Long-term follow-up of posttraumatic olfactory disorders*

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Summary

Objective: This study aims to determine the long-term recovery rate of posttraumatic olfactory disorders and to evaluate whether a lateralized disorder influences recovery.

Method: Olfactory function of 67 patients with posttraumatic olfactory disorders were examined twice using the 'Sniffin´ Sticks' test battery. Olfactory function was classified based on composite TDI (Threshold, Discrimination and Identification) score. Subjective impairment was rated by visual analogue scale ranging from 0 to 10.

Results: First and second examinations were conducted an average of 16.7 months and 74 months after trauma, respectively. From first to second examination, mean TDI score of the better nostril increased significantly, the number of patients with anosmia of the better nostril decreased, and number of hyposmic and normosmic patients increased. Subjective impairment decreased. Neither age, sex, nor side differences between nostrils affected improvement.

Conclusion: After the follow-up period, in 27% of the patients the TDI score improved ≥ 6 points score and subjective impairment decreased. A follow-up period of more than 2 years is recommended.

Key words: posttraumatic, olfactory disorder, long-term, follow-up

Introduction

Olfactory disorders due to head trauma are common and were first described in the late 1800's [1,2]. Even though severe trauma and long duration of amnesia increase the likelihood of posttraumatic olfactory disorders [3,4], these conditions can also occur after mild head trauma [5]. The incidence of posttraumatic olfactory disorder has been reported as 4% [6], 7% [3], or 12% [7], and even as high as 60% [8] or 67% [9]. This large range is likely because different authors report data from different groups of patients. Examining only patients presenting to smell and taste centers increases the observed prevalence dramatically. Moreover, the reported rate of posttraumatic olfactory disorder often varies within the same study, such as the reported range of 4 – 31% [3], which varied based on the severity of the trauma. In addition to complete anosmia, different degrees of hyposmia can also be present. In general, three different pathophysiological mechanisms are considered: 1) mechanical intranasal obstruction, 2) intracranial brain damage, and 3) shearing of olfactory fibers at the cribriform plate [10]. Mechanical intranasal obstruction can easily be detected with either intranasal endoscopy or computed tomography scans. Any intracranial lesions present can also be visualized with imaging techniques [11]. Moreover, a correlation between olfactory bulb/tract damage and deficits in odour identification has been demonstrated [12,13]. However, shearing of olfactory fibers at the cribriform plate cannot yet be visualized in humans and it is assumed that fibrosis of the cribriform plate follows olfactory fiber shearing. The type and severity of the lesion are likely to influence recovery.

The recovery rate of posttraumatic anosmia is currently thought to be between approximately 10% [14] and 36% [9,15,16]. The average observation time in these studies was 14 months [14], 38 months [15], and 66 months [17]. In a single case, the observation time was 9 years [18]. Whether general observation time after trauma is too short remains a matter of debate. Another complication for determining recovery time is that olfactory testing is routinely performed in a bilateral manner [19,20], which does not identify the lateralized disorders present in approximately one-fourth of patients with olfactory disorders, including patients with posttraumatic disorders [21,22]. However, identifying lateralization of the disorder itself might add crucial information concerning the prognosis of the disorder. In fact, it has been reported that an unilateral olfactory loss seems to be a predictor of a general olfactory loss [23]. Therefore, the aims of the present study were to: 1) examine a cohort of patients with posttraumatic olfactory disorder over a long period, and 2) evaluate whether lateralization of the olfactory disorder has an impact on prognosis.

Patients and methods

The study was performed according to the Declaration of Helsinki on Biomedical Research Involving Human Subjects. Approval of the study was obtained from the Ethics Committee of the University of Basel. Patients with a posttraumatic olfactory disorder were selected from our odour test database and these patients were contacted for a retest of olfactory function. All participants provided written informed consent.

Patients

A total of 67 patients (29 women and 38 men) with posttraumatic olfactory disorder participated in this study and were examined twice. These patients were selected from our database. Out of 173 patients with posttraumatic disorders that had been examined, only those examined a minimum of 5 years previously, were selected for consideration (n = 99). Of these 99 patients, we identified 35 patients with differences between the right and left nostrils of 6 or more points in TDI score and 40 patients with no side differences. These patients were comparable in age and were contacted to participate in the study. Finally, 31 of the 35 patients with side differences and 36 of the 40 without side differences agreed to participate in the study. The remaining eight patients did not want to participate for various reasons (no time, olfactory function has become better, olfactory function stayed the same, no reason at all). All patients received a thorough ear, nose, and throat (ENT) examination by an experienced otorhinolaryngologist including nasal endoscopy. A detailed medical history was also recorded. The diagnosis of a posttraumatic olfactory disorder was made according to the history and the close temporal connection between the trauma and the observed olfactory disorder as determined by initial olfactory testing. None of the patients had neurodegenerative diseases such as Alzheimer's or Parkinson's disease. Mean ± standard error of the mean (SEM) age of the patients at the time of trauma was 40.1 ± 1.7 years (range: 17 - 66 years). The mean interval ± SEM between trauma and first olfactory testing examination was 16.7 ± 3.8 months. The mean interval ± SEM between trauma and second examination was 74 ± 6.7 months.

