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Migraine and Olfactory Stimuli

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Abstract Migraine patients often report intolerance to odours. Migraineurs report odours may trigger attacks, that they experience osmophobia during attacks, and olfactory hypersensitivity between attacks. In this paper we discuss olfactory mechanisms in migraine. We also present data from a pilot questionnaire study in a group of young women diagnosed with migraine. The study results confirm that hypersensitivity to odour is a common feature in women with migraine. Migraine pathophysiology likely explains this particular vulnerability. We discuss these pathophysiologic mechanisms and hypotheses relating odour intolerances and migraine.

Keywords Migraine · Olfaction · Migraine triggers · Osmophobia

Introduction

Migraine is a common primary headache disorder with a one-year period prevalence in Sweden of 17% in women and about 10% in men [1]. In preschool children the prevalence of migraine varies from 0% to 7% and increases successively with age. The various subtypes of migraine are defined by the International Headache Classification ICDH-2 [2]. Triggers or provokers are factors that alone or in combination may induce migraine attacks in susceptible individuals. They precede the attack usually by less than 48 h. Triggers may vary between individuals and the presence of a trigger does not always cause an attack in the same person. Individuals do not identify a trigger in all attacks. Two-thirds of patients with migraine report one or more triggering factors. Triggers for attacks may vary widely. Migraineurs report certain foods, fasting, alcohol, menstruation, physical exercise, emotional stress, sleep disturbances, weather changes and sensory stimuli to provoke attacks. Triggers are more common in migraine without aura (MO) than in migraine with aura (MA) [3]. Migraine patients often report intolerance to smell as a trigger of attacks. Osmophobia or aversion to odours also occurs during attacks. Olfactory hypersensitivity (OHS), a general sensitivity to odours, can occur between attacks.

Three different systems process odourous stimuli. These are the olfactory, trigeminal, and pheromone systems [4]. Whilst all three systems have their origin in the nasal mucosa, the brain regions conveying the respective odorous signals are entirely different. The amygdala, the piriform cortex, the anterior insular and anterior cingulate cortex, the orbitofrontal cortex, and the ventromedial and the anterior thalamic nuclei process the perception of pure olfactory odours (signals transduced by the olfactory nerve) [4–7]. Monorhinally or birhinally presented odours involve processing in both hemispheres, with some right-sided predominance [8]. The olfactory as well as the trigeminal nerve mediate the majority of bimodal environmental odours and their signals [9]. Imaging studies show that smelling of trigeminal odours, such as acetone, activates the anterior and central insula/claustrum, the primary somatosensory cortex corresponding to the face area, and the posterior portion of anterior cingulate [9]. Interestingly, painful stimuli also activate these regions.

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For example, trigeminal stimulation by acetone activates their engagement and explains the burning sensation associated with exposure to this odorant. The third type of odorants consists of pheromones. They seem to primarily engage the hypothalamic networks [10]. No investigations on a pheromone-migraine relationship exist.

Olfaction and Migraine

Once having started, migraine is a life-long disorder with intermittent clinical attacks and often no apparent symptoms between the attacks. Population based twin studies have shown that the disposition for migraine is about 50% genetic and 50% environmental [11]. Thus, from time to time certain triggers elicit migraine attacks in persons with specific vulnerability. Evidence exists linking the aura symptoms to cortical spreading depression (CSD) [12] and the headache to trigemino-vascular activation [13]. The mechanisms initiating and coupling these phenomena and the role of trigger factors are largely unknown.

An hypothesis of general, interictal hyperexcitability also exists as a part of migraine pathophysiology [14]. Electrophysiological studies demonstrate altered thresholds and lack of habituation to different stimuli, such as visual and auditory stimuli, between migraine attacks [15]. Moreover, measurements of quantitative thresholds as well as questionnaires demonstrate increased sensitivity to light and sound in migraine patients, both during and between attacks [16, 17].

Descriptions of the association between osmophobia and migraine attacks exist from as early as the 2nd century [18]. Osmophobia is an unpleasant odour perception of a scent that normally is considered pleasant. To this day, limited literature exists on the topic. Thus, there is incomplete understanding of how olfactory stimuli trigger migraine, as well as, osmophobia during migraine attacks. An hypothesis suggests that triggers induce CSD in a pre-existing hyper-excitable or under-inhibited cortex of a migraine brain, initiating the process of pain generation [19]. Alternatively, the triggers could act at the level of trigeminal nuclear complex (TNC) in the brain stem. The TNC gates the ‘competing’ incoming trigeminal pain impulses with descending inhibitory signals from brain stem pain modulatory neurons, to get entry into the central nervous system [19]. If correct, descending fibres from the cortex carrying sensation of the triggers induce migraine by inhibiting this ‘gate’ mechanism at TNC. Odour as a trigger is also specific for migraine.

