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Migraine and triggers: Post hoc ergo propter hoc?

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Abstract

The influence of environmental factors on the clinical manifestation of migraine has been a matter of extensive debate over the past decades. Migraineurs commonly report foods, alcohol, meteorologic or atmospheric changes, exposure to light, sounds, or odors, as factors that trigger or aggravate their migraine attacks. In the same way, physicians frequently follow this belief in their recommendations in how migraineurs may reduce their attack frequency, especially with regard to the consumption of certain food components. Interestingly, despite being such a common belief, most of the clinical studies have shown conflicting results. The aim of the review is to critically analyze clinical and pathophysiological facts that support or refute a correlation between certain environmental stimuli and the occurrence of migraine attacks. Given the substantial discrepancy between patients' reports and objective clinical data, the methodological difficulties of investigating the link between environmental factors and migraine are highlighted.

Keywords

Migraine; Trigger; Environmental Stimuli; Headache; Precipitant

INTRODUCTION

From a clinical perspective, it seems to be quite clear that environmental factors influence the course of the clinical picture in migraineurs. Patients commonly report that certain external factors such as meteorological changes [1–6] or specific food components [5, 6] can influence the initiation or aggravate an ongoing migraine attack. An important caveat to consider is the difficulty to reliably identify migraine triggers. Two recent publications addressing headache triggers and causality concluded that natural experimentation is not a reliable method for individuals to identify migraine triggers [7, 8]. The authors proposed that formal experimentation or diary studies using advanced statistical modeling techniques may be necessary to assign causation to headache triggers [7, 8]. Therefore, we may not be equipped to correctly identify migraine triggers in clinical practice. This is an important question for diagnostic and therapeutic reasons. Schurks et al. have recently proposed that precipitating factors are important in the characterization of the migraine phenotype despite

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not being included in the current diagnostic criteria of headache disorders [9]. Moreover, there is significant controversy regarding what the therapeutic implications are [10].

From a pathophysiologic point of view, patients' reports suggest that these external stimuli may have an effect on the susceptible brain and lead to a series of cellular and molecular changes that result in an acute migraine attack. However, as attractive as this explanation may seem, the information provided by migraineurs as well as the existing objective data from numerous clinical trials do not exclude the possibility that the sequence of events is happening exactly in the opposite direction. It is well known that the pathophysiologic phenomenon of a migraine attack starts well before the onset of the pain phase [11]. In this context, premonitory symptoms, such as food cravings, yawning and alterations in the sleep wake cycle, have been reported to precede the pain phase of a migraine attack by up to 72 hours. Therefore, it may be postulated, that an altered brain state, that probably involves a transient inadequate function of central modulating structures such as the hypothalamus, may increase for example the feeling of hunger thereby inducing the observed food cravings, maybe even the craving for specific foods that are then misinterpreted as the initial cause of the migraine attack. The same may apply for external factors such as specific meteorological variables. In this case, during the early phases of a migraine attack, long before the pain starts, migraineurs perceive weather changes more intensely as a result of an enhanced neuronal susceptibility or even sensitization. Presently, it is not possible to conclude with certainty which of the two mechanisms is the pathophysiologic basis of the commonly reported connection between migraine and the environment. Even the possibility that both mechanisms coexist could be conceivable. However, what can be concluded is that the relationship between environmental factors and migraine appears to be far more complex than initially assumed. The type and extent of this relationship may also vary substantially among migraineurs. The pathophysiologic complexity is reflected in the discrepancy between migraineurs' clinical reports that highly suggest such a relationship and objective data of clinical trials that deliver inconclusive results. Given the amount of affected patients, the inconclusive results are probably the result of migraine heterogeneity, lack of pathophysiological understanding or methodological shortcomings in trial design, rather than a common misperception of millions of migraineurs.

Here, we review the clinical and pathophysiological facts that support or refute a correlation between certain environmental stimuli and the occurrence of migraine attacks. We also highlight the methodological difficulties of investigating the link between environmental factors and migraine.

Food and alcohol

Dietary items are among the triggers most commonly reported by patients and addressed by healthcare providers [12]. In 1960, Selby and Lance published a seminal observational study revealing that 25 % of migraineurs identified foods as triggers for their attacks [13]. Most recently, in a large retrospective study, Kelman evaluated 1,207 patients with migraine and confirmed that one out of four migraineurs reported food as a precipitant of their acute migraine attacks [1]. In a cross-sectional study at an outpatient headache clinic, 98% of patients identified dietary triggers, but these included fasting, in addition to foods and alcohol [14].

