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Singh, R., Humphries, T., Mason, S. orcid.org/0000-0002-1701-0577 et al. (3 more authors) (2018) The incidence of anosmia after traumatic brain injury : the SHEFBIT cohort. Brain Injury, 32 (9). pp. 1122-1128. ISSN 0269-9052

https://doi.org/10.1080/02699052.2018.1483028

The Incidence of Anosmia after Traumatic Brain Injury; the SHEFBIT cohort

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Abstract

Background: While anosmia is common after Traumatic Brain Injury(TBI) (prevalence 4-68%),studies differ in the associations found with other variables.

Aims: to assess the incidence of anosmia within a large, mixed TBI cohort and examine relationships with other injury or demographic features, including depression and global outcome(GOSE).

Design, Subjects and Setting: 774 consecutive TBI admissions over two years, assessed within a specialist neurorehabilitation clinic.

Methods: All patients assessed at 6-8 weeks and 1 year. Tools included the Extended Glasgow Outcome Scale(GOSE), Rivermead Head Injury Follow-up Questionnaire, Rivermead Post-Concussion Symptoms and the Hospital Anxiety and Depression Score. Olfactory function assessed with sensitivity to coffee granules.

Results: The overall incidence of anosmia was 19.7%; mild TBI(9.55%), moderate(20.01%), severe(43.5%). On a logistic regression, features of TBI severity ($p<0.001$ (95% CI 0.098-0.438)), medical comorbidities ($p=0.026$ (95% CI 0.301-0.927)) and depression ($p=0.006$ (95% CI 1.202-2.981)) were significant. 60% of patients with anosmia at one year were found to be clinically depressed, compared to 36% of patients without anosmia.

Conclusion: In the largest prospective study of post-TBI anosmia, the incidence increased with TBI severity and other medical illness. The presence of anosmia should also raise the clinical suspicion of depression.

Introduction

Traumatic Brain Injury (TBI) is a common cause of severe disability worldwide, often affecting a disproportionate number of young individuals. It is often referred to as a 'silent epidemic' due to the relatively low priority that the condition receives in the media.[1,2] Although incidence as high as 790/10^5 is reported[3] the incidence of TBI resulting in hospitalisation is much lower and estimated at 235/10^5.[1,] These cases represent more significant injuries which remain the focus of most TBI studies.

TBI is associated with a number of physical, psychological and social sequelae. Significant physical sequelae include: headache, pain, sensory disturbance, seizures and dizziness.[4]

Another common complication of TBI is Olfactory Disturbance (OD). OD may occur after damage to either the peripheral or the central pathways of olfactory system. The olfactory bulb and the olfactory nerves are at risk of damage due to shearing forces induced by acceleration-deceleration injuries (Figure 1). Damage to secondary olfactory centres such as the orbitofrontal cortex is also possible (Figure 2).[12] As OD usually manifests with frontal lobe pathology, it can be part of a complex clinical picture with other frontal lobe functions including cognitive impairment and depression.[9,13-14]

OD can be further categorised as significant loss of function (anosmia) as opposed to lesser degrees of olfactory loss (hyposmia) although other disorders such as altered sense of smell (parosmia) also exist. The clinical significance of hyposmia is unclear and many individuals are completely unaware of subtle changes in olfactory perception.[5] Furthermore, the wide range of available olfactory tests differ in their threshold for diagnosing OD, particularly hyposmia.[6,7] In part due to such differences in classification, as well as marked differences between the tests, the incidence of OD is unclear and ranges between 4-60%.[8-11]

Previous studies of OD differ considerably in methodology. This is particularly marked with regards to the recruitment of subjects. Many studies have very selected populations such as referrals to psychiatry or litigants. Furthermore there are wide variations in the established olfactory tests with different tests, number of items and varying thresholds. Unsurprisingly this has resulted in considerable variation in

estimated incidence of OD.

