Long-term Follow-up of Olfactory Loss Secondary to Head Trauma and Upper Respiratory Tract Infection

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Objective: To determine the extent to which olfactory function can improve after loss induced by head trauma or a previous upper respiratory tract infection (URI) and the time for this improvement for more effective patient counseling.

Design: Patients initially evaluated at the University of Cincinnati (Ohio) Taste and Smell Center were reevaluated for olfactory loss with the University of Pennsylvania (Philadelphia) Smell Identification Test 1 to 5 years after initial testing. Changes in score on this test were used to indicate improvement in sensory function. Subjective information on olfactory ability and olfactory symptoms was also collected.

Setting: University-based tertiary care center.

Patients and Other Participants: Forty-one patients with olfactory loss induced by head trauma (20) or previous URI (21).

Results: Seven (35%) of 20 patients with head trauma improved on the smell test by 4 points or more. Fourteen of 21 (67%) patients with a previous URI had improved scores of this magnitude or more. A statistically significant correlation was noted between the amount of improvement and length of follow-up for URI patients. Thirteen of these patients also reported improved olfactory function.

Conclusion: These findings for patients with head trauma are consistent with other reports of recovery of (or improvement in) olfactory function after trauma-induced loss. For patients with previous URI, these data indicate that improvement in olfactory function occurs, but the improvement may take several years.

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HEAD TRAUMA (HT) and previous upper respiratory tract infection (URI) are two of the most common identifiable causes of chemosensory dysfunction, especially olfactory impairment. These causes accounted for 44% of the patients presenting to the University of Cincinnati (Ohio) Taste and Smell Center with olfactory complaints between 1986 and 1990. Because a specific event preceded olfactory loss in these patients, it was possible to study the changes in olfactory ability as a function of time. Because of the effect chemosensory impairment can have on lifestyle, occupation, and quality of life, it is important to provide patients with timely and accurate information. This study was undertaken to provide concrete data on the probability of and the nature of the change in olfactory function that patients with HT and previous URI might be able to expect.

In cases of HT, the cause of olfactory loss is usually obvious; temporal contiguity between injury and loss of smell is the most important factor, although in cases of unconsciousness or incapacitation this contiguity cannot always be independently established. Radiologic information is useful, but is used in our clinic primarily to identify areas of injury. Facial or skull fractures do not need to have occurred to support a diagnosis of traumatically induced olfactory loss.[1] Additional information comes from the measurable degree of sensory loss, the absence of fluctuation in sensory experience, and the presence and timing of distorted (parosmia) or phantom (phantosmia) odor experiences. While reports vary on the exact numbers, about 5% of victims of HT experience anosmia.[1] Partial loss (hypos-

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METHODS

Patients asking to be seen at the University of Cincinnati Taste and Smell Center are sent an intake questionnaire to be filled out before their appointment. The questions relate to their complaint, ie, if it is an olfactory complaint, whether it is an increase or decrease in sensitivity, or whether they smell distorted odors or experience odors when no stimuli are present. Other questions cover medical conditions, with special attention to HT, toxic exposure, nasal allergies, medications used, and relevant antecedent events.[9,10]

Evaluation of olfactory functioning was accomplished with the UPSIT, which uses microencapsulated odorant patches.[11] Patients self-administer this scratch-and-sniff test. It consists of 40 microencapsulated odorants in a four-alternative forced-choice format. The number of correct answers of the 40 patches allows diagnosis of anosmia, hyposmia, or normosmia. Extensive normative data have been collected for this test by age and gender, making it a standard for olfactory function testing.[11]

The UPSIT was given to all 72 patients in initial testing. Long-term test-retest reliability of the UPSIT has been calculated (Pearson's Product-Moment Correlation coefficient, r=.918),[11] so follow-up testing of patients who scored in the hyposmic or anosmic ranges on the initial UPSIT was conducted at an interval no less than 7 months after the initial testing. In addition to the UPSIT tests, patients provided information at follow-up about their general health, current medications, and subjective impressions about changes in their ability to smell.

