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Olfactory function in migraine both during and between attacks.

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Introduction: Persons with migraine often report being osmophobic, both during and between acute migraine attacks. It is not clear, however, whether such reports are associated with true hypersensitivity to odors, as measured by psychophysical testing. In this case-control study we quantitatively assessed olfactory identification ability, which correlates with threshold tests of olfactory sensitivity, in patients with migraine at baseline (no headache), during migraine episodes, and after a treated attack and compared the test scores to those of matched control subjects.

Methods: Fifty episodic migraine subjects and 50 and sex- and age-matched controls without headache were tested. All completed University of Pennsylvania Smell Identification Test (UPSIT), a standardized and well-validated olfactory test.

Results: At baseline, the UPSIT scores did not differ significantly between the migraine and control study groups (median paired score difference: -1, $p = 0.18$). During migraine attacks, a minority of migraine subjects (8 of 42) developed microsmia (i.e., lower test scores by at least 4 points), suggesting that, as compared to their matched controls, olfactory acuity was somewhat impaired during migraine attacks ($p = 0.02$). This difference was less pronounced and not statistically significant after a successfully treated attack ($p = 0.15$).

Discussion:

Persons with episodic migraine were found to have similar olfactory function as age- and sex-matched controls, but a minority exhibit microsmia or hyposmia during acute attacks. The cause of this dysfunction is unknown, but could relate to autonomic symptoms, limbic system activation, or disorders of higher order sensory processing.

Introduction

Migraine is a complex neurologic disorder related to genetic and environmental factors consisting of headache, gastrointestinal symptoms, and multiple sensory disturbances including photophobia, phonophobia, and osmophobia in the absence of a causative secondary disorder. Hypersensitivity to sensory stimuli such as light and sound are classical diagnostic features of migraine [1], although migraineurs are also more likely to be bothered by odors than other persons. In fact, osmophobia may be a more specific symptom in differentiating migraine from other headache disorders [2,3], and including it as a diagnostic criterion may increase the sensitivity for accurately diagnosing migraine in populations where photophobia is less common [4]. Osmophobia is most prominent during acute migraine attacks, but discomfort may persist interictally in a subset of migraineurs [5].

Olfactory impairment is a common symptom found in a number of neurologic disorders, such as Parkinson disease, schizophrenia and myasthenia gravis, possibly due to degeneration and/or dysmodulation of dopaminergic, serotonergic and cholinergic systems [6]. Multiple studies have confirmed that migraine subjects are bothered by odors, especially noxious stimuli [7,8], and that odors may precipitate attacks. One H_2O-PET study showed abnormal cerebral activation patterns during olfactory stimulation in migraineurs with olfactory hypersensitivity [9]. The ability of persons with migraine to detect and discriminate odors, as determined by standardized olfactory testing, is less clear. In one study, a large number of migraine subjects had poor olfactory acuity [10], as measured by olfactory thresholds, and in another migraineurs had increased odor detection [11]. A more recent study of episodic migraine subject found that their

olfactory acuity was normal [5]. The effect of a migraine attack on olfactory ability during and after treated attacks is also unclear.

The objective of this study was to examine olfactory acuity in episodic migraine subjects as compared with age and sex-matched controls, using a reliable and well-validated test of olfaction. We also evaluated the effect of migraine on olfaction – both during and after a treated attack.

Methods

Formal approval of this study was obtained from the Institutional Review Board at Thomas Jefferson University. Subjects ranging in age from 18 to 65 were recruited from our clinic and the surrounding community who were diagnosed with episodic migraine, as defined by the International Classification of Headache disorders 2nd edition. We excluded subjects or controls with a history of significant headache trauma, nasal or sinus disease, neurologic disorders such as Parkinson disease, dementia, or multiple sclerosis. Persons who used medications that could influence smell function, such as anticonvulsants or opioids, barbiturates or neuroleptics – drugs often used to treat attacks – were excluded from consideration. Subjects were allowed to use simple or combination analgesics such as non-steroidal anti-inflammatory medications, including those with caffeine, and migraine-specific medications such as triptans. To ensure that we could determine the effect of a treated migraine on olfaction, we also excluded subjects which generally could not successfully treat migraines with medication. Due to the effect of gender and age on olfactory function [13], each subject was paired with a sex- and age-matched (from -2 to 2 years) control without disabling headache or migraine. For the

purposes of this study, controls were required to have a Migraine Disability Scale (MIDAS) score of zero. We did not specifically exclude persons with a family history of migraine.

