The JOEP Study: Justification of Olfactory Evaluation in Post-traumatic brain injury.

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Abstract (248 words)

Introduction(53): ENT-related findings are often observed in patients with skull base fractures, a sign of traumatic brain injury. However, olfactory evaluation is often overlooked, despite proven correlation between olfactory dysfunction and traumatic brain injury. Prevalence of olfactory dysfunction in post-traumatic brain injury population varies between 12.8 and 67%, compared to 5-15% in general population.

Method(47): We conducted a retrospective case series study in a single Dutch tertiary referral center. Medical records of patients diagnosed with skull base fracture were reviewed. Data was collected and analysed through Chi-squared analysis regarding patient demographics, trauma characteristics and radiographic findings, olfactory function and other ENT-related outcomes.

Results(76): Of 44 included patients aged between 18 and 75, 50% was female. 19 patients(43.2%) experienced subjective olfactory dysfunction. Olfactory outcome in 4 patients(9.1%) was missing. 30 patients(68.2%) experienced subjective hearing loss at admission, persisting in 18 patients(40.9%) at end of follow up. Vertigo and tinnitus symptoms were present in respectively 10 patients(22.7%) and 18 patients(40.9%). In 6 cases, ossicle luxation was seen. No significant distribution of outcomes on severity of trauma or olfactory function was found.

Conclusion(36): Given that subjective olfactory dysfunction has been experienced in 43% of patients and that olfactory dysfunction is associated with social insecurity and hazardous events, it is essential to evaluate olfactory function in post-traumatic brain injury population.

Recommendation(36): During hospital admission, olfactory loss should be actively assessed, with an objective olfactory test conducted after six weeks. Furthermore, prospective longitudinal studies are needed to fully investigate prevalence, treatment and recovery of olfactory dysfunction after TBI.

APPENDIX A. Abbreviations and definition.

Abbreviation	**Definition**
TBI	Traumatic Brain Injury
ENT	Otorhinolaryngology; Ear, Nose, Throat department
GCS	Glasgow Coma Scale
SST-12	Sniffin' Sticks test
χ^2-analysis	Chi-squared analysis
P-value	Probability value
SD	Standard Deviation

Introduction (317 words)

In 2021, 15.5% of the 72,437 trauma cases admitted to emergency departments in the Netherlands were categorized as severe head injuries. A skull base fracture was present in 15% of these cases.[1] Skull base fractures are a sign of traumatic brain injury (TBI) with numerous consequences and long-term disabilities.[2] Besides radiographical findings, several clinical exam findings are predictors for skull base fractures. These include hemotympanum, otorrhea or rhinorrhoea.[3]

In the Netherlands, it is common practice to consult Otorhinolaryngology department (ENT) in cases of skull base fracture.[4,3] Hearing loss is a primary consideration in patient assessment. The prevalence of hearing loss after TBI is significantly higher than in general population, as well as other ENT-related outcomes.[5,6] In addition, post-traumatic vertigo, tinnitus and facial nerve injury is often examined.

Olfactory function is often overlooked in cases of skull base fractures, despite the fact that the association between TBI and olfactory disturbance has already been proven in prior studies with prevalences of dysosmia varying from 12.8 up to 67%.[7,5,8] Prevalence of dysosmia in general population range from 4 to 15%.[9,10] Throughout life, the olfactory function declines over time, with significant higher prevalences of 13-30% in age of 60 years and above.[10,11]

Sense of smell affects important aspects of life. Among them are mood, dietary behaviour, safety and danger avoidance.[12,13,14] People with olfactory loss report increased social insecurity in intimate relationships and a higher frequency of encountering hazardous events.[14,15,16] Therefore, olfactory function is of great importance in daily life and there is a great potential in early diagnosing, treatment and counselling regarding potential risks of olfactory dysfunction.[12,17]

In this retrospective study, a University Medical Center Utrecht patient population with a skull base fracture in medical history is investigated considering main outcome olfactory dysfunction, as well as outcomes regarding hearing loss and vestibular dysfunction. The central question in this study is to what extent olfactory dysfunction is associated with skull base fractures.