Before follow-up studies were begun, all medical charts were reviewed to ensure the appropriateness of patient classification into the two causes of olfactory loss. The criteria used for both patient categories, eg, require temporal contiguity between the URI or traumatic event and olfactory loss, and the absence of any evidence of nasal or sinus disease as determined by endoscopic or radiologic evaluation or both. Patients for whom more than one cause of olfactory loss might apply were excluded from this follow-up study. All patients were contacted by mail and gave written consent to participate in the study.

mia) of olfactory function may occur in as many as 20% to 30% of the patients with HT.[2] The mechanism of impairment may vary according to the type of injury[1]; the olfactory nerve fascicles may be severed at the cribriform plate, or damage may occur to the nasal passages or to the central olfactory pathways. As many as one third of these patients may recover their olfactory ability[2]; however, as a group,[3] a notable change in olfactory function is not seen.

A diagnosis of previous URI as the cause of olfactory impairment is also made largely based on temporal contiguity between the viral episode and recognition of olfactory impairment. No simple diagnostic tests are available to identify these patients. They do not always seek medical help for the "cold" or "viral infection"; nor do they use the same over-the-counter medicines for relief. These patients tend to report the occurrence of dysosmia (parosmia or phantosmia) more often than do patients with other causes of olfactory loss, and the degree of sensory loss is, on average, less severe than for HT or nasal and sinus disease.[4] These patients tend to be older and more frequently are women.[3,5]

Neither the mechanism for sensory loss nor the prospects for recovery after URI are well understood. In one study of 750 patients tested at the University of Pennsylvania Smell and Taste Center, Philadelphia,[3] no improvement was seen in olfactory ability for patients who had had URI, based on mean scores on the University of Pennsylvania Smell Identification Test (UPSIT, Sensonics Inc, Haddon Heights, NJ). Knowing whether recovery can and does occur may help us to understand the mechanism of olfactory loss in these patients. In biopsy material obtained from patients with previous URI, cilia are missing from some of the olfactory receptor cells.[6] When damage or death of the olfactory receptor cells occurs, regeneration of a new population of cells should occur, with eventual restoration of function. If this damage were to the stem cells or the precursor cells of the olfactory receptor neuron, regeneration might occur more slowly or, perhaps, not at all. Alternatively, it may be that damaged olfactory epithelium is replaced with respiratory epithelium.[7,8]

Therefore, while the potential for recovery seems to exist, it is unclear what patients who have HT-induced or viral-induced olfactory loss can expect. Because the insult seems to be directly to the neuroepithelium or neural pathways, therapy for these patients is unavailable. However, understanding the natural history of the impairment will shed light on the pathophysiology of olfactory loss and may lead to the development of appropriate intervention and provide useful information for more effective counseling.

RESULTS

Testing data for the initial evaluation of patients who had olfactory loss caused by HT and previous URI have been presented elsewhere.[4] Of the 72 patients initially tested, we obtained follow-up data from 53% (20) of patients with HT and 66% (21) of patients with previous URI. Ages and UPSIT scores did not differ between the original groups and the subset of patients in the follow-up study.

Table 1 gives data for 20 patients with HT who participated in the follow-up study. The average age of patients with HT was lower than that of patients with URI, but no gender differences existed. The UPSIT scores for patients with HT at the initial evaluation and follow-up were not different between sexes, nor were the follow-up scores different than intitial evaluation scores for the group as a whole. We previously reported[4] that UPSIT scores for patients who had HT and dysosmia were higher than for patients who had HT without dysosmia; this difference was also seen in the subset of 20 patients; patients with dysosmia scored a mean of 20.4 points and patients without dysosmia scored a mean of 12.0 points. This difference was also seen at follow-up.

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Table 1. Results in Patients With Head Trauma

Characteristics	No. of Patients		Mean±SEM			
	With Anosmia	With Hyposmia	Age, y	First Test Score	Follow-up Test Score	Time Between Tests, mo
All patients (N=20)	16	4	40.6±3.4	15.4±1.6	15.4±1.8	38.1±3.6
Women (n=9)	7	2	40.6±5.3	14.9±2.3	18.8±2.6	35.2±4.4
Men (n=11)	9	2	40.7±4.5	15.7±2.2	12.5±2.1	40.3±5.7
Dysosmia (n=8)	4	4	47.3±5.3	20.4±2.8	19.6±3.4	...
No dysosmia (n=12)	12	0	36.3±4.0	12.0±1.1*	12.5±1.4†	...