During the first visit we administrated a focused questionnaire to all participants to obtain basic demographic and medical history information. We inquired as to whether odors caused them to develop headaches and whether any of five specific odors (perfume, paint, new carpet, gasoline, pesticides) were bothersome. Both the subjects and the controls completed a validated questionnaire for allodynia [14]. The initial recruitment began June 2010 and final kits were received in October 2011.

To determine olfactory function, all subjects completed the University of Pennsylvania Smell Identification Test (UPSIT), a well-validated and standardized 40-item forced choice olfactory test that is useful in detecting subtle olfactory deficits (12, 13). This test is more reliable, yet highly correlated, with traditional olfactory threshold tests. [15] There are a total of 40 odorants, with four booklets each containing ten odorants. The stimuli are embedded in “scratch and sniff” microcapsules at the bottom of each page. This inexpensive test is widely used clinically, and has been translated into 14 foreign languages.

The UPSIT was administered at the time of their first visit, when the subjects received instructions on how to perform the test at home. After the initial visit, subjects took the UPSIT again at home or in the office during an acute migraine attack and completed a short clinical survey about their symptoms during the attacks, including severity, location, and aura, if present. They also completed the UPSIT a third time after a typical migraine with successful treatment (either mild or no pain), at least 2 hours after the

attack. Based on previous studies using UPSIT to determine olfaction in various neurodegenerative disorders, and assuming a true difference between the mean UPSIT scores of 3 units, we determined that with 50 subjects there would be a 93% probability that the study will detect a statistically significant difference at a two-sided 5 percent significance level. We instructed 25 subjects to take the UPSIT at home during migraine, and to complete the final UPSIT after a treated attack. The other 25 subjects took the UPSIT after a treated attack first, then the final UPSIT during migraine. Controls repeated the UPSIT after the initial visit at least 2 weeks after the initial visit, and again at least another 2 weeks later. If subjects or controls completed the UPSIT at home, it was returned to our office in person or by mail.

Data from the migraine patients and age/sex matched controls were analyzed to determine the association between migraine and olfactory acuity. The baseline characteristics and scores between matched controls and migraine patients were paired and then compared. The paired data were skewed for UPSIT scores and other variables. To address this and test for significant differences between the migraine and control groups while accounting for the correlation within matched pairs, we applied the Wilcoxon Signed-Rank test of match-paired differences for continuous variables and McNemar's test of discordant match-paired 2-level responses (or the more general Stuart-Maxwell test of discordant match-paired multi-level responses) for categorical variables. For all tests, a significance level of $\alpha = 0.05$ was used. We accounted for missing data (subjects or controls who didn't return UPSIT kits) by comparing data with their matched pairs.

Results

Both the migraine and the control groups included 50 subjects who are matched by age and sex. (Table 1.) There were no significant differences between the groups with respect to distributions of age, sex, height, weight or BMI, although more subjects were white race (76% vs. 66% white in migraineurs vs. controls, $p = 0.36$). Allodynia was highly associated with migraine (92% subjects vs. 14% controls, $p < 0.01$). Of the migraine subjects, about 51% reported aura with visual aura being the most common and the majority (70%) experienced non-migraine headaches as well (Table 2). The majority of subjects (36/50 72%) reported a history of migraine of at least 10 years.

Of those subjects who experience migraines, 32 (65%) indicated that they found odors to be bothersome, while only 7 (15%) of the controls did, demonstrating a significant association between group (migraine or control) and sensitivity to odors (Table 1). In terms of the matched pairs, 18 of 45 (40%) had responses which agreed while 27 (60%) had differing responses. Of those 27 responses, 25 (93%) were migraine subjects who found odors bothersome and controls who did not. This discordance strongly indicated a significant association between migraine and sensitivity to odors ($p <0.01$).

The two groups had similar olfactory acuity at baseline, but the distribution of the match-paired differences was skewed in the positive direction (Figure 1). At the time of the initial baseline visit, migraine subjects had a median UPSIT score of 36 (between attacks), while the controls had a median score of 37. The median match-paired difference of -1 did not differ significantly from zero ($p = 0.18$). Forty-two subjects completed the UPSIT during acute migraine and 40 completed the UPSIT after a treated migraine. Of the age-sex matched controls, 3 completed the UPSIT once after the initial visit and the other 47 completed both follow-up tests.