Method (711 words)

Study population

We conducted a retrospective case series study in a single Dutch tertiary referral center and level 1 trauma center. Medical records of patients diagnosed with skull base fracture for whom ENT consultation had been sought were reviewed. All patients diagnosed with skull base fracture for whom ENT consultation had been sought in the period between January 2023 and February 2024 were identified. Medical records were retrieved and reviewed.

This study focuses on adults, therefore patients younger than 18 years of age at moment of trauma were excluded. Patients initially admitted to other medical centres for primary trauma care were also excluded. Out-patient follow-up care elsewhere was likewise reason for exclusion. Furthermore, death occurring before follow-up care or no-show on follow-up appointment were also reason for exclusion.

Classification of TBI

According to the American Veteran Affairs / Department of Defence, TBI is defined as a traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force.[18] It is diagnosed by new onset or worsening of at least one of the following clinical signs immediately following the event: loss of consciousness, post-traumatic amnesia, alteration of consciousness/mental state, neurological deficits, presence of intracranial lesion.

Patients were classified based on TBI severity. In this study, the Glasgow Coma Score (GCS) performed at the time of admission was used. A GCS score below 8 is considered as severe, 9 to 12 as moderate, and 13 to 15 as mild.[19,20]

Data extraction

The following variables were extracted from the medical records: patient characteristics (e.g. age, biological sex, medical history), characteristics of endured head trauma, GCS-score at admission, duration of admission to Intensive Care Unit, radiological findings, subjective olfactory dysfunction, objectified olfactory dysfunction through Sniffin' Sticks Screening test (SST-12), any experienced hearing loss or tinnitus, post-traumatic pure tone audiogram results, frequency of performed pure tone audiogram, type and severity of hearing loss, vestibular function, facial nerve function through House Brackmann Score.

Subjective hearing loss is defined as any awareness of post-traumatic hearing loss. Hearing loss is objectified through pure tone audiometry, conducted at 6 weeks of follow-up. Audiometry tests were repeated in case of persisting hearing loss. Hearing threshold levels were determined on the following frequencies: 0.5 kHz, 1.0 kHz, 2.0 kHz and 4.0

kHz. A Pure Tone Average, the calculated average of measured Hearing threshold levels, of more than 20 decibel is defined as objective hearing loss, in accordance with the American Academy of Otolaryngology – Head and Neck Surgery 1995 guidelines.[21] Type of hearing loss was categorized in conductive, sensorineural and mixed hearing loss and was based on most recent available audiometry.

Medical ENT history was assessed as relevant if there was involvement of the nose or ear. Relevant general non-ENT history was also recorded. Relevant medical history is defined as comorbidities or events in the past related to TBI, nerve damage and olfactory function. Specific medical history items related to ENT were explicitly investigated, including pre-existing hearing loss, olfactory dysfunction or ear surgery.

Subjective olfactory dysfunction is defined as any change in olfactory perception. It is common practice in University Medical Center Utrecht to objectify the degree of olfactory dysfunction by conducting an SST-12, a derivate of the more comprehensive Sniffin' Sticks test. Normosmia is defined as SST-12 ≥ 11 and anosmia as SST-12 ≤ 6. Hyposmia is defined as an SST-12 score between 6 and 11.[22] Olfactory dysfunction is classified in hyposmia, anosmia, parosmia. Respectively, these categories are described as reduced perception, complete loss of perception, incorrect perception.[23]

Missing data

In cases where the primary outcome was unknown, up to three attempts were made to obtain missing data regarding olfactory function through telephone contact. In this way, efforts were made to minimize missing data considering olfactory function. No further effort was made in the case of missing data for secondary outcomes. Missing data was processed as 'unknown'.

Statistical analysis

Results were tabulated and statistically analysed using SPSS 12.0 for Windows and Microsoft Excel spreadsheet. Correlation between subjective olfactory dysfunction and severity of injury, nature of trauma and sex is analysed through Chi-Square analysis (χ^2-analysis). Association between olfactory function, TBI severity and post-traumatic tinnitus, vertigo, facial nerve injury and hearing loss will be analysed in a similar manner. A probability value (P-value) of <0.05 was considered statistically significant.[24]

Results (1064 words)

Data selection

A total of 68 consecutive cases were identified. 24 individuals were excluded. The complete inclusion process is shown in figure 1.