Subjective rating

At both the first examination and second examinations, all patients were asked to rate their smell identification and smell discrimination abilities, as well as the resulting impairment in quality of life, on a visual analogue scale (VAS) of 10 cm length. The left hand end of the scale was labeled 'not present' or 'extremely poor' (0 units) and the right hand end was labeled 'extremely sensitive' or 'extremely high' (10 units) for smell identification/discrimination and quality-of-life impairment ('no impairment' = 0 units; 'very high impairment' = 10 units), respectively.

Clinical examination

Diagnosis

Diagnosis of posttraumatic disorder was made according to patient history, the close temporal connection between the trauma and the observed olfactory disorder and clinical examination. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain directly after trauma was performed only if indicated necessary by the physician initially examining the patient. Intranasal endoscopy was performed in all patients at both examinations and any intranasal pathology such as scarring, polyps, or symptoms of chronic rhinosinusitis were ruled out.

Smell testing

Olfactory testing was performed using the Sniffin´ Sticks test battery (Burghart, Wedel, Germany) consisting of a nonverbal threshold test, a nonverbal discrimination test, and a verbal identification test [24,25].

Threshold (T) testing involved the presentation of *n*-butanol in a dilution series, beginning with 4% *n*-butanol. Sixteen serial dilutions were made at 1:2 dilution ratios. Using a triple-forced choice staircase paradigm, detection thresholds for *n*-butanol were determined. Scores ranged from 1 to 16. Odour discrimination (D) testing was performed with 16 triplets of pens containing odorant: two pens contained the identical odorants and a third pen contained a unique odorant. Patients chose which of the three odour-containing pens had the unique odour. The patients' D-scores ranged from 0-16. Throughout both threshold and discrimination tests, the patients were blindfolded. Odour identification (I) was assessed using 16 common odours. Using a multiple-event forced-choice task, individual odours were identified from a list of four descriptors. Again, the scores ranged from 0 to 16.

TDI Score

Results of the three 'Sniffin´ Sticks' subtests (threshold, discrimination, and identification) were analyzed as a composite TDI score that was derived from the sum of the results obtained for threshold, discrimination, and identification. The TDI score ranged from 1 to 48. Functional anosmia was defined as a TDI score ≤ 15, hyposmia was defined as a 15 < TDI score < 30 and normosmia as a TDI score > 30 [26].

'Sniffin´ Sticks' testing was performed separately for each nostril. When one nostril was being tested, the patient closed the opposite nostril with their thumb. Threshold testing was performed first, followed by a short break of 5-10 minutes, and then discrimination testing in the alternating right and left nostril. After another short break of 5-10 minutes, odour identification was performed, first on the side with the poorer threshold, and followed by the other nostril.

A significant side difference was defined as a difference of 6 or more TDI score points between nostrils [21,22]. Each nostril was diagnosed based on the TDI score for that nostril and a diagnosis was also made based on the performance of the best nostril.

Trauma grading

Traumatic brain injury (TBI) was graded as mild, moderate, or severe [27,28].

Statistical analysis

Statistical analysis was performed using SPSS 19 for Windows (SPSS Inc., Chicago, IL, USA). Where appropriate, data from the first and second examinations were compared with Student's t-test for paired samples. Pearson's correlation coefficient was calculated to assess correlations and the alpha-level was set at 0.05. One-way analyses of variance were used to investigate the influence of side differences. The results are expressed as means and standard errors of the means.

RESULTS

Subjective rating on VAS

Within the observation period of more than 6 years, subjective impairment decreased significantly from 6.6 ± 0.39 to 4.7 ± 0.39 ($p < 0.001$). Additionally, patients rated their subjective identification ability (1.36 ± 0.27 vs. 2.79 ± 0.38, $p < 0.001$) and their subjective discrimination ability (1.16 ± 0.28 vs. 2.98 ± 0.41, $p < 0.001$) significantly better upon second examination.