Although the majority of migraine subjects had similar scores during migraine as in the initial visit (+/- 2 points), a minority had clinically significant decreases in acuity with 8 (19%) scoring 4 or more points worse during acute migraine. Regardless, during their migraine attacks, the median UPSIT score for migraine subjects was still 36 as compared to 36 for controls at their second test; however, the median match-paired difference of -1 was statistically significant ($p = 0.02$). This suggested that olfactory acuity during migraine was significantly impaired. After being treated, the median UPSIT of the migraineurs was again 36 compared to the median score of 37 among their matched controls at their third test. The median paired difference of -1 was not significantly different from zero ($p = 0.15$). The histograms in Figure 2 present a visual distributional summary of changes in UPSIT test scores from baseline during attack (panel A.) and after successful treatment of attack (panel B.) for the migraine group.

Considering a difference of three or more points on UPSIT to be clinically significant, thirteen migraine subjects had a decrease in UPSIT scores between baseline and during attacks of 3 points or greater, compared with 3 subjects after a treated attack. One patient had an increase in UPSIT of 4 points after a treated migraine, and no subject had an increase of greater than 3 points during migraine. Of the thirteen patients with clinically significantly lower scores during migraine, 12 reported allodynia during migraine, 8 had migraine with aura, 10 were female, and 9 reported a history of migraine greater than 10 years.

Discussion

The results of this study suggest that the majority of patients with episodic migraine have normal olfactory function. This agrees with the studies of Saisu et al [5] and Hirsch [10]

and supports the idea that migraine differs from neurodegenerative disorders such as Parkinson disease. However, a subgroup of our migraine subjects appeared to have experienced impairment during acute migraine, especially before successful treatment. This finding is similar to the 1992 study of Hirsch, which predates the classification of episodic and chronic migraine, in which 18% of migraine subjects were hyposmic or anosmic based on Pyridine odor threshold testing. The clinical and demographic characteristics of our migraine subjects who had significant olfactory impairment were not significantly different than those who did not in terms of allodynia, duration of disease, sex or age, although there was a trend for greater impairment in those with aura. The effect of migraine on olfaction was relatively modest in comparison to the olfactory dysfunction of neurodegenerative disorders [16] and other neurological disorders such as myasthenia gravis [17]. In a recent study of myasthenia gravis, 27 MG subjects exhibited a robust loss of olfaction relative to27 matched controls. It is unclear if the decreased UPSIT scores in our subgroup of migraine subjects have clinical relevance. Our suggestion would be to test olfaction in patients with clinical symptoms of olfactory difficulties, especially those with a history of previous serious viral illness, head trauma or neurodegenerative disease. It should be noted that the subjects in this study were generally fairly healthy with treatable migraine attacks. In a separate study, we plan to examine subjects with chronic migraine including those without significant headache-free time.

Our results confirmed several previous studies which confirm that persons with migraine report experiencing hypersensitivity to bothersome odors. The UPSIT is not a measure of osmophobia , is designed to be well-tolerated and did not trigger migraine attacks in this

study. However, no subject in our study exhibited UPSIT scores that would suggest increased olfactory sensitivity during migraine (with an increase of more than 3 points on UPSIT). Although some persons with migraine may be more sensitive to odors even outside of attacks, our findings are in disaccord with those of Snyder and Drummond [11] who found migraineurs to have hyperosmia. However, their test procedures differed from ours. They studied 20 migraine subjects and 21 controls using odor detection thresholds for acetone and vanillin. Acetone is a strong trigeminal stimulant and therefore is not a good measure of olfaction, per se. [18] Our findings are in agreement with the general notion that true hyperosmia is rare, regardless of the diseases involved. [19]. Taken together, olfactory hypersensitivity is more likely a perceptual distortion as opposed to one of increased threshold sensory function both interictally and during acute attacks. Persons with a sense of hyperacute odor detection usually do not have superior olfactory abilities. Pregnancy, for example, is not associated with hyperosmia. [20] Multiple factors influence olfaction including anatomic, genetic, and sensory processing differences. Changes in autonomic function are one possible cause of worsening olfaction during acute migraine. The sphenopalantine ganglion supplies autonomic projections to the nose. Increases in parasympathetic tone, which can manifest as tearing, swelling or congestion during migraine, is associated with engorgement of nasal turbinates [21]. Fluctuations in nasal engorgement are an overall indicator of autonomic tone [22] and correlate with measures such as rapid-eye movement sleep patterns [23] and cognitive abilities [24]. Allergic disorders are more common in persons with migraine and immunotherapy may be helpful to reduce migraine severity in younger patients [25]. It is

possible that simple changes in autonomic tone during migraine could affect performance on the UPSIT.