Odour as a Trigger of Migraine Attacks

Studies have investigated odour as a trigger of migraine attacks. One Ethiopian rural community study interviewed 15,500 subjects with different primary headache types. Migraine patients reported odour to be a trigger factor for 70% of migraine attacks [20]. MA was rare in this population. Fukui et al interviewed 200 consecutive migraine patients about trigger factors for migraine attacks. 36.5% of the patients reported odour as a trigger [21]. Kelman investigated 1,750 migraine patients with respect to trigger factors [22]. In this large study group 75.9% reported triggers, 43.7% of the patients reported perfume or odour as a trigger. Interestingly, results from this study indicated an association between triggers and severity. Attacks with triggers were more florid than attacks without identified triggers. Comparisons between episodic and chronic migraine showed that odour/perfume triggers were more common in chronic migraine. There was no significant difference between women and men with respect to odour triggers.

A very recent investigation of 172 US soldiers with headache revealed that 132 (77%) of them had migraine (21 subjects had MA) [23]. The most frequent trigger for headache was environmental factors (74%). There was no specific information on which type of environmental factors was the most frequent trigger. In an investigation of 200 children in India, aged 7–15 years, a frequent trigger for migraine attacks was smoke; 41% reported sensitivity to traffic exhaust fumes and 3.5% to cigarette smoke in the retrospective part of the study [24]. Osmophobia also seems to be very specific for migraine.

Osmophobia During Migraine Attacks

Blau and Solomon described in 1985 that osmophobia was present in about 50% of migraine patients [25]. A Norwegian study compared hypersensitivity to odours during TTH and migraine. Thirteen % in TTH compared to 46% in migraine experienced osmophobia [26]. In an Italian study of 1,005 headache patients 297/677 43.9% of patients with MO and 50/130 38.5% of patients with MA reported osmophobia whereas none of the patients with tension-type headache (TTH) suffered from osmophobia during headache attacks [18]. Patients with two or more forms of primary headache were excluded. None of the 198 patients (0%) of the TTH patients suffered this symptom [18]. Most frequently offending odours were scents (63.9%), food (55.2%) and cigarette smoke (54.8%). The authors suggested that osmophobia appears structurally integrated into the migraine history of the patient, a peculiar symptom favouring the diagnosis of migraine in the differential diagnosis with TTH. A study from Latin America involved 12 cities in five countries. Osmophobia was present in about 48% of the patients [27].

Osmophobia is also seen in children and adolescents. Raieli et al. visited 96 children with headache, aged 6–18 years, and classified migraine in 57% of these patients. The presence of osmophobia in migraine patients was 20%

[28]. Another study of osmophobia used a semistructured questionnaire in 275 juvenile headache sufferers with either migraine or TTH [29]. The prevalence of osmophobia during migraine attacks was 18.5%, (25.1% in MA) vs. 8.3% in TTH. Furthermore, in this study, osmophobia showed more specificity than phonophobia or photophobia in the differential diagnosis between migraine and TTH. Diagnosing migraine can be difficult in youngsters. Indeed, the authors discuss that some of the children with TTH could develop migraine later in life. They emphasize that these might be the subjects diagnosed as TTH with osmophobia. Such data will help determine if osmophobia is sufficiently specific for use as a migraine diagnostic tool. Less specific is interictal olfactory hypersensitivity.

Interictal Olfactory Hypersensitivity-OHS

Olfactory hypersensitivity (OHS) has been observed between attacks in migraineurs [26]. Olfactory hypersensitivity is the subjective perception of distress upon exposure to odours in concentrations perceived in the vast majority of the population as neutral or pleasant and do not cause any distress. Demarqay et al evaluated OHS between attacks in 74 migraine patients and 30 controls [30]. Twenty-six patients (35.2%) but none of the control subjects reported an interictal OHS ($P<0.001$). Furthermore, patients with OHS experienced a greater attack frequency, a higher number of odour-induced migraines and visual hypersensitivity when compared to other patients. No correlations existed between disease duration, age, gender, auditory hypersensitivity and OHS. In this study, OHS between attacks correlated with odour-triggered migraine.