Olfactory testing

Overall, olfactory function improved over time. The mean ± SEM composite TDI score of the right (12.76 ± 0.75 vs. 16.01 ± 0.94, $p < 0.001$) and left (13.58 ± 0.83 vs. 16.35 ± 0.97) nostril, as well as the mean score of the best functioning nostril (16.3 ± 0.84 to 19.4 ± 0.9, $p < 0.001$) improved significantly. Additionally, the

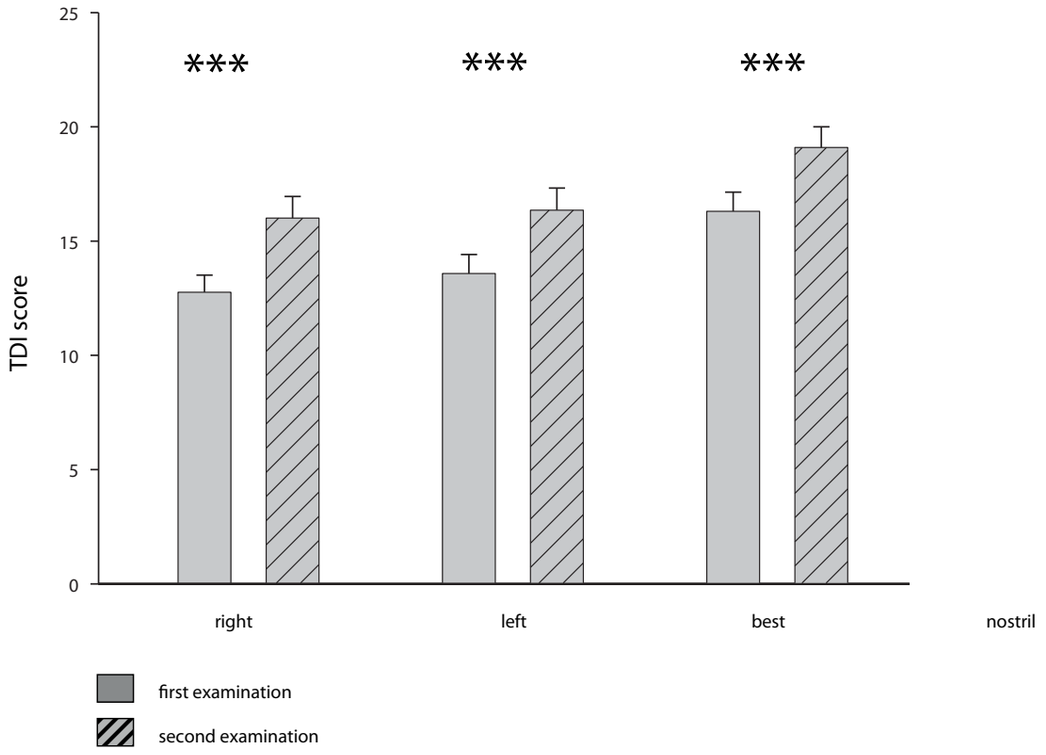

Figure 1. Improvement in TDI scores in each (right or left) nostril and in the best nostril from the first (plain bars) to the second (striped bars) examination.