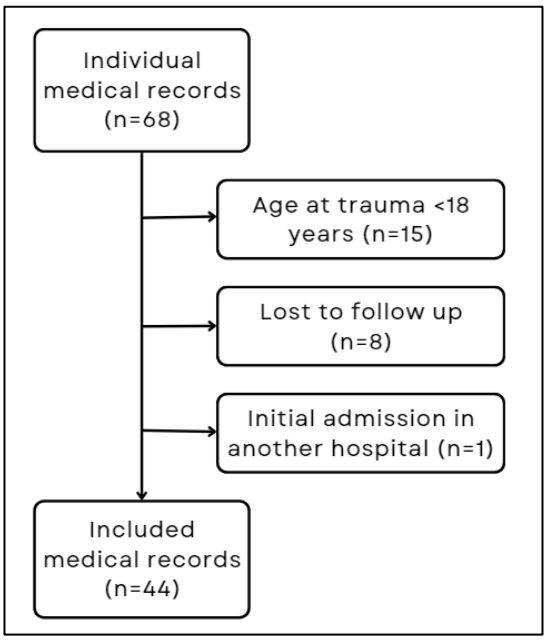

Figure 1. Patient selection and inclusion process.

Baseline characteristics are shown in table 1. 22 (50%) was female and 22 (50%) was male. Mean age was 47.5 years, ranging from 18 to 75 years. In two cases, there was pre-existing olfactory dysfunction, in the form of hyposmia. In appendix A, an overview is shown of cases with relevant medical history. Two patients had both relevant general and ENT-related medical history. In one case, a patient had a history of head trauma due to alcohol abuse and one patient had both head trauma and house dust mite allergy.

In 17 cases, impact of trauma originated from left. The same number of cases experienced trauma impact initially from right. The remaining 10 cases experienced bilateral impact or dorsal of ventral impact.

For 21 patients, a fall was the cause of TBI. In 20 cases TBI was due to traffic accident. In one case, aggression was reason for TBI. Two cases suffered TBI through other trauma mechanisms. One male patient was involved in a workplace accident in which his head became trapped between concrete walls and another male patient was tackled on the soccer field and landed on his head.

12 patients sustained severe TBI. 25 cases were classified as mild TBI, accounting for 56.8% of study population. Only 7 cases were classified as moderate TBI. 15 of 44 patients were admitted to the Intensive Care Unit. Admission ranged from 6 hours to 11 days.

Table 1. Baseline characteristics of included patients. SD: Standard Deviation; TBI severity, GCS: Traumatic Brain Injury severity based on Glasgow Coma Scale.

		Included patients (n, (%))
Total		44 (100)
Median age in years (range, SD)		47.5 (18-75, ±16.3)
Sex	Female	22 (50.0)
Medical history	Pre-existing hearing loss	6 (13.6)
	Pre-existing olfactory dysfunction	2 (4.5)
	Pre-existing tinnitus	2 (4.5)
	Ear-surgery	1 (2.3)
	Other relevant ENT medical history	9 (20.5)
	Other relevant general medical history	7 (15.9)
Lateralization of impact	Left	17 (38.6)
	Right	17 (38.6)
	Bilateral / dorsal or ventral trauma	10 (22.7)
Nature of trauma	Traffic accident	20 (45.5)
	Fall	21 (47.7)
	Aggression	1 (2.3)
	Other	2 (4.5)
TBI severity, GCS	Mild	25 (56.8)
	Moderate	7 (15.9)
	Severe	12 (27.3)
Admitted to Intensive Care Unit (range of duration)		15 (34.1) (0-11 days)