Olfaction in Migraine—Experimental Studies

Only a few studies exist on olfactory thresholds in migraineurs. The results are discordant. Hirsch investigated 67consecutive migraine patients with pyridine odour threshold tests [31]. Surprisingly, in this study 12 (18%) were hyposmic or even anosmic. Snyder and Drummond investigated olfactory thresholds for acetone and vanillin in 20 migraine sufferers and 21 controls. Migraineurs had lower thresholds for vanillin and unmodified thresholds for acetone [32]. Acetone activates the trigeminal system whereas vanillin activates the olfactory system. Grosser et al. investigated trigeminal and olfactory event-related cortical potentials (ERPs) in 19 migraineurs and 19 controls [33]. They used CO_2 for specific stimulation of the trigeminal system and H_2S for olfactory stimulation. Migraineurs exhibited greater responses to trigeminal stimulation as indicated by larger ERP amplitudes. The authors interpreted this as an indication of trigeminal hyperexcitability in migraineurs.

Recently, Demarquay et al investigated 11 migraineurs with OHS and 12 controls in a $H_2{}^{15}O$-positron emission tomography (PET) study, both during olfactory stimulation and in odourless condition [34]. During both olfactory and non-olfactory conditions, a higher rCBF in the left piriform cortex and antero-superior temporal gyrus occurred in migraineurs compared to controls. This occurred also in the left temporal pole, the left inferior and right middle frontal gyri, in the temporo-parietal regions, posterior cingulate gyrus and right locus coeruleus. The authors speculate that the observed changes in rCBF either cause or are a consequence of odour-triggered migraines and interictal OHS. They speculate further that the altered pattern during olfactory stimulation in migraineurs reflects an altered cerebrovascular response to olfactory stimulation due to the migraine disease or an abnormal top–down regulation related to OHS. The latter hypothesis is intriguing given that expected distress should result in avoidance as seen in multiple chemical sensitivity syndrome (MCS). In contrast to this study, MCS studies reveal decreased rCBF compared to controls with an hypothesized elevated top–down inhibition [35]. We performed a study to further assess the issues we have discussed.

Olfactory Factors in Young Women with Migraine A Questionaire Study

To investigate patterns of odour induced migraine we performed a study in a group of women with migraine. They were part of a larger study aiming to investigate olfaction and olfactory mechanisms. The ultimate aim was to investigate olfactory mechanisms in these women with imaging techniques.

Materials and Methods

We chose for this study a consecutive series of women aged 22–36 that visited our department during 2007 and received a migraine diagnosis according to IHS Classification [2]. We contacted all these subjects with the specific aim to identify migraineurs with odour trigger induced migraine attacks. They received a questionnaire by letter. Fifty-two of 95 subjects did not respond to the first letter and received a 2nd letter and questionnaire. In all, 60 subjects responded to the questionnaire and participated in the study.

Statistics

Most data are descriptive information, absolute numbers and percentage. For comparisons we used Fischers exact test (GraphPad Instat). We carried out age comparisons

using unpaired *t*-test. The significance level was <0.05 for all the comparisons.

Results

Demographics

The mean age of the women was 30.4 years (range 20–36 years, $n=60$). The mean duration of disease was 15.6 years. Twenty-nine subjects got their headache before the age of 15 years, and 31 subjects after the age of 15 years. Nine subjects were smokers (15%), 51 were non-smokers. Four subjects smoked more than 16 cigarettes per day. Fourteen of the non-smokers were former smokers. Forty subjects had MO (67%) and 20 subjects had MA (33%).

Location and Intensity of Pain

Forty-five of the subjects (75%) described their prime location of migraine pain in the eye region, followed by temporal region (57%) and forehead (57%). Other locations were skull, neck, upper or lower jaw. All subjects described their worst pain during an attack as at least 6 on the VAS scale, fifty seven (95%) scored their pain as VAS 8-10, and twenty-three as VAS 10 (25%).

Frequency of Attacks

The majority of subjects had migraine attacks about one to three times/month. About 1/4 of the subjects had attacks at least once/week or more often (Table 1).

Associated Symptoms

Subjects reported associated classical migraine symptoms as follows; Forty-eight (80%) had associated nausea in relation to attacks, 32 (53%) had vomiting, 56 (93%) had phonophobia and 52 (87%) had photophobia.

