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Smell and Taste Dysfunction are Markers of Early and Persistent Pathology Following Traumatic Brain Injury (TBI)

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Abstract

There are presently no quantitative clinical markers which can consistently identify patients after Traumatic Brain Injury (TBI). In 90 patients with TBI we measured smell function (by olfactometry), taste function (by gustometry), sensory distortions by subjective responses, quantitated these results and compared them to findings in normal subjects to determine if abnormalities of these functions might serve as these markers. All patients complained of smell and taste loss. Losses occurred rapidly after TBI and persisted. By tests, patient ability to smell or taste was significantly impaired; sensory distortions were also present. However, by test 71 patients with smell loss (83%) could recognize most odors and 77 (86%) could recognize most tastants. Twenty-three (26%) exhibited sensory distortions. Smell and taste function were subjectively impaired after TBI and abnormalities in smell and taste were consistently measured. Impairments occurred rapidly after TBI and were their longest lasting pathological findings. Smell and taste impairments are common events after TBI and are quantitative markers which identify these patients. Although smell and taste function were subjectively impaired they were measured in patients to some degree by use of olfactometry and gustometry. Results are consistent with the presence of smell and taste dysfunction but are inconsistent with dogma that patients exhibit anosmia, a total loss of smell function after TBI, which has been hypothesized to occur following severing of the fila olfactoria from the cribriform plate. Results are consistent with as yet not clearly defined functional biochemical/metabolic causes of these sensory changes.

Keywords: Traumatic brain injury; Smell loss; Taste loss; Hyposmia; Hypogeusia; Disease marker

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Introduction

Traumatic Brain Injury (TBI) is a common event in the United States affecting as many as one million people annually [1]. It is a common source of both morbidity and mortality [2,3]. There are diverse patterns of cognitive pathology after TBI with the elderly exhibiting worse outcomes than younger people [4,5]. Some patients do not regain all cognitive abilities they experienced prior to their TBI. However, most patients regain most cognitive function after TBI but they recognize impairments in these functions. It is this latter group of patients whom we have studied at The Taste and Smell Clinic in Washington, DC.

At present there are no specific objective non-invasive quantitative clinical/pathological markers by which TBI has been consistently measured in this patient group although there have been multiple searches for such markers [6,7]. Such markers have been identified and characterized but not accepted as definitively diagnostic by the physician community.

While there are multiple initial symptoms associated with TBI most commonly decrease over time. These symptoms are obvious and distressing to patients. Initial symptoms commonly include loss of consciousness, prograde and retrograde amnesia, seizures, nausea, vomiting, headache, diplopia and hearing loss [8,9]. There are also longer lasting symptoms such as loss of memory, verbal agnosia, acalculia, difficulty concentrating, emotional lability, sleep disorders and vertigo [8,9]. While vertigo is one of the most persistent symptoms following TBI it also usually decreases gradually in severity and commonly disappears [10].

On the basis of experience with patients who complained of taste and smell dysfunction evaluated at The Taste and Smell Clinic over the past 13 years, we have encountered many patients who

Table 1: Smell Function in 90 Patients with Traumatic Brain Injury Compared to Normals.

	PYRIDINE				NITROBENZENE			
	DT	RT	ME	H	DT	RT	ME	H
PATIENTS	7.90 ± 0.31*,a	8.98 ± 0.29[a]	33 ± 3[a]	-30 ± 3[a]	8.19 ± 0.40[a]	9.42 ± 0.37[a]	14 ± 3[a]	-6 ± 3[c]
NORMALS (55)	4.40 ± 0.20	7.80 ± 0.10	66 ± 5	-51 ± 5	4.10 ± 0.20	5.90 ± 0.20	56 ± 6	3 ± 1

	THIOPHENE				AMYL ACETATE			
	DT	RT	ME	H	DT	RT	ME	H
PATIENTS	8.21 ± 0.39[a]	9.44 ± 0.34[a]	18 ± 3[a]	-13 ± 3[a]	8.40 ± 0.40[a]	9.69 ± 0.36[a]	14 ± 2[a]	0.8 ± 2
NORMALS (55)	3.80 ± 0.10	7.40 ± 0.20	69 ± 6	-59 ± 4	3.90 ± 0.10	7.10 ± 0.20	53 ± 5	5 ± 1