Olfactory outcomes

After data collection through reviewing medical records on olfactory outcomes, there were 28 cases of missing data on olfactory functioning. After telephone interviewing, 24 patients were reached. All patients consented further questioning. 4 patients remained unreachable. Subjective olfactory dysfunction after TBI was experienced by 43.2% of patients. This olfactory dysfunction ranges from hyposmia to complete anosmia. In 9 cases of reviewing olfactory function through medical records, it was not possible to determine nature of dysosmia. In only one case olfactory dysfunction was resolved after 6 weeks of follow-up. In some other cases, there was mention of slight improvement, however without complete resolution. Extracted data on olfactory function is shown in table 2. Percentage distribution of affected olfactory function in relation to TBI severity is visualized in Figure 2. No significance was found between distribution of subjective olfactory dysfunction cases and TBI classification (χ^2-analysis: 7.56, p-value: 0.11), nature of trauma (χ^2-analysis: 8.43, p-value: 0.21) or sex (χ^2-analysis: 2.51, p-value: 0.29).

Not a single patient was referred to a rhinologist and no objective olfactory testing has been conducted in any case.

Interestingly, both patients with pre-existing hyposmia were amongst the 19 patients that experienced post-traumatic olfactory dysfunction. Both experienced an evident change in olfactory function. One patient experienced, although subjective, an increased degree of hyposmia. The second patient experienced new-onset parosmia.

Table 2. Outcomes regarding olfactory function. (n= number of cases, %: percentage); TBI: Traumatic Brain Injury.

		Total (n,%)	Mild TBI (n,%)	Moderate TBI (n,%)	Severe TBI (n,%)
Patients		44 (100)	25 (100)	7 (100)	12 (100)
Subjective olfactory dysfunction	Yes	19 (43.2)	9 (36)	4 (57.1)	6 (50)
	No	21 (47.7)	15 (60)	3 (42.9)	3 (25)
	Unknown	4 (9.1)	1 (4)	0 (0)	3 (25)
Subjective nature of loss	Anosmia	4 (9.1)	3 (12)	1 (14.3)	0 (0)
	Hyposmia	4 (9.1)	2 (8)	1 (14.3)	1 (8.3)
	Parosmia	2 (4.5)	1 (4)	1 (14.3)	0 (0)
	Not specified	9 (20.5)	3 (12)	1 (14.3)	5 (41.7)

