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MIGRAINE (R COWAN, SECTION EDITOR)

What Turns on a Migraine? A Systematic Review of Migraine Precipitating Factors

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Abstract Migraine attacks rarely occur spontaneously in the absence of any possible precipitating factors. A systematic literature review of 25 publications revealed a consistent set of stimuli that have been identified as factors associated with the onset of a migraine attack. The weighted average of the "Top 10" trigger factors was determined. Stress was cited as the overall most common migraine precipitating factor, which was identified as a trigger factor by 58 % of 7187 migraineurs. The incidence of migraine precipitating factors, across various populations globally, demonstrates the clinical consistency of migraine in the human population. Future efforts aimed at mitigating these precipitating factors have the potential to significantly improve migraine management. However, the current healthcare system is unlikely to be able to develop detailed personalized management plans. There is a need to develop a novel approach to the identification and management of multiple trigger factors in individual migraineurs.

Keywords Migraine · Triggers · Stress · Fasting · Fatigue · Hormones · Noise · Lights · Odors · Weather · Sleep · Alcohol · Sensory · Management · Personalized

Introduction

"*few headache specialists would question the view that a migraine attack is the end-result of a chain of events leading to this acute clinical syndrome*" [1].

An extremely wide variety of precipitating factors are believed to "trigger" or "precipitate" a migraine attack. A detailed understanding of these factors could and should, in theory, allow for improved clinical management of migraine. Indeed, there are multiple reasons to elucidate the relationship between various trigger factors and migraine. For example, although headache attacks are episodic, migraine is a potentially disabling clinical syndrome that tends to persist for decades in most sufferers. If an understanding of trigger factors leads to even a small effect on the severity, duration, or frequency of attacks, then the lifetime benefit would be substantial. Second, migraineurs may be vaguely aware of the factors that may be associated with their attacks, but few have analyzed their various potential triggers in detail or systematically. Third, therapeutic interventions are well known to be more effective when used early in the course of a migraine attack, so that an awareness of converging trigger factors could increase the likelihood of early therapeutic intervention(s). Fourth, and very important from a clinical perspective, patients will often benefit greatly from gaining a sense of control, however modest, over their condition.

This review is based on a systematic literature review and summation of migraine trigger factors in an attempt to document the "Top 10" factors that have been associated with the onset of a migraine attack. A search of the medical literature using the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) identified 25 publications that assessed the frequency of various migraine trigger factors in multiple populations of migraineurs [2–12, 13•, 14–16, 17•, 18, 19•, 20–24, 25•, 26].

Multiple studies have been performed both retrospectively and prospectively to determine the prevalence of trigger factors in migraineurs. The epidemiologic techniques used to ascertain these data have varied widely. Most of these studies have been retrospective, cross-sectional studies wherein patients were interviewed directly or were asked to self-report specific migraine triggers. Some of the studies have been clinic-based, and some have been population-

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based. The studies have been completed across the globe. Overall, the 25 publication dataset comprises a diverse group of migraineurs in terms of their demographics. By combining the results of a large number of independent studies in the present systematic review, it was hoped that patterns might emerge that might be useful for future studies, as well as in potentially elucidating any commonalities between migraine trigger factors.

The clinical benefit to a better understanding of migraine trigger factors is clear since these precipitants are believed to be cumulative in their overall effect. Thus, management of even a few "modifiable" trigger factors, none of which is independently strong enough to prevent a migraine, might prevent the patient from reaching the theoretical threshold that initiates the migraine attack [27].

The "Top 10" Migraine Precipitating Factors

Data on the reported incidence of migraine trigger factors were abstracted from each of the 25 publications. The "weighted average" of each precipitating factor was then calculated for each general subgroup. For example, "stress" has been defined variably by different investigators, with different terms being used to describe a similar phenomenon. Therefore, for the purposes of this review, terms such as "psychological upset" [13•] were considered synonymous with "stress". The term "trigger factor" was also considered to be synonymous with "precipitating factor".

Based on this review and analysis, the "Top 10 Migraine Precipitating Factors" are presented in Table 1. The total number of subjects evaluated to for each factor involved is also provided. A brief summary of each precipitating factor is provided below.

Table 1 "Top 10" migraine precipitating factors

Precipitating factor (general)	% of migraineurs	Total # subjects assessed
Stress	58	7187
Auditory	56	397
Fatigue	43	2577
Fasting	44	3374
Hormonal[a]	44	4461
Sleep	43	5347
Weather	39	5527
Visual	38	5176
Olfactory	38	5251
Alcohol	27	3695

[a] In females only.

No. 1. Stress

Stress has often been cited as one of the most common precipitating factors in migraine [1, 28–34]. Indeed, the role of stress as the most commonly recognized migraine trigger factor is supported by the data in Table 1, derived from analyses involving over 7000 migraineurs.

Stress can be defined as a specific adaptive and defensive physiological reaction by the nervous system in response to a wide variety of physiological and/or psychological stimuli. Neuroendocrine components activated by stressors include the increased secretion of epinephrine and norepinephrine from the sympathetic nervous system and adrenal medulla, the release of corticotropin-releasing factor and vasopressin from parvicellular neurons into the portal circulation, and within a few seconds, the secretion of pituitary adrenocorticotropin, leading to secretion of glucocorticoids by the adrenal gland [35]. Therefore, the effects of stress on both the entire body and nervous system are significant.