DT: Detection Threshold [in Bottle Units (BU)]
RT: Recognition Threshold [in Bottle Units (BU)]
ME: Magnitude Estimation (in percent)
H: Hedonic Evaluation (in percent)
* Mean ± SEM
( ) Subject number
With respect to normal
a p<0.001
c p<0.02

complained of taste and smell dysfunction after TBI [11]. In studies of these and many other patients [11] we developed and applied specific and well defined measurement techniques to characterize these sensory dysfunctions. While many prior studies have described smell loss in patients after TBI and post traumatic ageusia has also been described presence of both smell and taste dysfunction after TBI has not been well recognized, characterized, quantitated or their relationship to onset and persistence of these changes after TBI defined [10,12-14].

Impairments of smell and taste function have been successfully measured by specific psychophysical techniques by several groups of investigators [15,16]. These techniques are consistent with methods by which we defined and characterized presence of smell and taste dysfunction after TBI [11]. These tests demonstrate objective methods by which smell and taste dysfunction after TBI have been functionally determined by non-invasive techniques and quantitated to demonstrate their presence, persistence and character [11]. We now present data using these sophisticated techniques to define changes in smell and taste function which occur in patients after TBI.

Materials and Methods

Patients

Ninety patients who experienced TBI and self-reported dysfunction of smell and taste as a result of TBI were evaluated at The Taste and Smell Clinic in Washington, DC over a period from 2002-2015. Patients were aged 17-82y [47 ± 2y (mean ± SEM)] and comprised 49 men aged 17-74y (44 ± 2y) and 41 women aged 22 ± 82y (51 ± 3y). All patients complained of loss of smell and taste (i.e., flavor perception) upon presentation to The Taste and Smell Clinic. Length of time over which these sensory dysfunctions were present prior to presentation at The Clinic was from 0.2-5.5y [4 ± 1y (mean ± SEM)].

Measurement techniques

Smell and taste function were initially evaluated by obtaining a careful history of their TBI. Physical examination of their head and neck was performed. Measurements of smell and taste function were obtained by standardized olfactometry (for smell) and by standardized gustometry (for taste) on at least two occasions over a period of 2-4 weeks by methods previously described in detail [11]. Only results of the best test (closest to normal responses) were used. These tests demonstrated accuracy of determination of smell and taste function in these patients as shown previously in a double blind study and by others [15-17]. Results of these tests were compared to those obtained in healthy normal volunteers.

Smell function (olfactometry) was determined by a three stimuli, forced choice, staircase technique by which detection and recognition thresholds, magnitude estimation and hedonic characteristics for four stimuli – pyridine (pungent), nitrobenzene (bitter almond), thiophene (petroleum) and amyl acetate (banana oil) [11]. By these tests Detection Thresholds [(DT) (the least amount of stimulus detected as different from two blanks)] indicating quantitative presence of receptors [11], Recognition Thresholds [(RT) (the least amount of stimulus correctly recognized as that stimulus)] indicating quantitative presence of interactions between brain and receptors [11], Magnitude Estimation [(ME) (the intensity by which perception of each stimulus was quantitated)] indicating number of receptors per event [11] and Hedonics [(H) (the intensity by which the pleasant or unpleasant character of each stimulus was quantitated)] indicating brain responses to the presented stimulus [11] were determined. Unpleasant odorants were usually pyridine (pungent) and thiophene (petroleum) whereas pleasant odors were usually nitrobenzene (bitter almond) and amyl acetate (banana oil). Abnormal H values indicate pathology in both receptor/brain function interactions [11].