The list of dietary factors implicated in the precipitation of migraine attacks is very extensive. Some of the most frequently cited triggers in this category include: chocolate, cheese, nuts, citrus fruits, processed meats, monosodium glutamate, aspartame, fatty foods, coffee, and alcoholic drinks, especially red wine and beer [12]. Many patients recognized multiple dietary triggers and relatively inconsistent effects. It is possible that most dietary

precipitants in isolation are insufficient to trigger an attack. This makes formal investigation and recommendations for practical management problematic. Additionally, it is important to keep in mind that the mechanisms by which food may precipitate a migraine attack remain largely unknown. In a recent editorial article, Pascual and Oterino have discussed the different hypotheses, including the “amine hypothesis” and hypersensitivity mediated by IgE and IgG antibodies [15]. However, none of them has been well established. A study including 56 migraineurs and their matched controls found that 100% of patients but only 26% of healthy controls had elevated titers of IgG antibodies against different foods [16]. The number of foods associated with elevated IgG titers ranged between 6 and 30 among migraineurs, while in control subjects the maximum was four. In the same study, all the patients were then placed on a diet excluding the foods that were associated with elevated IgG titers for each individual during 6 months. Forty-three of the 56 patients reported no migraine attacks, 4 improved and 9 did not change. It is important to consider that there was no sham diet to blind the patients, but the results suggest that IgG-based elimination diet is worth investigating in controlled studies [16].

The so-called “migraine diet” or “migraine elimination diet” has received a lot of attention for several decades. However, despite having devoted followers and fierce opponents, there is no scientific evidence to support recommending patients to adapt a standardized “migraine diet”. Within the last few years, efforts have been made to come up with individualized dietary recommendations based on well-designed clinical trials. Alpay et al. published a randomized, double-blind, cross-over trial assessing the effect on migraine prevention of tailored diet restrictions based on IgG antibodies against food antigens [17]. They determined IgG antibodies against 266 food antigens and found that most patients had at least moderate titers and all had positive reactions to several foods (7 to 47 abnormal reactions in individual patients). After a baseline period, patients were randomized to an individualized diet excluding or including foods associated with elevated IgG antibodies. The elimination or provocation diets were prepared by a dietician. After 6 weeks on their respective diet, all patients returned to their usual diet for 2 weeks and were then switched to the opposite diet for 6 weeks (provocation diet following elimination diet or vice versa). Patients and the physician evaluating their headaches were blinded to the diet assignments. Headache diary data revealed that migraine days and number of attacks were significantly reduced during the elimination diet period, however, attack severity or duration did not change. Half of the patients had at least a 30% reduction in number of headache days and one out of five patients had over 50% reduction in number of headache days on the elimination diet period compared with the provocation diet [17]. Although these results need to be confirmed in a larger study, the findings are promising and further investigation of potential mechanisms are warranted. A subsequent smaller study with a similar design investigated the effect of IgG-based elimination diet in patients with migraine and concomitant irritable bowel syndrome [18]. Aydinlar and co-workers conclude that elimination diet based on IgG antibodies may improve both conditions. However, they observed an improvement in the number of headache days on the provocation diet relative to baseline and no difference between the provocation and elimination diet in several parameters, suggesting that the cross-over design is not ideal or that perhaps some of the benefits seen are the result of a placebo effect [18]. Mitchell et al., in a larger randomized, sham-controlled, single-blinded, 12-week trial, found that the benefits of the IgG-based elimination diet were less robust than previous studies suggested. There was no benefit in migraine-related disability or number of headache days at 12 weeks. Only at 4 weeks they observed a statistically significant decrease in number of headache days from 8 to 7 ($p=0.04$), which may suggest a mild placebo effect [19]. Therefore, more research is needed to settle this question, improve our understanding of the causes of acute migraine attacks, and optimize patient management.

Finally, alcohol, and especially red wine, has been classically reported as a migraine trigger, mostly based on retrospective studies and anecdotal reports [20, 21]. Littlewood et al. demonstrated that red wine, but not vodka, reliably precipitated a migrainous headache, mostly within 3 hours, in patients that felt that red wine was a trigger for them but not in other patients or healthy subjects [22]. In a recent study at an Italian headache center, Panconesi et al. found that only 5% of patients with migraine without aura and none of those with migraine with aura or tension-type headache reported alcoholic drinks as a trigger [23]. Nicoletti et al. have demonstrated that high doses of ethanol (equivalent to 3–4 glasses of wine) promotes neurogenic inflammation in guinea pigs through activation of the transient receptor potential vanilloid 1 in the trigeminal nociceptors and release of neuropeptides [24]. However, the mechanisms by which alcoholic drinks may precipitate a migraine attack in humans remain unknown.