A more interesting potential explanation is that migraine affects areas in the brain which cause difficulty in perceiving odors when impaired. Pain-sensitive neurons from the thalamus project widely to multiple cortical regions, including the primary somatosensory cortex, the parietal association cortex, and the primary and secondary visual cortices. This suggests a mechanism for cortical dysfunction in migraine other than cortical spreading depression [26]. A recent functional MRI study found deficient habituation in the trigemino-nociceptive pathway, but not in the olfactory system suggesting the possibility that a thalamo-cortical network may be an important aspect of migraine as opposed to a single neuronal modulator. [27] Migraine is associated with activation of the amygdala and limbic system during acute attacks in a way similar to other pain disorders. The amygdala is highly involved in both odor intensity [28] and odor memory [29]. Since activation of the limbic system is a hallmark of pain disorders, it is possible that these changes may not be unique to migraine and olfactory abilities in other persons with episodic pain disorders remains unclear. A minority of persons with migraine can experience olfactory hallucinations before or during headache, which usually involves a very specific and bothersome odor [30].

Olfactory problems in neurodegenerative diseases involve injury to dopaminergic, cholinergic, serotonergic, and noradrenergic systems, microglial activation and inflammation [6]. Although our subjects generally had normal olfaction at baseline, the development of hyposmia during attacks may indicate abnormal brain functioning, perhaps at the level of the basal ganglia or higher cortical structures [31]. Many common

migraine premonitory symptoms, such as hunger or yawning, are also thought to be related to dopamine and linked to the hypothalamus [32].

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Table 1. Descriptive summary of study group characteristics.

	Migraine **n = 50**	**Control** **n = 50**	**p**
Age, n (%)			0.99
<30	21 (42)	20 (40)	
30-39	12 (24)	12 (24)	
40-49	12 (24)	12 (24)	
50+	5 (10)	6 (12)	
Sex, female, n (%)	37 (74)	36 (72)	0.99
Race, n (%)			0.36
White	38 (76)	33 (66)	
Black	11 (22)	6 (12)	
Asian	1 (2)	5 (10)	
Hispanic	0 (0)	4 (8)	
Others	0 (0)	2 (4)	
Height (in.), n (%)			0.93
<66	24 (48)	24 (48)	
66-71	21 (42)	20 (40)	
72+	5 (10)	6 (12)	
Weight (lbs.), n (%)			0.98
100-149	18 (36)	19 (38)	
150-199	23 (46)	22 (44)	

200+	9 (18)	9 (18)	
BMI, n (%)			0.09
Normal (<25)	18 (36)	28 (56)	
Overweight (25-30)	21 (42)	12 (24)	
Obese (30+)	11 (22)	10 (20)	
Allodynia, n (%)	46 (92)	6 (14)	<0.01
>1 odors bothersome, n (%)	32 (65)	7 (15)	<0.01

BMI: body mass index (kg/m^2)

Table 2. Descriptive summary of migraine patient characteristics (n = 50).

Age at onset, mean ± SD	18.8 ± 10.42
Age at onset, n (%)	
<10	6 (13)
10-19	23 (48)
20-29	9 (19)
30+	10 (21)
Aura, n (%)	25 (51)
Aura Type*, n (%)	
None	26 (52)
Blind spots	1 (2)
Confused	1 (2)
Sensory	6 (12)
Visual	21 (42)
Motor	2 (4)
Non-Migraine HA, n (%)	35 (70)

SD: standard deviation; HA: headache; * Multiple choices are possible so percentages may not add up to 100.

Table 3. Summary of UPSIT scores.

	Migraine	Control	Paired Difference	p*
Interictal/Baseline, Median	36	37	-1	0.18
Min-Max	30 - 40	30 - 40	-6 - 8	
mean ± SD	36.1 ± 2.5	36.6 ± 2.6	-0.48 ± 3.04	
During Attack/2nd Test, Median	36	36	-1	0.02
Min-Max	27 - 40	25 - 40	-13 - 10	
mean ± SD	35.0 ± 3.2	35.9 ± 3.0	-1.29 ± 4.13	
After Attack/3rd Test, Median	36	37	-1	0.15
Min-Max	22-40	29-40	-5 - 10	
mean ± SD	35.6 ± 3.2	36.2 ± 2.8	-0.55 ± 3.27	

***** Wilcoxon Signed-Rank test of zero median difference (migraine minus control) in match-paired scores.

Figure 1. Difference in baseline olfactory acuity (UPSIT scores) between migraine patient and matched control pairs.