By these tests patients were categorized into four types of smell loss [11]. Total loss of smell was characterized as anosmia (DT=0, RT=0, ME=0, H=0), a rare change after TBI; this total loss was demonstrated by inability to detect or recognize any odor or judge intensity of any odor [11]. The next lesser degree of smell loss was termed type I hyposmia (DT>0, RT=0, ME=0, H=0). In this designation patients could detect odors but could neither recognize nor judge correctly intensity of any odor [11]. The next lesser degree of smell loss was termed type II hyposmia (DT>0, RT>0, ME>0, H<normal) which is the most common smell loss encountered among these patients. In this type patients could both detect and recognize odors and judge intensity but all measurements (thresholds and intensity) were less than normal [11]. The least degree of smell loss was termed type III hyposmia (DT=normal, RT=normal, ME<normal, H<normal); in this type DT and RT of odors were normal but ME was less than normal [11].

Table 2: Taste Function in 90 Patients with Traumatic Brain Injury Compared with Normals.

	NaCl				SUCROSE			
	DT	RT	ME	H	DT	RT	ME	H
PATIENTS	4.01 ± 0.22*,[a]	4.66 ± 0.29[a]	56 ± 3[a]	-31 ± 4[d]	3.74 ± 0.23[a]	4.37 ± 0.30[a]	42 ± 3[a]	24 ± 4
NORMALS (55)	2.30 ± 0.10	3.10 ± 0.20	68 ± 4	-18 ± 4	2.50 ± 0.10	3.20 ± 0.1	60 ± 4	35 ± 4

	HCl				UREA			
	DT	RT	ME	H	DT	RT	ME	H
PATIENTS	3.93 ± 0.19[a]	5.00 ± 0.28[a]	51 ± 3[b]	-37 ± 3[a]	5.15 ± 0.23[a]	5.88 ± 0.30[a]	40 ± 3[a]	-36 ± 3[d]
NORMALS (55)	3.10 ± 0.20	3.50 ± 0.10	66 ± 4	-58 ± 4	3.20 ± 0.10	3.40 ± 0.10	68 ± 4	-49 ± 5

DT: Detection Threshold [in Bottle Units (BU)]
RT: Recognition Threshold [in Bottle Units (BU)]
ME: Magnitude Estimation (in percent)
H: Hedonic Evaluation (in percent)
* Mean ± SEM
( ) Subject number
With respect to normal
a p<0.001
b p<0.005
d p<0.05

Taste function (gustometry) was determined by a similar three stimuli, forced choice, staircase technique by which DT, RT, ME and H for four taste stimuli – NaCl (for salt), sucrose (for sweet), HCl (for sour) and urea (for bitter) [11]. By these tests, similar to previously determined degree of smell loss, four types of taste loss were determined [11]. Total loss of taste was labeled ageusia (DT=0, RT=0, ME=0, H=0) similar to anosmia for smell loss; the next less severe taste loss was labeled type I hypogeusia (DT>0, RT=0, ME=0, H=0) similar to changes in smell loss; the next lesser degree of taste loss was labeled type II hypogeusia (DT>0, RT>0, ME>0, H<normal) and the least degree of taste loss was labeled type III hypogeusia (DT=normal, RT=normal, ME<normal, H<normal) similar to changes in smell loss.

For DT and RT, values were converted into Bottle Units (BU), as previously described by which mean ± SEM were determined and values compared to values obtained in normal subjects [17]. For ME, values were obtained arithmetically in percent with mean ± SEM determined on a 1-100 scale and results compared to values obtained in normal subjects [11]. By means of these results specific quantitative characteristics of presence of olfactory and taste receptors (DT), olfactory and taste receptor number and function (ME), olfactory receptor and neural interactions (RT) were obtained and interactions between receptors and brain function (RT, ME) were obtained. For H, values for stimuli considered pleasant (on a +1-100 scale in percent) or unpleasant (on a +1-100 scale in percent) were obtained for substances considered both pleasant and/or unpleasant with means determined arithmetically and subsequent mean ± SEM obtained for each stimulus with results compared to values measured in normal subjects [11]. Unpleasant tastants were usually sour (HCl) or bitter (urea) whereas sucrose (sweet) was usually considered pleasant. Results of all tests were collated and mean ± SEM of each sensory quality was determined and compared to similar results obtained in normal volunteers. Differences were compared using Student's t-test with $p<0.05$ considered significant.