Weather

A relationship between weather and migraine has been analyzed in numerous clinical studies; most with inconclusive results. Initial studies aimed at analyzing a relationship between weather and headache without differentiating any further among primary headaches. As pathophysiologic mechanisms underlying the different types of primary headaches differ substantially, the majority of these trials did not prove a direct correlation [25]. Multiple studies were also conducted prior to the publication of the first edition of the Headache Classification of the International Headache Society impeding the creation of homogenous study groups which are the basis for reliable study results [25–29]. In this context, Barrie et al. [26] and Wilkinson et al. [27] did not find a link between weather variables and migraine. In contrast, other studies revealed a significant correlation between migraine frequency and specific meteorological variables, especially atmospheric pressure [28, 29]. In this regard, Osterman et al. [28] observed that high atmospheric pressure correlates with a higher attack frequency, while Cull et al. [29] observed the opposite. With the publication of the first edition of the Headache Classification in 1988 and its latest revision in 2013 [30], which clearly define the clinical syndrome of Migraine, the creation of homogeneous and standardized study groups was finally possible. Despite this, subsequent clinical studies failed to dissect specific effects of weather variables such as atmospheric pressure, temperature or relative humidity [1, 2, 31, 32]. These studies identified a correlation between migraine and weather but due to their rather unspecific approach, their contribution to the pathophysiologic understanding and clinical significance is limited.

In an effort to overcome challenges related to study design inherent to the matter of study, new techniques have been employed more recently. However, several trials failed to identify a relationship between specific parameters and migraine [33–35] while others observed specific correlations [36–38]. Prince et al. [38] and Hoffmann et al. [36] found a relationship between low ambient temperature and high relative humidity and the incidence of migraine. Kimoto et al. observed a correlation between decreases in atmospheric pressure and increases in migraine frequency, which underlines the previous results as low atmospheric pressure (or its decrease) is commonly associated with low temperature and high humidity due to precipitation [37]. Importantly, the study by Hoffmann et al. also revealed that only a subgroup of migraineurs seem to be weather-sensitive, providing a possible explanation as to why clinical studies have substantial difficulties in proving such a common patient perception [36].

Interesting results from preclinical *in vivo* studies point in the same direction. Messlinger et al. elegantly showed that decreasing barometric pressure increased discharge rates of neurons in the trigeminal nucleus caudalis of rats [39]. The subgroup of second order

neurons responsive to changes in barometric pressure received corneal input and frequently convergent input from the dura. However, units with meningeal but not corneal input did not seem to respond to changes in barometric pressure [39]. Further studies in this line will improve our understanding of the pathophysiological mechanisms by which environmental factors may initiate and maintain a migraine attack.

Taken together, clinical and experimental data seem to indicate that in a subgroup of migraineurs, the incidence of migraine attacks may be associated with low temperature, high relative humidity and low atmospheric pressure. However, these results need confirmation by larger, carefully controlled and designed, prospective clinical studies with long observational periods to exclude potential confounding factors such as circadian or seasonal influences.

Electromagnetic fields

Only a few sources of electromagnetic activity have been studied for their potential influence on migraine. Most studies have focused on low frequency atmospherics (sferics) which are a meteorological phenomenon characterized by alternating electric and magnetic fields originating from atmospheric discharges (lightning) as migraineurs commonly report a relationship between weather conditions associated with falling or low atmospheric pressure (rain, falling or low temperature) and their migraine attacks. Most of the existing studies suffer from small sample sizes but nevertheless point into the same direction by indicating a possible correlation between sferics and the incidence of migraine [40–43]. All studies investigating a relationship between a certain weather variable and the incidence of migraine are hampered by the fact that most variables are associated to each other, resulting in substantial difficulty in dissecting each of them in relation to its ability to trigger or aggravate a migraine attack. This methodological challenge is particularly accentuated when studying the influence of electromagnetic discharges on migraine because thunderstorms usually coincide with low barometric pressure and ample precipitation requiring complex study designs. In addition, due to the relatively low measurable intensity of sferics - the magnitude of their magnetic component usually does not exceed 60 nanotesla (nT) [42],- the required sensitivity of the recording equipment as well as potential influences of technical equipment in the vicinity of the recording site has to be meticulously evaluated. An observational cohort study with 90 migraineurs conducted by Martin et al. investigated the correlation between the occurrence of lightning on a given day (lightning day) and the incidence of migraine and compared the result to days without lightning (non-lightning day) [43]. They found that the number of days with migraine increased by 28% on lightning days compared to non-lightning days. Statistical adjustment for associated weather variables indicated that these factors do not completely explain the correlation, suggesting a significant effect of electromagnetic discharges on migraine [43].