Numerous formal studies have shown that subjective ratings of stress are significantly higher in migraineurs than in age-matched controls. Between 50 % and 70 % of migraineurs show significant, substantial, and meaningful temporal correlations between their daily stress and their daily migraine activity [32]. Numerous studies have documented that the stress may precede the onset of the migraine attack by a number of days. For example, a diary analysis of 33 patients showed that a significant increase in stressful events and a decline in physical activities for the 4 days leading up to and including each headache day [30].

Evidence of increased stress on the day preceding the migraine attack were obtained from a 6-month longitudinal study that examined whether migraine attacks were preceded by or occurred on stressful days [36]. Every evening, subjects (n=13) assessed their daily level of stress. Analyses tested whether migraine attacks occurred more often than expected by chance 3, 2, or 1 day after or on the day when stress scores were in the upper third of the subject's distribution. Increased stress was often observed on day 1 before the attack and on the migraine-attack day itself, but was generally not observed on days 2 and 3 before an attack [36].

Slightly contrary results were reported recently in a study of 17 migraineurs (median age 44 years) who completed 30 days of diaries that assessed perceived stress levels [37••]. The daily level of stress was reported to not be associated with migraine occurrence. However, a decline in self-reported stress from 1 evening diary to the next was associated with increased migraine onset over the next 6, 12, and 18 hours. The authors concluded that a reduction in stress from one day to the next is associated with migraine onset the subsequent day [37••].

No. 2. Auditory

Migraine precipitation secondary to noise has also been cited frequently. Both "noise" and "sounds" are terms that have been associated with the precipitation of a migraine attack [8, 13•, 21, 23]. Although auditory stimuli is ranked as the second most common migraine precipitating factor, it should be noted that it has been assessed in only 397 migraineurs (ie, the smallest number compared with the other factors) (Table 1).

No. 3. Fatigue

A physical state of fatigue has often been associated with the precipitation of migraine [2, 6–9, 14, 23, 25•]. The relationship between a feeling of fatigue and stress remains unclear, but migraineurs often report feeling a significant decrease in what they perceive to be a normal amount of physical strength and/or energy.

No. 4. Fasting

There is a well-documented association between fasting, whether by design or as a result of missing a meal, and migraine [4–6, 8, 12, 13•, 14, 15, 17•, 21–23, 26]. These data are consistent with a study [38] that showed that a headache occurred in 39 % of individuals who fasted compared with only 7 % of individuals who did not fast during the Jewish observance of Yom Kippur. Symptoms of nausea, vomiting, phonophobia, and photophobia, were more common in individuals with a history of headache [38].

No. 5. Hormonal

The association of a migraine with specific phases of the menstrual cycle is perhaps the most commonly known and accepted migraine precipitating factor. In general, there is an increase in migraine frequency in the premenstrual period, when estrogen levels drop, as well as a significant decrease in migraine during pregnancy when estrogen levels are high. An association has been noted by an average of ~50 % of women in across multiple trials [2–8, 12, 13•, 14, 15, 19•, 22, 23].

No. 6. Sleep

Disturbances or changes in sleep patterns is also among the most frequently cited migraine trigger factors [39]. The terminology used to describe the association has varied. Terms such as "sleep disturbance" [10, 12, 19•, 25•], "sleep deprivation"[23, 20, 17•, 22], "lack of sleep" [8, 24, 26] are a few of the more common descriptions of the association between sleep and migraine.

No. 7. Weather

Weather changes represent another type of migraine precipitating factor for which a wide variety of terminology has been used. Terms such as "weather changes" are most commonly associated with migraine although "strong winds" (which are indicative of a weather change) has also been associated. For example, the Chinook winds in Canada have been associated with an odds ratio of 1.19 for the onset of migraine [40]. However, only 27 % of men and 20 % of women were found to be sensitive to the effects of the winds. This is an excellent example of a common observation: migraine precipitating factors may affect only subgroups of migraineurs.

No. 8. Visual

A variety of visual stimuli have been associated with the onset of a migraine attack. Visual stimuli may produce discomfort and pain in migraineurs. The terms "lights" and "glare" are the most frequently cited factors [5, 8, 13•, 12, 21, 23]. However, a variety of other visual factors that precipitate or aggravate migraine have also been cited, most of which relate to flickering lights or contrasting patterns (eg, road stripes) [41].

No. 9. Olfactory

Certain odors that are perceived as aversive are reported commonly as migraine trigger factors. In general, these odors tend to be generated by organic compounds such as perfumes, nail polish, paint, gasoline, and cleaning products [26, 42]. Prolonged exposure to these olfactory stimuli should be easy to avoid for most migraineurs.

No. 10. Alcohol

The use of alcoholic beverages has long been associated with migraine. However, the current literature review suggests that this association is somewhat less than expected. It is ranked as the 10th most common migraine precipitating factor and has been reported by an average of only 27 % of migraineurs (n= 3695). It is possible that alcohol, per se, does not induce migraine but that only certain types of alcohol may be associated with migraine (such as red wine [43]).