*Significantly different from patients with dysosmia (P<.01).
†Significantly different from patients with dysosmia (P<.05).

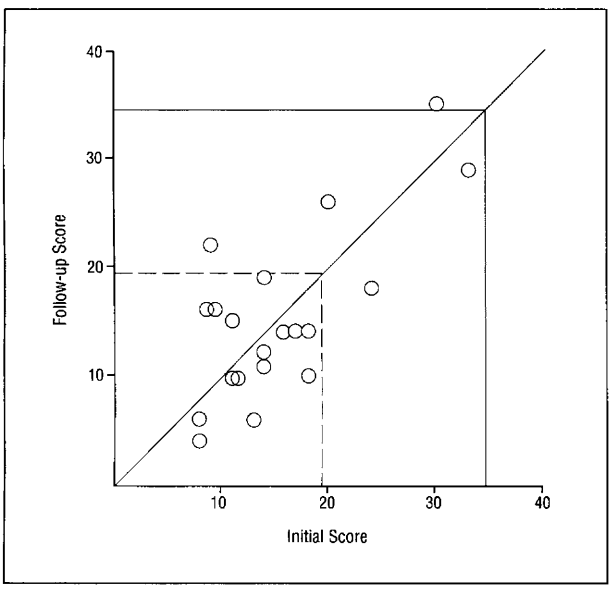

Figure 1. *Initial and follow-up scores on University of Pennsylvania Smell Identification Test for 20 patients with head trauma. Dashed lines indicate function score limits for patients with anosmia; solid lines, patients with hyposmia. The diagonal line indicates scores of no change.*

Figure 1 shows initial and follow-up UPSIT scores for the 20 patients with HT. Each point represents the initial and follow-up UPSIT score for a single patient. The average time between initial visit and follow-up evaluation was 38.1 months. Only three patients reported subjective improvement; of these three, only two had measurable improvement. The mean UPSIT score at follow-up for all patients with HT was not statistically different from the initial score, although seven of 20 patients had an increased score of at least 4 points, with an average time between tests of 33.6 months. When a group of patients with diverse causes of olfactory loss were retested with the UPSIT after at least 6 months, mean UPSIT scores changed by only 0.62 points, which is not statistically significant (t=1.09, df=51, $P>.05$) (recalculated from Doty et al[11]). Thus, the increases in UPSIT scores in these seven patients with HT are larger than would be expected from retesting alone. Others have reported a rapid initial improvement in posttraumatic smell loss in the first year after injury.[2] The data in Figure 1 represent a later phase of recovery, beyond the initial year. Of many factors examined (ie, sex, age at injury, presence or absence of dysosmia, and degree of olfactory impairment at initial evaluation), none were reliably associated with recovery of olfactory function, although this may be a consequence of the small number of patients with improved olfactory function. Although these seven patients had improved scores, all but one continued to have notably diminished function. Only two patients moved to a higher function diagnosis (ie, anosmia to hyposmia).

Data for patients with previous URI are given in **Table 2**. The mean age of these patients is higher than that for patients with HT. The frequency of dysosmia is higher in this group of patients; all but two had parosmia or phantosmia after the onset of their olfactory loss. The UPSIT scores at initial testing are significantly higher in these patients than for patients with HT. Initial and follow-up UPSIT scores are shown in **Figure 2**. A one-sample Student t test shows a significant difference; but, more importantly, 19 of 21 patients had higher UPSIT scores after a mean of 36.9 months; 13 of the 21 patients reported that their sense of smell was better or even normal. Fourteen of these patients had increases of 4 UPSIT points or more. In addition, a significant correlation (r=.56, $P<.01$) was found between the change in UPSIT score and the time between the two UPSIT evaluations.

Further analyses of the data from the UPSIT scores for patients with previous URI provide additional evidence for improvement in olfactory function over time When patients are grouped according to changed UPSIT scores of fewer than 5 points or more than 5 points, those with large changes in UPSIT score had significantly longer times between tests than those with small changes (t=2.20, $P<.05$). When patients are grouped according to whether they were retested within 3 years or more than 3 years of the initial test, Student's t test shows a significant difference between the changes in UPSIT scores (t=2.33, $P<.05$).