When investigating the relationship between technical sources of electromagnetic activity and the incidence of migraine, the situation becomes less clear. Despite patients' reports of headache resulting from structures or devices inducing an electromagnetic field such as a high voltage overhead power line [44], an antenna emitting a radio signal [45], or mobile phones and WLAN/WIFI devices [44], these results could not be confirmed in a large systematic meta-analysis [46]. However, these studies did not specifically discriminate between different types of primary headaches.

Taken together, the influence of electromagnetic fields on the incidence of migraine is still controversial. While studies investigating the correlation of migraine to atmospheric electromagnetic activity generally seem to indicate a relationship, results from studies focusing on technical sources of electromagnetism do not confirm this observation.

Therefore, further large and well-structured trials are needed to elucidate a potential link between migraine and electromagnetism.

Light and sunlight exposure

The association between migraine and light is multifaceted. The most evident example is photophobia, which is a common element of the clinical syndrome of migraine. To elucidate the complex relationship between light and migraine, research has focused on clarifying whether migraineurs are also more sensitive to light during the interictal periods than healthy control persons, whether light can trigger migraine attacks, and whether the duration of sunlight exposure and its seasonal variation has any influence on the attack frequency. Several studies have addressed a possible interictal hypersensitivity to light in migraineurs. Results of these studies suggest that migraineurs are interictally more sensitive to light [47] as well as to certain visual stimuli such as a pattern glare when observing striped patterns or black-and-white striped gratings and flickering light [48–50]. In this context, certain visual tasks may even be processed more rapidly by migraineurs than their matched control subjects [50, 51]. Despite speculations about an interictal cortical hyperexcitability, the pathophysiological basis for this altered visual perception and processing remains largely unknown.

The ability of light to trigger attacks in migraineurs has been suggested by several clinical studies [1, 6, 32, 52–56]. Most of the studies are based on data obtained through a questionnaire with the associated recall bias resulting from self-reporting and the usually retrospective design [32, 52, 53, 55, 56]. Recently, Hougaard et al. tried to experimentally provoke migraine attacks with bright or flickering light in migraineurs that previously reported light being a trigger for their migraine attacks [54]. Interestingly, none of the patients that had reported that light was a consistent trigger for them developed a migraine attack after being exposed to bright lights in an experimental setting. However, all of them described the photostimulation as unpleasant, which could represent interictal photophobia. It is also important to note that most patients that report light as a trigger will admit that they are often exposed to bright lights without any consequences. A plausible explanation for the inability to trigger migraine attacks with photostimulation in the laboratory may be that other factors occurring simultaneously or a certain level of susceptibility may be necessary for light and other stimuli to trigger an acute migraine attack. It is likely that multiple concurrent factors and a lower threshold resulting in a migraine attack are more commonly present outside the experimental setting. At the present time, whether bright or flickering light can trigger migraine attacks remains unclear. Therefore, more studies are needed to clarify whether light may trigger acute migraine attacks and to unveil the involved mechanisms.

A separate question to answer is whether the long-term exposure to light as such is able to modulate the attack frequency. This hypothesis has been analyzed mostly in arctic populations as the extreme seasonal variation of sunlight exposure in arctic regions offers the possibility to observe potential variations in migraine frequency over the course of a year in the same individuals. In a large study conducted in northern Norway, seasonal headache variation was assessed in 1052 patients over a 2-year period. Almost 12% of migraineurs reported an increase in attack frequency during midnight-sun season, suggesting that long-term exposure to light may increase the susceptibility for the initiation of a migraine attack. Interestingly, patients with non-migraine headaches showed the opposite pattern with an observed increase of headache frequency during polar night [57]. This seasonal periodicity has been confirmed in subsequent clinical studies [58, 59] as well as in a series of case reports [60]. The results of a study conducted by Alstadhaug et al. suggest that the observed seasonal variation is more prominent in patients suffering of migraine with aura than those

without aura [59, 61]. Interestingly, in female migraineurs suffering from menstrually-related migraine attacks, a seasonal variation or a correlation of attack frequency with light exposure could not be identified [62].