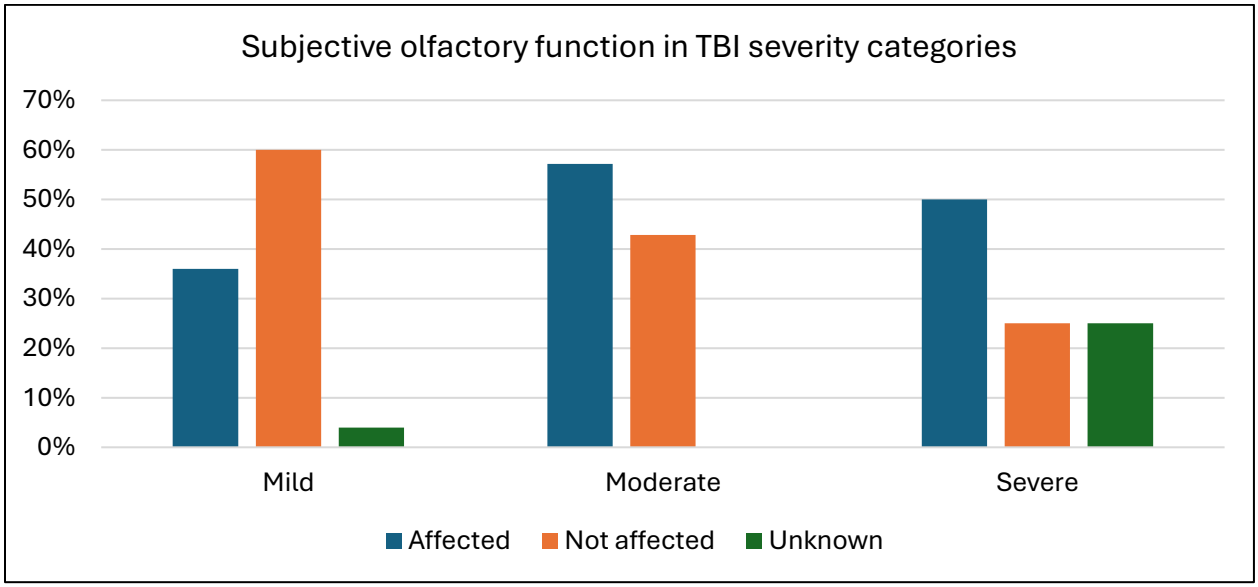

Figure 2. Percentage distribution of subjective olfactory dysfunction in TBI severity categories, based on GCS.TBI: Traumatic Brain Injury.

Secondary outcomes

Figure 3 outlines primary and secondary outcomes in the study population. Ossicle luxation was seen in 6 patients. Missing data was seen in facial nerve injury, tinnitus and vertigo. In 8 cases, there were symptoms of facial nerve injury with a House Brackmann

Score higher than 1. There were no cases of bilateral facial nerve injury. Increase or new-onset tinnitus symptoms occurred in 10 patients. There were two patients with preexisting tinnitus. One of these patients experienced an increase in tinnitus symptoms, in contrast to the second one with no perception of increased tinnitus symptoms. Vertigo symptoms were seen in 18, accounting for 41% of 44 included patients. An overview of data corresponding to figure 3 is shown in appendix C.

Chi-squared analyses of secondary outcomes are shown in table 3. No significant distribution of outcomes in classification of TBI severity or in olfactory dysfunction was found. Correlation between ossicle luxation and TBI severity is near significant; in 4 of 6 cases of ossicle luxation, the patient sustained severe TBI, indicating that the risk of ossicle luxation might be higher in severe TBI. Correlation between subjective experiences of hearing loss and subjective olfactory dysfunction is also borderline significant, indicating that there might be increased risk of presence of olfactory function if patient experiences also hearing loss and vice versa.

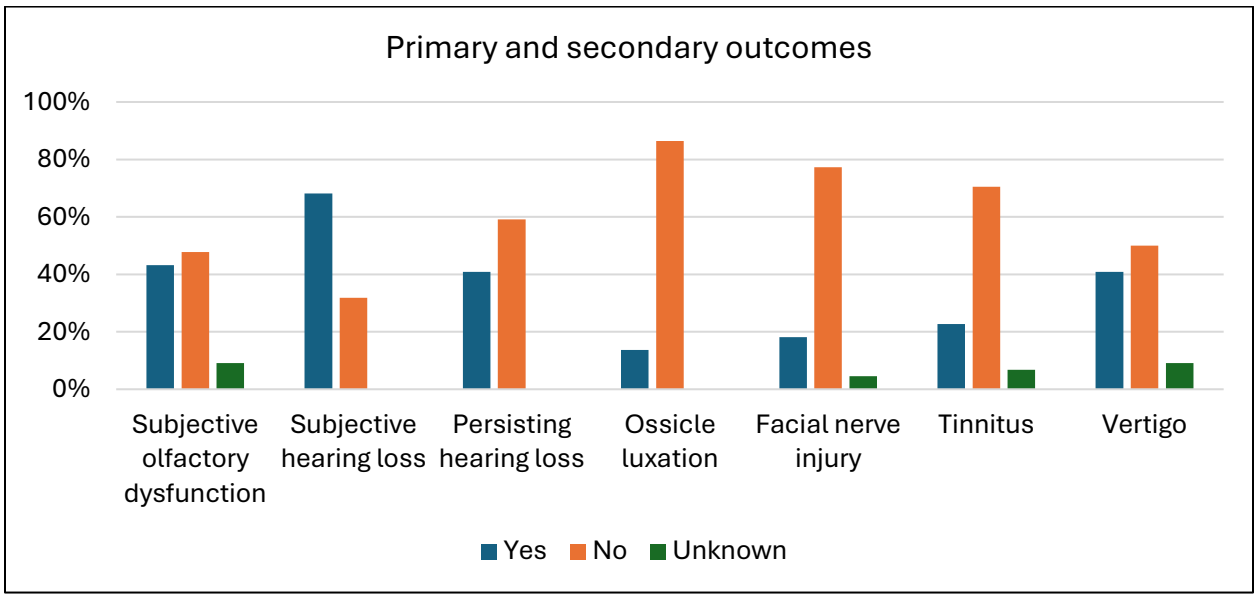

Figure 3. Primary and secondary outcomes in study population, percentage distribution.