As a result of this uncertainty and because anosmia affects quality of life and can be associated with other frontal lobe dysfunction[9,33], the rationale of this study was to assess the incidence of OD and whether any associated injury or demographic features could be identified. This was examined in a large mixed TBI population, representative of hospitalized cases and therefore of clinical relevance to all health professionals in TBI. However an attempt was made to identify only clinically significant OD rather than sub-clinical levels of dysfunction such as hyposmia, whose significance is unclear. Hence the term anosmia is preferred to terms such as OD or hyposmia. This was identified with a single strong smell (coffee) which is quick and easy to perform and which has been validated in TBIy[43] Associations of anosmia with population and injury features were also sought. No a priori hypotheses were made as to the variables that may form associations with OD in order to avoid any potential bias in study. It was hoped that any positive findings would help to inform clinicians and individuals of the likely risk factors, prevalence and possible prognosis.

Methods

The SHEFBIT (Sheffield Brain Injury after Trauma) cohort is a large outcome study of adult TBI patients admitted to a large teaching hospital and assessed and treated by a Rehabilitation Medicine team in outpatients. It is a prospective, observational cohort, encompassing the full spectrum of severity and aetiology of TBI and represents the condition as seen and treated by clinicians worldwide.[15]

Patients admitted with TBI between August 2013 and July 2015 were screened for inclusion. Eligible participants had a minimum of one night's stay in hospital and a CT brain scan. Exclusion criteria included children (<17) (seen at a separate hospital), previous TBI requiring hospital admission, dementia or residence out of Region. There was no upper age restriction. The diagnosis of TBI was confirmed using the Common Data Elements criteria.[16]

Admitted patients were screened within 24 hrs by the rehabilitation liaison team or the lead author (RS). Follow-up clinic appointments for TBI rehabilitation were arranged for 9-12 weeks after injury in the Brain Injury clinic, run by a Consultant in Rehabilitation Medicine(RS). All patients were subsequently followed up at 1 year to

measure outcomes including psychosocial outcome, depression and anosmia. Only assessments at 1 year are used in the study. Patients received letters, a text message and a phone call from clinic staff to facilitate attendance at 1 year. Non-attenders were telephoned to re-arrange appointments. All clinic patients were seen by the same clinician (RS). Records were examined for information on injury features, such as Glasgow Coma Score(GCS) on admission and head CT findings. Demographic factors including employment and family support were recorded as well as past medical and psychiatric histories. The latter was defined by any episode with psychiatrist, clinical psychologist or diagnosis by general practitioner. Alcohol intoxication at time of injury was taken from patient history or ambulance/medical records from admission.

Mechanism of TBI was classified according to the Trauma Audit and Research Network (TARN) classification system as falls, assault, road traffic collisions (RTC) and other mechanisms which predominantly consisted of work place injuries, sports injuries and falls greater than 2 metres.[17] CT scan findings were documented with location and type of each lesion. Only initial scan was used in case of repeat scans being taken. Scans were classified using the “overall appearance” of the CT scan which grades the severity of CT abnormalities after TBI; these are graded as normal, mild focal injury, medium focal injury and diffuse injury.[18] Medical comorbidity was assessed with the Cumulative Illness Rating Scale (CIRS) with a cut off >10 establishing significant level of comorbidity.[19] Pre-injury employment status was recorded as working (including full-time students), unemployed or retired. Work status at follow-up was recorded in three categories; unable to work, partial return to work and a complete return to work or the capacity for work for those who were retired or unemployed. The study was approved by both the Hospital Trust (STH16208) and the University of Sheffield Ethics Committees (Ref008315).

Assessments

Anosmia was described as a binary outcome and function was tested by a brief assessment of odour identification with coffee granules in a container with holes to avoid identification. Granules were changed at each clinic and held directly under the nose. Patients who reported no change in olfactory function and were able to correctly identify coffee were described as ‘normosmic’, whereas those who were

unable to identify the coffee were described as having anosmia, irrespective of their self-report. It is acknowledged that there are a number of different methods of defining degrees of OD which is discussed later. However single odour identification with self-report has been shown to be reliable and is the standard technique taught in textbooks of neurology and medicine.[20,40-42] Our parallel study confirms that coffee produces similar result to a validated test (Sniffin Sticks) with a sensitivity of 93% and specificity 96%. More detailed tests take considerable time and in a busy clinic are not possible. This was a pragmatic approach to recognizing significant impairment of olfactory function although we recognize that it is not perfect.