Table 1 Frequency of migraine attacks in 60 migraine patients

Frequency	n	%
<1/year	1	2
2 to 3/year	2	3
5 to 6/year	7	12
1/month	15	25
2 to 3/month	19	31
1/week	7	12
2 to 3/week	8	13
Almost daily	1	2

Triggering Factors

To a list of multiple choice factors/substances that could trigger headache subjects reported the following; Stress/anxiety was a trigger in 95% of the subjects, weather changes in 71.7%, smell/odour in 63 %, hormonal changes in 60%, red wine in 50%, hard liquor in 25%, chocolate in 11.7%, beer 6.7% and cheese in 3.3%. Results are also shown in Fig. 1.

Odour

Thirty-eight subjects reported odour as a triggering factor for migraine attacks. Thirteen of them had MA (34%). Twenty-two subjects reported "No" to triggering of migraine attacks by odours. The onset of the attacks for those who reported odour as trigger for migraine attacks and the time to headache pain is seen in Table 2.

Twelve subjects reported that the same odour always triggered a migraine attack and 25 subjects reported "no" to this specific question, i.e. several odours could trigger attacks. Subjects could choose pre-defined triggers in a multiple choice question. There was no trigger listed without any answer. Table 3 lists odours and the frequency of these triggers. Table 4 lists the number of odours reported by these 38 patients. Other, spontaneously reported, smells to triggered attacks were strong body odours from others such as sweat and bad breath (2), incense (1), candles with scent (1), garlic (1), mould (1), flowers with strong scent (1), horse (1), coffee (1), shower gel (1), sesame seed (1) and pineapple (1).

Osmophobia

Forty-nine subjects reported increased sensitivity to smell during migraine attacks (81.7%), 16 of these subjects (32.7%) had MA. Thus, the group with osmophobia is larger than the group reporting odour triggered attacks, i.e. 11 patients with osmophobia did not report odour as a trigger.

Avoidance

Twenty-eight of the 38 subjects with odour triggered migraine (73.7%) reported that they usually avoid specific situations with the above described smells because of the risk of triggering a migraine attack. Twenty-three subjects described avoidance behaviour due to other problems than migraine; the most frequent symptom was nausea ($n=14$).

OHS

Thirty-two subjects reported increased sensitivity to odours even between attacks. All of these subjects did also report odour as a trigger for migraine.

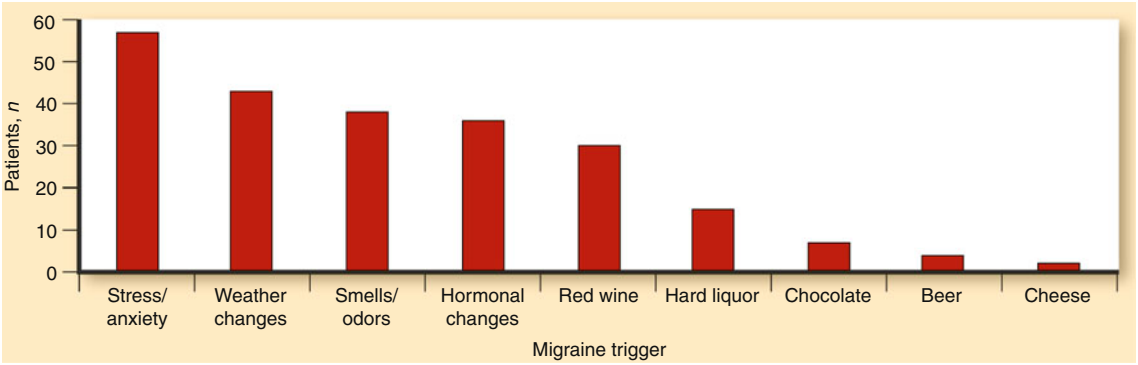

Fig. 1 Triggering factors for migraine

Comparisons Between: Subjects with Odour Triggered Migraine Attacks and Subjects with Non-Odour Triggered Migraine Attacks

Trigger Factors. Comparisons of triggers in odour triggered migraine subjects and non-odour triggered migraine subjects showed differences in weather changes (p=0.037) and chocolate (p=0.0405) with increased frequency in the olfactory sensitive patients. Results are shown in Table 5.