Table 3. Chi-squared analysis with subsequent p-values of distribution of secondary outcomes in TBI classification and related to subjective olfactory dysfunction. TBI: Traumatic Brain Injury; χ2: Chi-squared analysis.

	Severity of TBI	Subjective olfactory dysfunction
Subjective hearing loss	χ^2: 0.65, p-value: 0.72	χ^2: 4.75, p-value: 0.09
Persisting hearing loss	χ^2: 1.02, p-value: 0.60	χ^2: 0.82, p-value: 0.67
Ossicle luxation	χ^2: 5.73, p-value: 0.06	χ^2: 1.31, p-value: 0.52
Facial nerve injury	χ^2: 0.53, p-value: 0.77	χ^2: 1.41, p-value: 0.49
Tinnitus	χ^2: 3.60, p-value: 0.46	χ^2: 2.76, p-value: 0.60
Vertigo	χ^2: 6.78, p-value: 0.15	χ^2: 3.24, p-value: 0.52

Hearing outcomes

30 patients experienced post-traumatic hearing loss directly after TBI. When evaluating hearing tests at 6 weeks of follow up, 26 showed objective hearing loss, based on a Pure Tone Average of above 20 decibels. Subjective and objectified hearing loss did not correspond completely. In 7 cases of abnormal audiometry, no hearing loss was experienced and another 7 patients experienced hearing loss with normal audiometry. Part of the explanation may be that subjective perception was assessed during the hospital admission, while hearing tests were conducted 6 weeks later. When evaluating most recent available audiometry tests, 18 patients experienced persisting hearing loss, including all 6 patients with pre-existing hearing loss.

Nature of hearing loss, based on most recent available abnormal audiometry Pure Tone Average, is depicted in figure 4. Post-traumatic unilateral complete deafness was seen in 2 cases, accounting for 2 of 9 cases of sensorineural hearing loss. Due to the bilateral conducted audiometry and mostly unilateral skull base fracture, only audiometry interpretation of affected side is analysed. In the 5 cases of bilateral fracture, most recent bilateral audiometric tests were analysed. In 2 of these cases, there was unilateral conductive loss with contralateral no abnormal audiometry. Persisting conductive hearing loss was seen in 4 other patients. Mixed hearing loss was observed in 3 patients.

Due to the lack of data regarding the nature of pre-existing hearing loss, no definitive conclusions can be drawn regarding the extent of TBI influence on the pre-existing hearing impairment. This subsection of study population is separately depicted in figure 4.