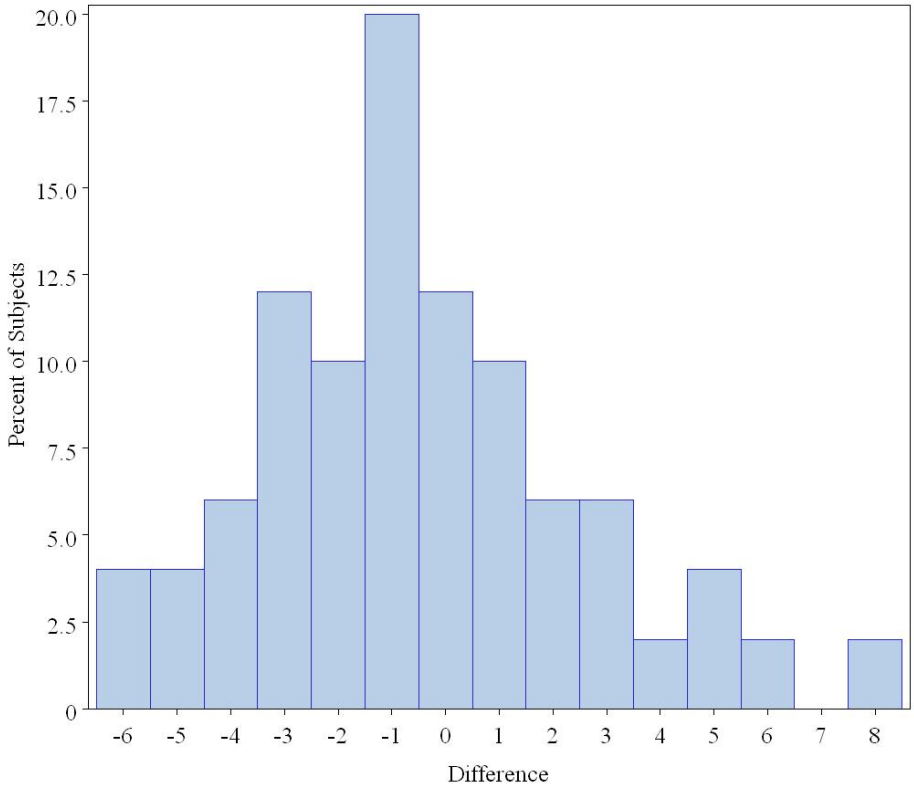
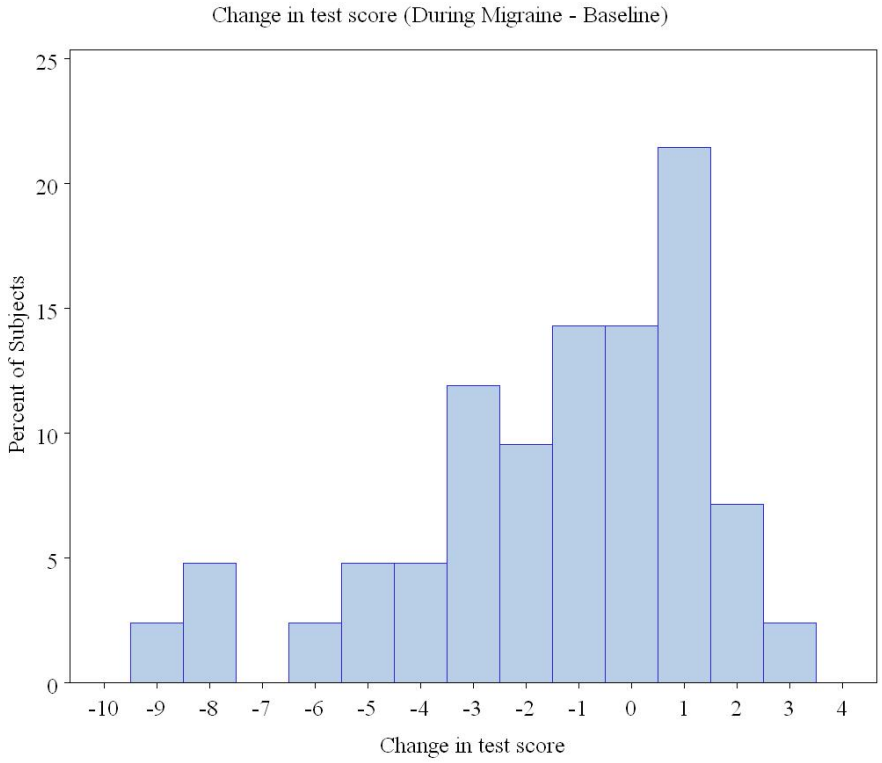


Figure 2. Histograms of changes in migraine group UPSIT test scores from baseline during migraine attack (panel A.) and after attack (panel B.).

A.



B.