Frequency of Attacks. Thirty-four (89%) out of 38 subjects with odour triggered migraine attacks reported a migraine frequency of once per month or more, 24 had a frequency of two to three times/month or more frequent and 12 had a frequency of at least once/week or more often. Fifteen (68%) of 22 subjects with non-odour triggered migraine reported a migraine frequency of once per month or more, 12 had a frequency of two to three times/month or more frequent and 5 had a frequency of at least once/week or more often. The number of subjects reporting migraine at least once per month was non-significantly higher in odour triggered migraine compared with non-odour triggered migraine (p=0.08). When comparing frequency of at least once per week the result did not differ between the groups.

Health Status. Table 6 describes self-scored health status during the last month. Fourteen (37%) out of 38 subjects in the odour triggered group reported very poor or quite poor health status and 3 (14%) out of 22 subjects in the non-odour triggered migraine group reported very poor or quite poor health status (p=0.08).

OHS. Thirty-two (84%) of the subjects in the odour triggered group reported olfactory hypersensitivity between attacks. In the non-odour triggered group only three of the 22 subjects (13%) reported OHS. This difference was highly significant (p<0.0001).

Age at Onset and Duration of Disease

The mean age for disease onset in the non-odour triggered migraine group was 17.4 years and the mean age in the odour triggered migraine group was 13.7 years. This difference was significant (p=0.049). Duration of disease was 12 years in the non-odour triggered group and 16.4 years in the odour triggered migraine group, p=0.036.

Discussion

Odour is of importance in migraine in several ways—as a trigger of attacks as well as intolerance to certain odours

Table 2 Time (seconds to minutes) to headache after odour exposure

Time	n
Instantly	1
After a few seconds	5
After 1–5 min	10
After 6–10 min	4
After 11–20 min	6
After more than 20 min	5
Multiple answers[a]	3
No answer	4

[a] One patient reported both instantly and to a few seconds, 1 patient reported 1–10 min and one patient reported 11 to >20 min

Table 3 Odours provoking migraine attacks in young women with odour triggered migraine

Substance	n	%
Perfume	33	86.8
Car exhaust/exhaust fumes	17	44.7
Cigarette smoke	16	42.1
Detergent	10	26.3
Petrol	11	28.9
Smoke	9	23.7
Vanilla	4	10.5
Fried food	3	7.9
Grilled food	3	7.9

Table 4 Numbers of odours reported in the odour-triggered migraine group

Odours	n (total n=38)
1	8
2	6
3	13
4	8
5	3

during attacks. Osmophobia seems to be quite specific to migraine. At least in adults studies comparing intolerance to smell in migraine and TTH show specificity to migraine [18, 36].

We report here our investigation of olfactory sensitivity in a consecutive series of women with migraine referred to our neurological department. We found a high frequency of patients reported odours as triggers of migraine attacks, hypersensitivity to odours during attacks and also hypersensitivity to odours between attacks. These results are consistent with former larger studies. We found a large proportion of the patients reported avoidance behaviour due to the risk of triggering attacks, as well as because of a general hypersensitivity to odours. The initial specific aim of the study may have biased reporting of the high frequency of odour related migraine. We had informed subjects that the research involved study of olfactory mechanisms in migraine. Perhaps this information and the questionnaire motivated subjects to report odour triggered migraine. Nevertheless, we used a consecutive series of subjects from our department. If we performed an analysis on the whole series of patients and assumed that all non-respondents had non-odour triggered migraine the frequency of odour associated migraine would still be high. In this scenario, odour as a migraine trigger occurs in 38/95 (40%) and osmophobia in 49/95 (51.6%). The frequency of MA in our material was quite high, but the proportion of MA and MO were almost the same in both odour- and non-odour triggered groups as reported in previous studies.

Table 5 Comparisons of triggers in the odour triggered migraine group and non-odour triggered migraine group

Trigger	Non-odour (n=22)%		Odour (n=38) %		p-value
Stress or anxiety	21	95.4	36	94.8	1.00
Weather changes	12	54.5	31	81.6	**0.0376**
Hormonal changes	11	50	25	65.8	0.2797
Red wine	8	36.3	22	57.9	0.1799
Hard liquor	5	22.7	10	26.3	1.0000
Chocolate	0	0	7	18.4	**0.0405**
Beer	2	9.1	2	2.7	0.6194
Cheese	0	0	2	5.3	0.5277

Table 6 Self-reported health status during last month in all patients

Scored health	N=60
Very poor	3
Quite poor	13
Fair	15
Quite good	20
Very good	6
Multiple answers/no answer[a]	3