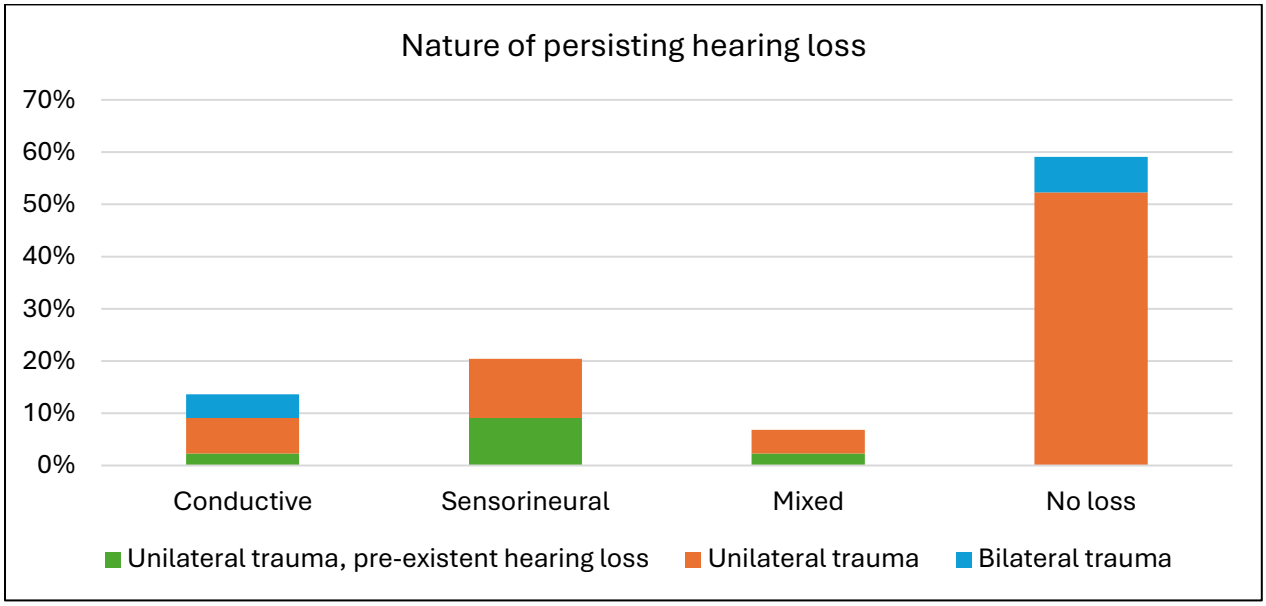

Figure 4. Nature of persisting hearing loss, based on most recent available audiometry.

Table 4. Frequency of conducted audiometric tests.

Frequency of audiometric tests	Number of cases
1	24
2	14
3	2
4	2
5	2

Post-traumatic bilateral audiometry was conducted in all cases. No patients had undergone pre-traumatic audiometry. Frequency of conducted audiometry is shown in table 4. Six patients underwent three or more audiometric tests. One patient underwent 5 hearing tests to evaluate conductive hearing loss. Ultimately, a middle ear inspection surgery showed an ossicular chain dislocation. After chain reconstruction through placement of a Partial Ossicular Replacement Prosthesis, the patient experienced significant postoperative improvement. The other patient undergoing 5 audiometric tests also considered middle ear inspection. However, it was decided not to proceed with a surgical option and instead chose hearing aids. Both patients undergoing 4 audiometric tests also started using hearing aids.

Discussion (850 words)

This study describes olfactory and other ENT-related outcome in 44 patients with sustained TBI. Subjective olfactory dysfunction was frequently present in our study population with a prevalence of 43.2%. In 4(9.1%) cases, olfactory outcomes were unknown. Pre-existent dysosmia was observed in 2(4.5%) patients of study population. This number is comparable to the prevalence in the general population.[9,10] In our study, post-traumatic olfactory loss prevalence is almost a tenfold higher than in general population. Previous studies report post-traumatic prevalences, varying from 12.8 to 67%.[5,7,25]

Despite its high prevalence, olfactory function was initially assessed in only 16 of 44 cases. Moreover, in three of 16 cases, only other departments as rehabilitation medicine and neurology documented on olfactory function. This contrasts with hearing loss, which is assessed by ENT-consultants in all patients with subsequent audiometry tests. This may have various reasons, such as the fact that hearing loss is readily noticeable when a doctor speaks directly to the patient or that the loss of smell is overshadowed by more disabling and life-threatening conditions, such as facial nerve injury, vertigo or tinnitus symptoms.[5,8] This is also reflected in requested additional testing. A total of 76 bilateral audiometry tests have been conducted, in contrast to zero objective olfactory tests.