Depression was assessed using the HADS (Hospital Anxiety and Depression Scale). This is a self-filled questionnaire with seven questions for both anxiety and depression resulting in an overall score of 0-21 for each.[22] Only the depression subscale was used.Patients also completed a Rivermead Head Injury Follow-up Questionnaire and a Rivermead Post-concussion Symptom Score. The former is a ten item questionnaire for psychosocial function after TBI and the latter is a commonly used checklist of sixteen common head injury symptoms graded in Likert style from 0-4. Both of these have been validated in TBI populations.[23,24] Overall global outcome was assessed by structured interview using the Extended Glasgow Outcome Scale (GOSE).[25]

Analysis

Patients with/without anosmia at follow-up were compared for demographic and injury variables using a univariable regression for continuous variables such as age or χ^2-test for categorical variables such as employment or socioeconomic class. When χ^2-test assumptions were not met, a Fisher Exact test was used. Further analysis was carried out with a multivariable logistic regression analysis with anosmia as the outcome of interest and variables entered to determine the independent predictors of anosmia. Significance level was taken as $p<0.05$. Statistical analysis was performed using SPSS version 23.

Results

Patient Demographics

A total of 774 patients were enrolled into the study; 690 patients completed the one year follow up. Despite calls and letters, 46 individuals did not attend follow-up and 38 had died. This represents a follow-up of 94% of the study. The demographics of patients who completed both appointments are shown in Table 1 compared to those who were lost to follow-up. Individuals lost to follow up were older by 7 years and had slightly milder TBI but otherwise showed no major difference to those who attended follow-up.

Prevalence of Anosmia

The primary outcome of this study was to measure the prevalence of anosmia within a mixed TBI population. At twelve months post-injury this was 19.7% (n=136). Three individuals could not smell the granules due to a common cold and were considered normosmic. The prevalence of anosmia was lowest in patients with mild TBI (9.55%) followed by moderate TBI (22.01%) and highest in those with severe injuries (43.5%).

Univariable Analysis

Within a univariable analysis, a number of factors were found to be significant ($p < 0.05$): TBI severity, ($p<0.001$); Previous Psychiatric History, ($p=0.011$); GCS at time of injury, ($p<0.001$); CT Scan Appearance ($p<0.001$); intoxication at the time of the injury ($p<0.001$); medical comorbidity ($p=0.010$); depression and anxiety at twelve months follow up ($p<0.001$),($p<0.001$); GOSE at twelve months ($p<0.001$), RHFUQ and RPCS scores at twelve months ($p<0.001$),($p<0.001$). Employment status at twelve months post-injury was also significant ($p<0.001$), as a large proportion of patients failed to return to work to the same standard as before TBI. Aetiology of TBI, gender, ethnicity and pre-injury employment status were not significant. The univariable p-values are shown in the first column of Table 2.

Multivariable Analysis

A multivariable logistic regression was conducted to analyse the impact of all the variables assessed within the study. For this analysis, GCS was used as the marker

of severity. Anosmia was the dependent variable. The results are shown in Table 2 with 95% confidence intervals.

Significant relationships were found with comorbidity (p=0.026); depression at twelve months (p=0.006) and TBI severity (p<0.001). All other variables dropped out of the final model.

The overall model was highly significant (p<0.001), Nagelkerke R^2 was 0.271. The model correctly classified the outcome in 83.0% of cases compared to the model with no predictors that classified 80%. While this is a small improvement, it is a significant one. The AUC was 0.806 (95%CI 0.768-0.841). The Hosmer-Lemeshow Goodness of Fit statistic was satisfactory (χ^2=5.765, df8, p=0.674).