[a] One subject reported both quite poor and fair (odour triggered migraine patient) another subject reported both fair and quite good (non-odour triggered patient) and there was no answer for one subject

Olfactory sensitive migraine patients score their health status somewhat lower than non odour triggered migraine patients, although the difference was non-significant in this material. Whether migraine or a more negatively tuned perception in general explains this is unclear. In the future follow-up of these two populations of migraine subjects we will add evaluation of personality traits as well as scorings of depression. A substantial proportion of the patients with migraine in our study also reported avoidance to odours due to other problems than migraine. That the most frequently reported symptom in this group was nausea raises the question of a possible overlap between migraine and the self reported syndrome multiple chemical sensitivity [37]. Several similarities can be noted for migraine and MCS; e.g. an indication of autonomic nervoud dysfunction [38, 39]. These observations warrant further investigations.

Many patients were very specific about odour triggers in migraine. Many patients also reported avoidance to certain odours, even between migraine attacks, which lead to limitations in their everyday life. Another feature of this cohort was a lower age at onset of migraine. This raises the question as to whether odour related symptoms could evolve gradually or if they characterize a particular subtype of migraine. Is olfactory sensitivity in migraine sufferers a negative prognostic factor? This needs attention in future studies. Does brain excitability differ between odour and non odour triggered migraine? Could brain excitability induce CSD or open the “gate” at the TNC at lower thresholds? Such scenarios are congruent with observations of significant and persistent drops in pain perception thresholds together with onset of nausea following stimulation with light [40, 41]. This indicates that various forms of sensory stimulation may interact with the trigeminal system.

We found that weather changes and chocolate were more common triggers in odour triggered migraine subjects. According to self-reported surveys weather can trigger migraine headaches. A Canadian study could not find any association between weather changes and emergency room visits in a case-crossover design of 4,039 visits for

migraines [42]. These emergency room visits likely represent a highly selective group of migraine patients. Chocolate is often a migraine trigger in reports. However, in a review of intolerance to dietary biogenic amines in headache, migraine and urticaria, two oral provocation (conclusive) studies found no effect of tyramine on migraine. One conclusive study demonstrated no relationship between the amount of phenylethylamine in chocolate and headache attacks in individuals with headache [43]. Still the results from our study are interesting findings, but the sample size is small and the present observations need further confirmation.

A population based study of 1,387 individuals from Sweden reported general odour intolerance in one third of the subjects. Intolerance was twice as common in women than in men [44]. The great majority of subjects complained of symptoms from the upper respiratory tract and headaches. Whether migraine is over-represented among odour intolerant individuals is unknown. Furthermore, the data about possible sex-differences is very sparse. Kelman [22] did not find any difference between men and women with respect to frequency of odour as a trigger for migraine. More extensive investigations are, however, necessary, especially when considering that a higher prevalence of odour intolerance in women might in part explain why women are more prone to suffer from migraine. Although men and women process olfactory stimuli in a similar manner [45] further study is of interest in the physiology of olfaction in women and men with and without odour triggered migraine.

Can the basic physiology of olfaction explain the olfactory hypersensitivity in migraine? Such hypersensitivity has been reported in relation to both trigeminal and olfactory odorants [32]. The majority of odorous compounds activate the amygdala. One possibility is that amygdala activation renders patients susceptible to odours during migraine attacks. This is congruent with the fact that stress triggers migraine and the amygdala in the primary relay node for psychosocial stress stimuli [46].

Spreading depression in migraine involves the amygdala and long term potentiation of its lateral nuclei (involved in olfaction). One possibility is that repetitive migraine attacks eventually lead to amygdala hyperexcitability and odour-related symptoms. That disease duration seems longer in migraine patients with olfactory hypersensitivity supports this notion. On the other hand, osmophobia in children and adolescents is independent of numbers of attacks and duration of disease. Alternatively, or concurrently, this category of patients could have an impaired connectivity between the medial prefrontal cortex and amygdala, leading to impaired top–down regulation. If true, an altered sensitivity of the amygdala, independent of the exact cause, should have other clinical features, such as anxiety, fear, emotional imbalance, which all need independent evaluation. Specific comparisons between odour sensitive and insensitive migraineurs with respect to personality traits, depression and anxiety scores, as well as fear and avoidance reactions need evaluation. Such studies may provide not only new insights about the physiology of migraine, but also about new treatment strategies in patients with odour triggered attacks.

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