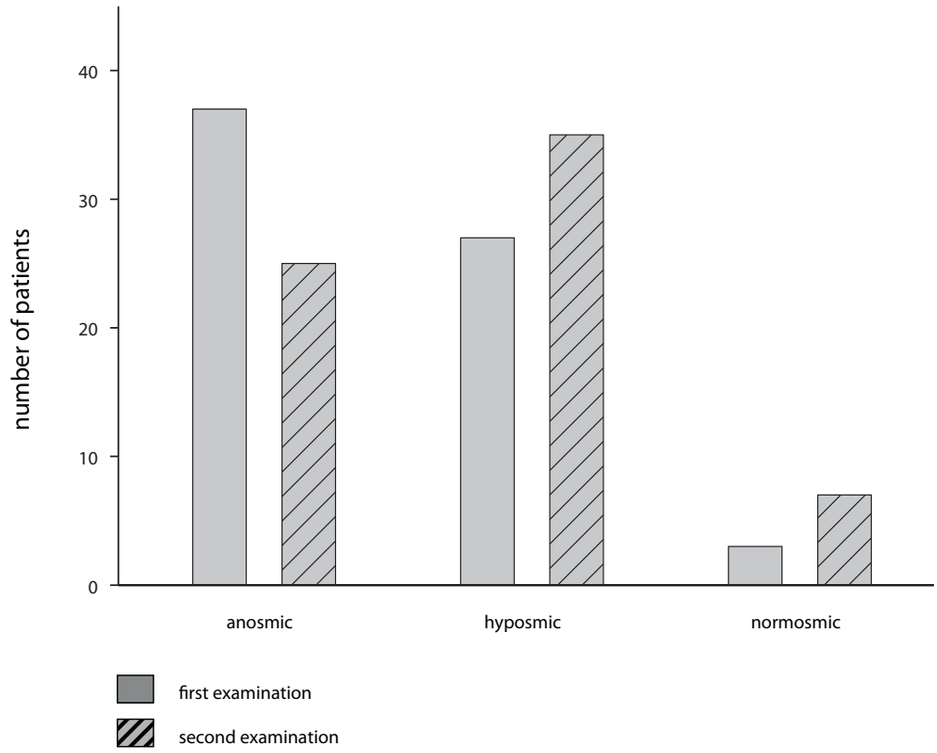

Figure 2. Anosmic, hyposmic, and normosmic classification according to the nostril with the best olfactory function on first (plain bars) and second (striped bars) examination.

mean score of each subtest (threshold, discrimination, and identification) improved significantly over time (Figure 1). According to the results of the best nostril, classification of the patients at first visit was anosmia in 37 cases (55.2%), hyposmia in 27 cases (40.2%) and normosmia in 3 cases (4.5%). At the second visit, 25 patients (37.3%) had anosmia, 35 patients (52.2%) had hyposmia, and 7 patients (10.4%) had normosmia (Figure 2). In 18 patients (27.0%) olfactory function improved as indicated by an increase in TDI score of 6 or more points, 46 patients (68.5%) had no change (change in TDI score ± 5.5 points), and the olfactory function of 3 patients (4.5%) got worse as indicated by a decrease in TDI score of 6 or more points.

Improvement in olfactory function over time correlated significantly with a decrease in subjective impairment caused by the olfactory disorder (r_{67} = -0.37, p = 0.002).

A side difference, which was defined as a difference of 6 or more TDI score points between the right and left nostrils, was evident in 31 patients (46.3%) at the first examination considering only the numeric TDI score. However, when a side difference of 6 points occurring within the TDI range of 0-15 (anosmia) was considered irrelevant because the difference was likely due to chance, only 26 patients (38.8%) exhibited a relevant side difference of 6 or more TDI score points between the nostrils at the first examination. On the second examination, also excluding the side difference within the TDI range of 0-15 (anosmia), 24 patients exhibited a side difference of 6 or more TDI score points (35.8%). While 6/24 patients (25.0%) did not have this side difference at the first examination, 18/24 patients (75.0%) did exhibit this difference at the first examination. Trauma grade was distributed equally among all patients: of the 67 patients, 21 (31.4%) were graded as mild, 24 (35.8%) as moderate, and 22 (32.8%) as severe.

The rate of improvement was not significantly influenced by age at time of trauma, trauma grade, the initial TDI score, or the initial presence of a side difference in TDI score.

Discussion

In our study we made two significant observations: 1) The anosmia rate was 55.2% (37/67 patients) when measured 16 months posttraumatically, which improved to only 37.3% (25/67 patients) when measured 74 months posttraumatically; and 2) Existing side differences between the right and left nostrils were present in 38.8% (26/67 patients) at the first examination, and did not correlate with the improvement rate of olfactory function. After a follow-up time of 74 months, which is to our knowledge the longest observation period in a group as large as 67 patients, 63% of the patients in this study were either hyposmic (52.2%) or normosmic (10.4%). From the first to the second

examination, 33% (22/67) of the patients in this study exhibited olfactory function improvement, which consisted either of an improvement in the TDI score of 6 or more points or an improvement from anosmia to hyposmia with an increase in the TDI of 5 to 5.5 points. The overall reported recovery rates of posttraumatic disorders were 10% [14], 25%, and 39% [3,9,15], but the time of follow-up in these previous studies was much shorter. Among the large number of patients examined by Sumner et al., a majority of the 39% of patients who recovered did so within the first 3 months after trauma. In our experience, many patients will not undergo examinations by ENT physicians within the first 3 months after the trauma especially if the olfactory disorder has resolved by then. Additionally, only small groups of patients are generally examined over a long-term period. Duncan and Seiden reported an improvement rate of 35% (7/20 patients) 1-5 years after initial testing [15]. In a single case, recovery after a period of 9 years has been reported [18]. A much greater percentage of patients, 63%, was considered hyposmic or normosmic in our study. Improved olfactory function was evident between first and second visit in 33% of the patients studied. This number is consistent with other recovery rates previously reported, but is remarkable because of the long time after trauma that this observed recovery took place. Patients with posttraumatic disorders are usually informed that olfactory function can improve within the first 2 years after trauma. However, the data in this and other studies indicate that this period might be too short.