Discussion

The incidence of anosmia was 19% although this varied markedly with severity of TBI. This falls in the middle of the range of previous estimates which vary considerably from 4- 60%.[10,11]

This is by far, the largest prospective study on anosmia in consecutive TBI admissions to hospital. The group is typical of the patients seen in clinical practice and therefore relevant to all clinicians. It suggests that screening for anosmia can be done simply and quickly even in busy clinics. Apart from TBI severity, it was also found that anosmia was strongly associated with significant medical comorbidity and depression. These findings have been reported in previous literature. A number of variables including psychosocial outcome (RHFUQ) and global outcome (GOSE) were significant on univariable but not on multivariable testing.

The differences in previous studies can in large part be attributed to wide differences in study methodologies. In many instances, patient recruitment is limited only to STBI. Other studies use patient self-report or are based on convenience samples such as referrals to psychiatry or ENT. We are not aware of any study that has prospectively examined anosmia in consecutive TBI admissions in a systematic manner.

The finding of increased incidence of anosmia with increasing TBI severity has been well described.[11,26] In STBI, the incidence can be as high as 50% [6] and in combined moderate and severe injuries, 35%.[14] MTBI estimates vary from 4-16%.[27,28] These

are similar to the findings here. Such figures may be useful in advising patients after TBI with respect to the prognosis of long-term anosmia.

However, it should be noted that some studies have shown no relationship to TBI severity.[10]

In contrast to findings with TBI severity, there was no association with severity of CT findings and anosmia. This may reflect the inability of the classification system to specify the exact location of CT lesions rather than specifically to the frontal lobe where olfactory function is located.[18] In this respect, MRI may offer better imaging than CT in the investigation of anosmia.[39]

Medical comorbidity was an independent predictor of anosmia. It is possible that this is subject to a number of confounding factors; several medical conditions such as Type II diabetes mellitus and hypertension have been identified as potential causes of anosmia as well as drugs such as antihypertensives.[29,30] Unfortunately we have not subclassified comorbidities so cannot separate the effect of different conditions or drugs.

Anosmia can be considered a manifestation of frontal lobe pathology and association between anosmia and additional frontal lobe dysfunction including verbal fluency and executive function is well documented.[6,9] The results of this study, demonstrating a significant association between anosmia and depression after TBI, are of particular interest.[37] This association may occur due to an anatomical relationship between the two functions. As the OFC plays a key role in mood regulation, as well as the recognition and differentiation of smell,[20,31] it is likely that this shared location is at risk of damage after TBI (Figure 2). The finding cannot be explained simply by increased severity of TBI as most studies show no link of depression and TBI severity.[32]

It is known that anosmia can be detrimental to quality of life(QOL).[33] A number of TBI outcomes, although not QOL, were measured in this cohort. Unfortunately many of these factors were highly correlated with one another. It has been shown that many outcome measures evaluate the same concept of “emotional distress” and can be expected to be simultaneously elevated or normal in individuals .[34] This was demonstrated in the multivariable analysis where outcome measures, including GOSE, dropped out of the model, having been highly significant on univariable tests. Therefore in this study, there was no association between anosmia and global outcome.It has been suggested that the GOSE is a relatively crude measure and

may lack sufficient sensitivity to detect subtle changes. It is also possible that anosmia affects quality of life but not the actual functioning and abilities of an individual (the “quantity of life”). Hence global outcome is unaffected. The use of a QOL measure would have been helpful in assessing this.

