being capable of triggering cluster headache-like attacks in a gardener with a history of cluster headaches [65]. It was later discovered that this mechanism was mediated by the activation of the transient receptor potential (TRP) ankyrin 1 (TRPA1) [66][67], followed by the release of calcitonin gene-related peptide (CGRP) [66]. CGRP is also released through the activation of vanilloid receptors, following stimulation with nitric oxide [68] or ethanol [69][70], one of the most relevant cluster headache triggers. TRPA1 has also been involved in the responses to some inhaled chemicals, including the smoke of cigarettes [71], chloride [72][73] hydrogen peroxide-containing substances [73] or formalin, the noxious compound largely used in pain models [74].

It has been reported that up to 70% of migraineurs can develop a headache after the stimulation with some odorants, which happened around 25 minutes following the exposure [75], and there is a case report of migraine improvement following the imposition of mandatory masks in the workplace during the COVID-19 pandemic [76]. Increased sensitivity to smells can be part of the premonitory-like symptoms experienced by migraineurs; therefore, certain smells may be misinterpreted as the trigger for a migraine attack, which might not be a necessary factor for its occurrence [77][78]. As a consequence, the results of studies that assess migraine triggers have debatable interpretations.

Nevertheless, the presence of osmophobia may be related to more florid migraine phenotypes and greater disability, and a scale has been developed recently for the quantification of quality of life related to osmophobia [79]. Migraineurs that present with ictal osmophobia may have more painful headaches [80][81]. Ictal and interictal osmophobia have been associated with a longer history of migraines or high frequency of the attacks, as well as other associated symptoms, such as cranial allodynia [82][83][84], suggesting a central sensitization process [85]. Vomiting can also be more common in the presence of osmophobia [81][83]. Osmophobic migraineurs may also have a higher prevalence of psychiatric comorbidities than those without it [80][86][87][88].

Osmophobia has been proposed as a specific marker, helpful for the diagnosis of migraine [81][86][89][90][91][92][93][94]; however, it is not very sensitive [84]. Around half of the patients with migraines reported an increased sense of smell or reduced tolerability to smells [91][95]. Remarkable examples of patients reporting hyperosmia include the smell of a rose from more than 5 meters of distance, or soap from a different room, and the main scents triggers for osmophobia arose from food, specifically fried food and onions, cigarettes or self-care products, and perfume or paint specifically were reported as triggers [95]. More recently, forty percent of patients with chronic migraine reported osmophobia [96], and a similar number suggested odours or perfumes as potential triggers of a migraine attack [63].

Paradoxically, despite their hypersensitivity to smells, migraineurs have a lower capability for the threshold, identification and discrimination of smells [97][98]. Patients with episodic migraine were found to have a similar olfactory acuity to controls, and furthermore, around one fifth of them developed hyposmia during the attack [99]. Taste abnormalities in migraineurs [95] are a matter of debate [100].

Patients with migraine and osmophobia have neuroanatomical alterations. A significantly reduced volume of the olfactory bulb was observed in 1.5 Tesla MRI, compared to patients with other types of headache [101], and might be more pronounced on the left, in comparison with controls [102]. In migraineurs with reported hypersensitivity to odours, regional blood flow in a study using $H_2{}^{15}O$-positron emission tomography was found to be increased in areas of the left piriform cortex and antero-superior temporal gyrus, as compared to controls, both with and without multiple odour stimuli [103]. During odour stimulation, blood flow was found to be decreased in bilateral fronto-temporo-parietal regions, as well as the

posterior cingulate gyrus and right locus coeruleus [103]. Another study using fMRI to compare responses to the smell of roses found higher blood oxygen level-dependent activity in the amygdala and insular cortices of the amygdala and also in the midbrain, particularly the rostral pons. However, the smell of roses did not show significant interictal differences compared to the controls [104]. Activation of the amygdala and orbitofrontal cortex might be related, respectively, with the intensity and valence of the smell emotional experience [105]. The amygdala and cingulate cortex also showed abnormal activation in patients with multiple chemical sensitivity [106][107], which is associated with a high prevalence of headache [108] and was observed in up to 20% of migraineurs [109].

Olfactory hallucinations or phantosmia is a hallmark of temporal lobe epilepsy, and currently a no man's land when it presents in the form of aura. It is a rare symptom, with a reported prevalence of 0.66% in a headache center [110]. The majority of reported cases had normal electroencephalograms that were, however, taken during the interictal period, and usually respond to antiepileptic drugs.

The reported cases showed that the episodes have an average duration of less than 10 min and the onset occurs prior to the migraine attack [110][111]. Patients with symptoms of phantosmia scanned with FLASH and eco-planar imaging MRI techniques showed increased activation of different brain areas associated with the process of the sense of smell, such as the prefrontal, cingulate, temporal or insular cortex MRI activation was inhibited by typical antipsychotics that perform its activity through a wide range of binding receptors [112]. Peripheral blocking activities can alleviate phantosmia [113].

4. Neuro-Otological Manifestations

In 1984, Kayan and Hood described how vestibulocochlear symptoms were frequently reported, in up to 60% of patients with migraine, and these can be important or disabling enough for the patient to be the primary reason for referral to a specialist. The incidence of neuro-otological symptoms for migraineurs seemed homogeneous throughout all ages in males, but had a peculiar distribution in females. For women who reported audiovestibular symptoms only when asked during the study, a positive skew distribution could be observed, with the peak situated in the 3rd decade. However, the female patients whose reason of referral was the presence of disabling audio-vestibular symptoms had a peak in the peri-menopausal 5th and 6th decades. This group with disabling symptoms had a higher incidence in males [114]. They compared 80 patients referred for vestibulocochlear symptoms with 500 patients with multiple sclerosis for benign positional vertigo and Méniere's [114]. Only migraineurs described cochlear sensations, such as tinnitus, distortion of pitch, or hearing loss [114].

The frequency of migraine in Méniere's disease is higher than in normal subjects, and phonophobia has a high prevalence in these patients, independently of the presence of migraine headache [115].

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