Therefore, olfactory function should be systematically assessed in all patients following traumatic brain injury. There is a great potential in early diagnosing, treatment and counselling regarding potential risks of olfactory dysfunction.[12,17] People with olfactory loss report amongst other things increased social insecurity and experience significantly more hazardous events.[14,15,16] Lee et al observed in a population with olfactory dysfunction that in a 5 year period, 32.2% faced a spoiled food incident and 14.8%

experienced a gas incident. Up to 72% were concerned with hazard avoidance and lack of food enjoyment, greatly impacting emotional well-being, as a consequence of living in fear.[14]

Treatment should consist of olfactory training. Olfactory training has emerged as an effective treatment option for olfactory loss. Olfactory training is based on the deliberate and repeated exposure of odorants to strengthen and train residual neurological pathways to compensate for severed nerve connections. Studies have demonstrated its efficacy in different patient populations. Significant improvement of olfactory function was observed in 33-36% of TBI study populations.[26,27,28]

Recommendations

Given that subjective olfactory dysfunction has been experienced in 43% of patients and that olfactory dysfunction is associated with social insecurity and hazardous events, it is essential that we prioritize this issue. We must initiate the implementation of olfactory function assessment during ENT consultations in patients who have sustained TBI.

It is our recommendation to address olfactory dysfunction similar to hearing loss. For every patient, an audiometry is performed six weeks after initial assessment to objectify hearing loss. During hospital admission, active inquiry regarding olfactory loss should be made and an olfactory test should be conducted after six weeks to objectify olfactory loss.

Furthermore, significant research gaps exist regarding the pathophysiology, incidence and recovery of post-TBI olfactory dysfunction. Prospective longitudinal studies are needed to fully investigate incidence and treatment of olfactory dysfunction after TBI.[5,27,29]

Strengths and limitations

This study provides a comprehensive overview of the ENT-related effects of TBI, since many variables have been included. Prevalences of different pre-existent diseases and secondary outcomes do correspond with previously reported prevalences in other studies, indicating that our study population is well-aligned and comparable to other post-TBI populations. The study population is substantial with 44 individuals included. Despite the retrospective nature of the study, there were few missing data, and adequate efforts are made to prevent missing data on the main outcome.

However, limitations of this study relate amongst other things to selection bias. Since our study population is single centered in a University Medical Center and patients who did not show up at follow-up appointments were excluded, there is a possibility that our study population consists of more severe cases and is not as evenly distributed as presumed.

The retrospective study design contributes to risk of missing data, exclusions and unclear follow-up time for secondary outcomes. Furthermore, medical records on radiographic

features were of limited use due to the absence of a systematically applied TBI classification system.[30,31] In a prospective study, these issues could be easily addressed.

Due to the absence of olfactory tests, only subjective olfactory function is investigated. Previously mentioned prevalences are objectified through different olfactory threshold measurements.[7,9,32] It is somewhat questionable whether we can derive definitive conclusions from objective and subjective prevalences. Tinnitus and vertigo outcomes are likewise only subjectively assessed. Prior studies have described discordance in self-awareness of olfactory dysfunction. Haxel et al mention a self-awareness of 57% in olfactory dysfunction after head trauma. In their study, 14 of 82 participants scored low on BSIT, indicating olfactory dysfunction of some kind. However, only 8 of those reported a decreased sense of smell.[7] Neumann et al showed, based on BSIT in 106 participants with 59 cases of olfactory disturbance, a dysosmic self-awareness of only 36%.[25] However, this discordance in self-awareness and objectified dysfunction also indicates that there may be significant underreporting of olfactory dysfunction. This provides even more reason to thoroughly evaluate olfactory function in post-traumatic brain injury setting.

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APPENDIX B. Relevant medical history

Relevant ENT medical history, diseases	**Frequency in study population**
Hay fever / house dust mite allergy	2
Nicotine abuse	1
Septum deviation	1
Functional Endoscopic Endonasal Surgery	2
Alcohol abuse	4
Total*	9

* One patient had a history of both nicotine and alcohol abuse.

Relevant general medical history, diseases	**Frequency in study population**
Head trauma	3
Insulin Dependent Diabetes Mellitus	3
Multiple Sclerosis	1
Total	7

APPENDIX C. Data corresponding to figure 3.

Outcome	**Yes**	**No**	**Unknown**
Subjective olfactory dysfunction	19	21	4
Subjective hearing loss	30	14	0
Persisting hearing loss	18	26	0
Ossicle luxation	6	38	0
Facial nerve injury	8	34	2
Tinnitus	10	31	3
Vertigo	18	22	4