Results from the group of patients in this study indicate no correlation between the severity of trauma and improvement rate, which is consistent with data reported by Sumner in 1964 [3]. The likelihood of olfactory damage has been shown to increase with the severity of trauma and longer duration of posttraumatic amnesia [3,4]. In the large group of patients that Sumner studied, however, most patients were only followed for 1 year after trauma, while the patients in our study were first examined at a mean of 16 months. Patients in whom anosmia has resolved by 16 months likely do not present at the hospital independent of trauma severity. All patients in this study who were initially graded with mild or moderate TBI (traumatic brain injury) still experienced olfactory disorders 16 months post-trauma when first presenting to the hospital. This fact might therefore be considered 'selection bias' contributing to the lack of a correlation between severity of the trauma and improvement in the sense of smell.
Neither the side difference initially observed in the patients in this study nor the initial TDI score were prognostic factors in recovery. It has been previously shown that mainly age and the initially observed olfactory score, but not the origin of the olfactory disorder, are prognostic factors of improvement [17,29]. However, regarding the origin of the olfactory disorder the chance for improvement to normosmia in posttraumatic patients is significantly lower than in patients suffering from sinunasal or post URTI disorders [29], which is consistent with other studies reporting that patients with postinfectious olfactory disturbances recover to a greater extent than patients with posttraumatic olfactory disorders [14,15].

Recent studies have reported that lateralized olfactory disorders are present in all types of olfactory disorders [21,22] and that reduced unilateral smell predicts future global smell loss [23]. More than one-third of patients (26 patients, 38.8%) in our study exhibited a lateralized disorder at the first examination. This number of patients is rather high considering the different pathomechanisms of posttraumatic disorder. However, because all previous studies had tested in a bilateral manner, this present study is the first to report long-term follow up in lateralized posttraumatic disorders. Intranasal damage and scarring was ruled out by intranasal endoscopy, and therefore we hypothesize that either shearing of the olfactory fibers or direct intracranial damage have occurred. Initial post-trauma CT or MRI imaging data was used to rule out intracranial damage without focusing primarily to olfactory regions, making it impossible to evaluate the initial posttraumatic images accordingly. For example, histopathological examination in patients with posttraumatic disorders have identified disrupted olfactory epithelium, and a lack of cilia and axon tangles just below the basement membrane [30]. These findings and the associated lack of recovery can be explained by fibrosis of the lamina cribrosa. However, in cases in which recovery was observed, it can be postulated that olfactory axons were either able to pass through the lamina cribrosa or were never completely sheared. Because the shearing of the fibers cannot yet be visualized with current technology, the explanation is uncertain and is based on the few existing histopathological studies. We were unable to differentiate whether damage was primarily intracranial or caused by shearing injuries to the olfactory fibers because images used to evaluate intracranial lesions of olfactory regions were not always adequate. Interestingly, posttraumatic olfactory loss can also be lateralized. However, this lateralized loss has no prognostic value and, if present initially, seems to remain lateralized in almost three-fourths of the patients with lateralized loss present upon the first examination.

In this study, subjective impairment caused by olfactory disorders significantly decreased over time and correlated with the measurable improvement of olfactory function as measured by TDI score. This decrease of subjective impairment over time is additional important information that may be offered patients seeking advice, as most patients complain severely about the olfactory loss. The exact reason for the decrease of subjective impairment remains speculative; all of the following three, adaptation mechanisms, answers given in a special study setting or loss of olfactory memory over time are possible explanations for this observed decrease in subjective impairment over time.

Despite that, in general, self-assessment of olfactory function is rather poor [31], patients in this study over time subjectively rated both olfactory function and olfactory discrimination as better compared to the first visit.

This study does have some weaknesses that should be considered. For example, the patients who dropped out may have caused a selection bias and this possibility cannot be completely ruled out. Additionally, patients were only examined twice and the exact time between first and second examination at which improvement occurred is unknown.

In conclusion, in this group of 67 patients with posttraumatic disorders followed-up over 74 months, olfactory function improved in 33% of patients, with 63% of patients being either hyposmic or normosmic. These results are higher than expected and patients may benefit from being informed that improvement is possible after a longer period and that follow-up examinations for a longer duration are warranted. In this group of patients, a lateralized disorder was of no prognostic value and the disorder stayed lateralized over time. Lastly, subjective impairment did decrease significantly over time.

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