COMMENT

Literature reviews[1,2] suggest that about 5% of head injury victims lose their sense of smell, while as many as 30%[12] have a partial disruption in olfactory ability. The likelihood of trauma-induced anosmia increases with the severity of the injury.[13,1] While difficult to demonstrate in patients, one presumed mechanism for anosmia after head injury is the tearing of the olfactory nerves as they pass through the cribriform plate after contrecoup forces. This leads to degeneration of the

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Table 2. Results in Patients With Upper Respiratory Tract Infection

Characteristics	No. of Patients		Mean±SEM			
	With Anosmia	With Hyposmia	Age, y	First Test Score	Follow-up Test Score	Time Between Tests, mo
All patients (N=21)	8	13	55.0±2.0*	21.2±1.7†	26.2±1.5*‡	36.9±3.8
Women (n=14)	5	9	58.4±2.0	21.6±2.1	27.6±1.7‡	38.1±4.6
Men (n=7)	3	4	48.1±2.9§	20.3±3.1	23.4±2.7	36.8±9.4
Dysosmia (n=19)	7	12	55.2±2.0	22.1±1.8	26.7±1.6	...
No dysosmia (n=2)	2	0	53.5±13.5	13.0±1.0	22.0±3.0	...

**Significantly different from patients with head trauma (P<.001).*
†Significantly different from patients with head trauma (P<.05).
‡Significantly different from first test (P<.001).
§Significantly different from women (P<.05).

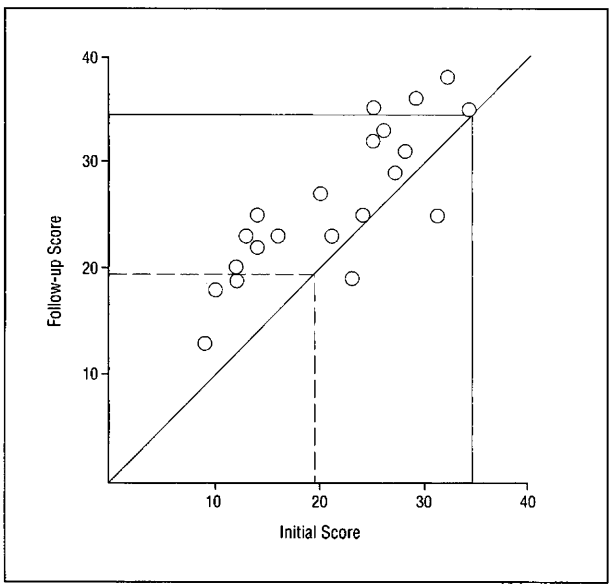

Figure 2. *Initial and follow-up scores on University of Pennsylvania Smell Identification Test for 21 patients with previous upper respiratory tract infection. The dashed lines indicate function score limits for patients with anosmia; solid lines, patients with hyposmia. The diagonal line indicates scores of no change.*

olfactory receptor cells, followed by regeneration of these cells. If regrowth of the axons of these cells is possible through the cribriform plate, olfactory function may return.

Jafek et al[14] showed the existence of disrupted olfactory epithelium in patients with posttraumatic anosmia. Hasegawa et al[15] showed evidence of degenerated olfactory cells in the early stages after trauma. Examination of olfactory biopsy material from patients with HT and anosmia at different times after injury may show us the spectrum of changes that occur in patients who recover olfactory function compared with patients who do not. The time for recovery after trauma-induced anosmia is not well documented, but may require 5 years.[2] Follow-up data from our study showed improvement in test scores in seven (35%) of 20 patients. These data are consistent with those seen by Costanzo and Becker.[2] Deems et al[3] reported no increase in olfactory ability, based on mean UPSIT scores. We also found no difference in mean UPSIT scores for all patients with HT. This suggests that in patient counseling, the proportion of patients who can expect improvement in olfactory function may be more useful than the level of improvement (or nonimprovement) seen across all patients with HT, especially since a statistically significant improvement of 4 UPSIT points does not infer a clinically significant level of improved function.