Strengths and weaknesses

The main strength of this project is the large size of the prospective cohort when compared to other studies. The SHEFBIT cohort is representative of hospitalised TBI with a good mix of mild, moderate and severe TBI.[16] These are sufficient numbers to make relevant inferences about the subgroups in a clinically relevant setting. Much of the previous literature is in highly selected groups e.g. referred for olfactory testing or in litigants. The results are therefore relevant to all clinicians who we hope, will be able to screen for anosmia with a simple but effective test.). Similarly, the patient assessments occurred in a setting that will be familiar to clinicians treating TBI; individuals were followed up in a specific Brain Injury Clinic shortly after injury and again at 1 year. The assessments were pragmatic in terms of the time taken to evaluate a number of clinical parameters including anosmia. It is important to minimise patient burden as extensive and detailed assessments lead to poor patient attendance and distress.[35]

A particular strength of the study was the ability to facilitate re-attendance by use of letters and phone calls. This undoubtedly led to an excellent follow-up rate (94%), much higher than other TBI studies where losses of up to 70% at 6 months are reported.[38]

The use of a single observer for all assessments minimizes inter-observer variation. The main weakness of the study is the diagnosis of anosmia using coffee granules. While this is a very potent stimulus and single odour identification is the standard technique taught in textbooks of neurology and medicine [20,40-42], it is by no means the gold standard. In a parallel study we found sensitivity of 93% and specificity of 96% in comparison of coffee with a 12 item Sniffin Sticks test kit; this suggests excellent validity. Indeed there is no agreement on which of the many available tests is the best and considerable variation exists.[6-7,36] Unfortunately, detailed assessments using a battery of as many as 40 different smells can take up to an hour to administer and in a busy clinical setting, such assessments are unlikely to be possible. The more detailed tests however will identify milder forms of OD such

as hyposmia which we have not done. However the clinical significance of such disorders is unclear; many patients are unaware that they have these subtle degrees of altered smell and tests vary considerably in the diagnostic threshold.[5] It is also accepted that the coffee test does not detect parosmia or altered sensation although no individual reported this on testing. By contrast anosmia is a far more significant complication and it is rare for an individual with anosmia to have not noticed such a change.

Other weaknesses are that smoking has not been corrected in the model and that there is no control group for the study. It was also not possible to test for taste dysfunction due to time constraints but this may have yielded further information.

Future work needs to establish the nature of the relationship between anosmia and depression with particular regards to the anatomical link and frontal lobe damage. Documentation of CT abnormality needs to describe the exact location of the lesions rather than the extent of lesions. In addition the relationship with other possible frontal lobe impairments such as executive function or verbal fluency may be conducted. It is important to distinguish between subtle changes in smell which are often unnoticed by the individual and more significant, clinically relevant anosmia which has been investigated in this study. Within constraints of busy clinical practice, assessment has to be reliable but practical and much of the established literature is impractical for busy clinicians.

An examination of the temporal relationship between depression and development of anosmia may also allow the determination as to whether one of these features leads to the other in a particular chronology. In other words, does anosmia lead to depressed mood as a result of loss of pleasurable smells or could depression result in a blunted response to appreciation or distinguishing of smells. This will require repeated assessments of individuals and is unlikely to be achieved in a cohort of this size.

The ease of testing and the accuracy of the single odour test should encourage busy clinicians to screen TBI patients for anosmia. We suggest that positive findings may then need to be referred for further detailed assessment by ENT specialists.

Conclusions

The incidence of anosmia was 19.7% in a mixed TBI population and was significantly

associated with TBI severity.Even in a busy clinical setting, screening for anosmia can be done quickly and accurately. Despite often being regarded as an innocuous outcome after TBI, the relationship between anosmia and depression demonstrates the significance of anosmia within the clinical picture of TBI and the relationship with overall outcome requires further exploration.

Declaration of Interest

The authors report no declarations of interest.

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Table 1; demographics at 1 year and comparison to non-attenders