Additional Factors

A number of additional precipitating factors have been identified but all of them failed to make the "Top 10 List". For example, physical activity in the form of exercise, exertion, and/or straining is cited by approximately 25 % of migraineurs as a precipitating factor. "Foods" are cited as a migraine trigger by approximately 20 % of migraineurs, with chocolate

being the most frequently cited type of food trigger. Numerous other factors have been cited but none that have been reported in multiple populations at an overall incidence average of greater than 20 %.

Conclusions

Migraine is a clinical syndrome that has been shown consistently to be strongly associated with a number of precipitating or trigger factors. These associations have been reported globally and across all age groups. Stress is the most frequently identified factor, with fatigue being only slightly less frequent. In addition, sensory stimuli such as flickering lights, bright sunshine, noise, and strong organic odors are perceived as potential migraine triggers. Alterations in the patterns of daily life (such as missing meals, sleep disturbances, hormonal fluctuations) are often cited frequently in association with migraine.

The common link between all of the identified trigger factors appears to be an intrinsic difficulty in adapting to internal and external environmental changes. In particular, a unifying theme amongst the various factors is an intrinsic difficulty in dealing with a decrease in certain stimuli: estrogen, barometric pressure, food intake, sleep, and stress. The scientific basis of these associations remains an interesting area of speculation but without a clear causal basis [34].

Of major clinical relevance is the obvious conclusion that migraineurs should attempt to avoid all stimuli that might be associated with their headaches. Clearly, this advice is far easier said than done for a variety of reasons. First, many of the known precipitating factors are essentially unavoidable (eg, hormonal changes, weather changes). Second, factors such as stress and fatigue are not amenable to easy avoidance.

Third, factors such as missing a meal appear to be easy to avoid yet the migraineur must be aware of the skipped meal, as well as have a handy source of nutrition available at all times. In the setting of stress and fatigue, avoidance of trigger factors becomes even less achievable for most migraineurs.

Moreover, the reality of current clinical medical practice is that few providers have the time or resources available to identify and manage the potential trigger factors for each of their patients. Since only a few clinical trials have tested the hypothesis that avoidance of trigger factors will decease headache frequency [43], the impetus to focus on this area of migraine management is less than might be expected. Indeed, a comprehensive assessment and active management of trigger factors in migraineurs has never been reported.

Nonetheless, the list of potential management approaches to migraine trigger factors is extensive. These nonpharmacologic therapies include meditation, biofeedback, mindfulness-based stress reduction, acupuncture, exercise, dietary management, sleep optimization, use of sunglasses, etc. The potential clinical utility of these techniques has been suggested, yet the data to support their widespread use remains minimal.

Stress and fatigue are excellent examples of the need to personalize migraine management options. More than 60 years ago, Dr. John Graham hypothesized that "migraine is an inherited disorder occurring in people who have both an undue tendency to seek stress and at the same time a deficiency in their physiological adaptation to stress" [28]. This hypothesis is certainly consistent with the results of the current systematic review. However, the observations made by Graham continue to illustrate the challenges that have yet to be overcome.

For example, Graham noted that common fatigue factors in migraineurs included "extra guests, prolonged close work, crowds, prolonged responsibility, confusion, hurry, shopping, over-crowded schedule, driving, physical work, worry" [28]. Clearly these fatigue factors all remain today and may even be worse than in the mid-20th century. Also, it is likely that Dr. Graham had far more time available to spend with each of his patients, compared with current healthcare providers who have neither the time nor expertise, in general, to evaluate and manage the perceived stresses of daily life.

If successful migraine trigger factor management is to become a viable option for migraineurs, the challenge moving forward will be to find a way to assist migraineurs in identifying, understanding and managing their precipitating factors. This process will likely need to be highly personalized, as the sensitivity to multiple precipitating factors is known to vary widely between migraineurs. How can management advice be transmitted to migraineurs on a day to day basis? How can the effectiveness of different therapeutic interventions be assessed? How can migraineurs be persuaded to take responsibility for the daily management of their condition? There are no simple answers to these questions, as evidenced by the near lack of effective intervention techniques for trigger factors that have been well known for more than 100 years.

The opportunity moving forward, therefore, will be to develop personalized management programs that can identify interventions that significantly decrease the frequency, duration and/or severity of migraine attacks. The development of such personalized intervention, however, will have to be both time and cost effective. The means by which they are developed will also have to be acceptable to both the migraineurs and practitioners. At present, the current healthcare system in the United States does not seem capable of developing personalized migraine management programs that focus on the identification and management of precipitating factors.

However, if a successful personalized migraine management program were to be developed, the net clinical benefit of this approach would significantly decrease the morbidity of migraine over the lifetime of an individual. Therefore, the

challenges of personalized migraine trigger factor management are significant, but the potential benefits are much greater. Novel interventional solutions are likely to be needed if the ability to manage migraine trigger factors is to become a reality.

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Compliance with Ethics Guidelines

Conflict of Interest Stephen J. Peroutka declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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