Six patients showed decreased UPSIT scores of 4 points or more. This may be caused by increasing difficulty in identifying odors that have not been experienced for some time, but no correlation was found between the amount of decrease in UPSIT score and the time between tests.

Leigh[16] reported that patients who had dysosmia after trauma-induced olfactory impairment were more likely to recover olfactory ability than were patients without dysosmic symptoms. While our patients with dysosmia maintained a higher level of olfactory function according to UPSIT scores, the amount of improvement seen at follow-up did not differ from that in patients without dysosmia. Of the seven patients who demonstrated increases in UPSIT score, only three had reported dysosmia. Our data do not support the conclusion that recovery of olfactory function is more likely to occur in patients with dysosmia.

Although the pathogenesis of viral-induced olfactory loss is unknown, many studies have documented olfactory epithelial damage. Yamagishi and Nakano[17] have shown several immunohistochemical markers in the olfactory epithelium. Two of these, neuron-specific enolase and S100, a glia-specific marker, are present a few weeks after viral-induced loss, but disappear by about 3 months. Henkin et al[18] examined patients 3 months to 10 years after viral-induced olfactory loss and described the nasal mucosa as dry and pale, and noted that the serous and mucous glands were decreased in number. Jafek et al[6] performed biopsies on several patients with postviral anosmia and hyposmia. Most notable of their findings is the reduction in olfactory receptor cells with intact cilia, the presumed location of odorant receptors. This reduction in receptor cells is greater in patients with anosmia than in patients with hyposmia. In addition, the olfactory epithelial region contains more patches of respiratory epithelium than seen in normal patients,

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although this could be a consequence of the greater age of the patients who had viral infections.[19,20] It has been assumed that in patients with olfactory loss, the epithelial changes described are a consequence of degenerative processes,[6] but, in light of the improved olfactory capability seen in our patients, some regeneration may be occurring and could account for the epithelial changes.

It is reasonable to expect that greater epithelial damage results in greater impairment of olfactory function, and it may be that with a certain level of damage, recovery might not occur. This has been a common view about URI-induced loss of smell,[6,21] and others have reported no improvement in olfactory function in these patients. Our data suggest, however, that these conclusions may be premature. Our patients thought they had improved, and this improvement was measurable. Four patients who initially tested as anosmic are now hyposmic. Four patients who were hyposmic now have a normal olfactory function. While we cannot claim that patients with previous URI will experience complete recovery, we believe that these data on improvement in olfactory functioning are an important contribution to the prevailing views on URI, especially about the correlation between time and amount of improvement. The data suggest some hypotheses about the mechanisms of damage. For example, if cells must degenerate and then regenerate, one of these processes is slower than we have thought,[6] or measurable olfactory function requires more complete regeneration than we might expect. Although the data from Jafek et al[6] and Yamagishi and Nakano[17] are compelling and convincing, they do not address the process of the reinnervation of the olfactory bulb. Data from our study show that the deficit in function 1 year after viral infection is not necessarily permanent, as previous studies suggest. Regenerative processes in the epithelium, and between the epithelium and olfactory bulb, may continue for a long time.

Deems et al[3] have also reported that patients with previous URI do not recover olfactory function, but their data about the time at which patients with previous URI were retested are unclear. Data we have obtained from patients with previous URI 1 year after initial testing disclosed no evidence of improvement; we believe that 1 year may be too soon to retest. Alternatively, perhaps defining improvement based on mean UPSIT scores for an entire etiologic group is inappropriate; the proportion of patients who have increased UPSIT scores may be a better measure of improvement. In addition, the criteria for inclusion as URI-caused loss of smell must be considered; if the criteria do not preclude patients whose smell loss is idiopathic or from nasal sinus disease, the lack of recovery seen in the mean data of Deems et al[3] may be caused by multiple factors.

In conclusion, the results from this study provide the patient with a previous URI with an alternative prognosis. Recognizing that improvement can occur in these patients also may point us in directions appropriate for medical intervention and allow us to provide patients with more accurate information about prognosis. As our knowledge about the controlling factors for degeneration and regeneration of the olfactory receptor cell develops,[22] new therapeutic regimens for these patients may emerge.

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