	Followed up, n= 690	lost at follow-up, n=46	χ^2 or t-test, df, p-value
Mean Age yrs (95% CI)	46.5(45.6-48.3)	53.2(46.2-55.8)	5.39 df825 p=0.022*
Gender			
Male N(%)	484 (70.1%)	28(60.9)	1.56 df1 p=0.212
Ethnicity N(%)			
White	641 (92.9)	44 (95.7)	2.116 df4 p=0.714
South Asian	33 (4.8)	2 (4.3)	(Fisher Exact Test)
Black	11 (1.6)	0 (0)	
Oriental	3 (0.4)	0 (0)	
Other	2 (0.3)	0 (0)	
(Non-white)	49 (7.1)	2 (4.3)	0.508 df1 p=0.510
Employment N(%)			
Yes	488 (70.7)	26 (56.5)	5.22 df2 p=0.074
No	96 (13.9)	5 (10.9)	
Retired	106 (15.4)	15 (32.6)	
Aetiology N(%)			
Fall	233 (33.8)	13 (28.3)	3.4 df4 p=0.494
RTC	187 (27.1)	15 (32.6)	
Assault	137 (19.9)	6 (13.0)	
Sport	48 (7.0)	4 (8.7)	
Other(work)	85 (12.3)	8 (17.4)	
Any Comorbidity N (%)	249 (32.2) ?	12 (26.1)	2.83 df1 0.092
Alcohol at injury N (%)	206 (26.6)	13 (24.5)	0.111 df1 0.739
Previous Psychiatric Hx N (%)	152 (22.0)	9 (19.6)	0.148 df1 0.701
Mean GCS at injury	11.9(11.7-12.1)	12.9(12.3-13.6)	3.26 df825 0.013*
Severity by GCS N(%)			
Severe(3-8)	108 (15.7)	7 (13.2)	0.609 df2 p=0.738
Moderate(9-12)	268 (38.8)	19 (35.8)	
Mild(13-15)	314 (45.5)	27 (50.9)	
Median Length of Stay in Days (IQR)	3.0 (8)	2.0 (7)	U=19639, p=0.597 (Mann-Whitney Test)

Table 1: Demographics of study cohort and non-attenders at 1 year
Figures are number(%) for categories and mean(95% Confidence Interval) for continuous data except Length of stay, expressed as median (interquartile range) *p<0.05

Table 2. Univariable and Multivariable Analysis of anosmia

					95% CI for OR	
Variable	Univariable p-value[1]	B	Multivariable p-Value	OR	Lower	Upper
Gender	0.260	0.337	0.197	1.401	0.839	2.339
Ethnicity (White)	0.463	-0.636	0.116	0.530	0.240	1.169
Age	0.710	-0.001	0.944	0.992	0.982	1.017
Aetiology	0.088		0.258			
Fall(baseline)			-	1		
RTC		0.737	0.079	2.089	0.917	4.756
Assault		0.461	0.242	1.586	0.732	3.437
Sport		0.970	0.028	2.637	1.110	6.268
Other		0.550	0.343	1.734	0.557	5.403
Alcohol	<0.001*	0.203	0.458	1.225	0.717	2.091
Psychiatric History	0.011*	0.048	0.857	1.049	0.622	1.768
Pre-injury Job	0.072		0.936			
Employed(base)			-	1		
Unemployed		-0.105	0.815	0.900	0.373	2.173
Retired		-0.006	0.990	0.994	0.370	2.671
CT Scan	<0.001*		0.297			
NAD(baseline)			-	1		
Focal		-0.062	0.895	0.940	0.374	2.362
Adjacent Lobes		0.541	0.194	1.717	0.760	3.881
Diffuse		0.154	0.677	1.167	0.565	2.413
Comorbidity	0.010*	0.590	0.026*	1.893	1.202	2.981
Return to work	<0.001*		0.311			
Full(baseline)			-	1		
Partial		0.680	0.143	1.974	0.795	4.906
No work		0.555	0.150	1.741	0.818	3.707
GCS	<0.001*	-0.265	<0.001*	0.796	0.713	0.889
HADS-D	<0.001*	0.152	<0.001*	1.164	1.012	1.422
RHFUQ	<0.001*	0.003	0.869	1.003	0.963	1.045
RPCS	<0.001*	0.013	0.464	1.013	0.979	1.048
GOSE	<0.001*	-0.229	0.203	0.795	0.559	1.132
Constant		1.907	0.259	6.733		

Table 2; Univariable and Multivariable Analysis of anosmia

[1] univariable regression for continuous and $\chi 2$-test for categorical variables. * significant at $p<0.05$

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