Taken together, clinical evidence indicates that migraineurs are not only more sensitive to light during but also in between their attacks. Furthermore, the exposure to light seems to contribute to the initiation of migraine attacks and higher attack frequency is seen with increasing duration of daily light exposure. However, as observed with the influence of weather in migraine, lights may only affect a subset of migraineurs. These observations further support the idea that different trigger factors may elicit migraine attacks through distinct mechanisms, which merge into a common pathway leading to the well-defined clinical picture of migraine.

Odors

Similarly to what occurs with lights, sensitivity to odors, or osmophobia, is a common symptom during a migraine attack as well as interictally. Therefore, distinguishing between enhanced sensitivity to smells in the early phase of the attack, before pain has started, and olfactory stimulation as a trigger is challenging [63]. In a study including 96 male migraineurs, Marmore de Lima et al. found that odors, especially perfume, cigarette smoke and cleaning products, were the second most frequently reported trigger (48%) following stress (59%) [64]. Silva-Neto et al. interviewed 400 headache patients, 200 with migraine and 200 with tension-type headache, regarding odorant substances as headache precipitant [65]. They found that 70% of migraineurs, but none of the patients with tension-type headache, had at least one migraine attack in their lifetime triggered by odors. Perfumes were again the number one culprit and the median latency from exposure to onset of pain was 10 minutes [65]. Importantly, migraine patients appear to have normal olfactory discrimination based on a study using an odor stick identification test [66]. However, migraineurs in this study found certain odors (perfume, rose and Japanese cypress) more offensive or unpleasant than control subjects [66].

Two recent neuroimaging studies have evaluated olfactory hypersensitivity in migraineurs. In a PET study, Demarquay et al. studied migraineurs with interictal olfactory hypersensitivity and control subjects scanned in the presence and absence of odor stimulation [67]. The authors found different patterns of activation in migraineurs at baseline and during olfactory stimulation as well as compared with control subjects. These differences were seen in multiple brain and brainstem regions implicated in migraine and olfactory processing [67]. Stankewitz and May used fMRI to investigate neuronal processing in response to olfactory stimulation (rose odor) in migraineurs, ictally and interictally, as well as in healthy controls [68]. There were no differences between controls and migraineurs interictally or between migraineurs with and without ictal osmophobia. Compared to their baseline, migraineurs had stronger activations in the amygdala, insular cortex, temporal pole, superior temporal gyrus, rostral pons, and cerebellum during their migraine attack in response to odors. This study suggests that there is an interaction between olfactory processing and the trigeminal nociceptive system [68].

Conclusion

Whether or not migraineurs are more sensitive to environmental stimuli remains an open and fascinating question. Patient reports and research data suggest that migraineurs are in fact more sensitive to environmental stimuli, although controversies still exist. More importantly, *what are the biological mechanisms that underlie the association between multiple environmental stimuli and the onset of a migraine attack?* Studies exploring how different

environmental stimuli influence migraine manifestations are crucial for a better understanding of the disease and for better therapies.

What should we recommend patients? Patients are generally advised to avoid triggers, sometimes leading to a restrictive lifestyle. However, the evidence to support these therapeutic recommendations is insufficient. Furthermore, the concept of trigger avoidance as an important aspect of migraine management has been challenged by Martin et al. [69–71]. He puts forth the idea of "coping" with triggers as opposed to "avoiding" them based on the theory that strict avoidance may further sensitize the individuals to those headache-precipitating factors.

In our opinion, if an individual patient has identified an avoidable trigger, such as for example red wine or chocolate, that reliably induces attacks shortly after exposure, avoidance may be considered. However, the associated reduction in quality of life should be considered, especially as strict avoidance may induce stress and frustration which in turn may eliminate a potentially beneficial effect or even aggravate the situation. In addition, there are situations where avoiding the stimulus at all cost may be difficult and possibly lead to increased sensitivity; such is the case of lights (individuals that overuse sun-glasses may become even more photophobic). However, there are potential triggers such as fasting or sleep deprivation, for which avoidance seems the most sensible approach.

To conclude, we call for common sense and individualized recommendations for patients reporting sensitivity to environmental factors. Until we have better scientific evidence, healthcare providers should carefully consider a balance between trigger avoidance and coping based on the individual patient and precipitating factor.

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* Of importance

** Of outstanding importance

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