Smell and/or taste distortions labeled dysosmia and/or dysgeusia, respectively, were expressed subjectively. Dysosmia was characterized by either phantosmia (the presence of an abnormal smell in the nose in the absence of any odor) or aliosmia (presence of an abnormal smell associated with the presence of an external odor). Phantosmia was described as burned, smoky, metallic or chemical (labeled torquosmia) or rotten (labeled cacosmia) as was aliosmia [11]. Dysgeusia was characterized by either phantageusia (presence of an abnormal taste in the mouth in the absence of any oral stimulus) or aliageusia (presence of an abnormal taste associated with the taste of food or beverages). Phantageusia was usually described as chemical, bitter or burned (torquegeusia) or rotten (cacogeusia) as was aliageusia [11].

These distortions were quantitated on an arithmetic scale from 1-100 with 1 reflecting the least intense distortion and 100 the most intense distortion experienced. These distortions, once experienced, were usually maintained with the same character and intensity once their presence was experienced. To quantitate these measurements mean ± SEM of patient distortions were calculated.

Results

Patient History after TBI

Each patient recognized and reported onset of smell and/or taste dysfunction as soon as they were stabilized after TBI. Each usually reported a significant loss of ability to obtain flavor from any food or beverage with their first experience of taste of foods or beverages. They usually reported a loss of ability to obtain the character of any odor, e.g., a diminished ability to recognize the smell of flowers and the flavor of food that might be present in their hospital room. Most usually recognized a decrease in ability to obtain their previously appreciated sweetness or sourness of foods or beverages. They commonly reported an increased awareness of these symptoms over time.

All patients were initially surprised by onset of these symptoms, particularly smell and flavor losses since they had no prior knowledge that these symptoms might occur. They did not understand onset or persistence of these symptoms. Upon reporting these symptoms to their treating physician they were usually told that these symptoms were possible but that they would probably be transient and that they would recover their normal sensory function over time. When these symptoms did not revert to normal they were commonly told that they may have "severed their olfactory nerves", that their fila olfactoria were severed from the cribriform plate and that this was the cause of their sensory losses [18,19]. At that point they were commonly told

Table 3: Smell and Taste Loss Type in Patients Following Traumatic Brain Injury.

	Smell Loss Type					Taste Loss Type				
		Hyposmia					Hypogeusia			
	Anosmia	I	II	III	Normal	Ageusia	I	II	III	Normal
Patient Number	4	15	66	5	0	2	0	68	9	11
Patient Percent	4	17	73	5	0	2	0	76	10	12

that they might never recover their normal sensory function and that there were no treatments for these dysfunctions [18,19].

Over time, usually weeks or months, some patients (23 of 90 or 26%) recognized not only loss of sensory function but also presence of distortions in their smell and/or taste function. These distortions, labeled dysosmia (for smell) and dysgeusia (for taste) had several characteristics as previously described. These symptoms usually occurred spontaneously; however, smell distortions could be initiated by presence of a strong external odor (labeled allodynosmia) and for taste by the presence of a strong taste (labeled allodyngeusia). Aliosmia and aliageusia occurred with some or all foods or beverages, were usually persistent, and could be severe enough to cause patients to decrease food intake since these distortions initiated a repugnant appreciation of most foods or beverages; because of these symptoms patients commonly lost appetite and had significant weight loss [11]. They were usually told that these symptoms would be transient but they commonly recognized that over time they were persistent and could become more intense.

Prior to presentation at The Taste and Smell Clinic most patients experienced one or more attempts at evaluation or treatment from a healthcare professional. These included treatment with antibiotics, nasal corticosteroid sprays, systemic corticosteroids, trace metals, alpha lipoic acid, hypnosis, acupuncture or chiropractic. None of these therapies were successful in restoring any aspect of their smell and taste dysfunction to or toward normal which caused each patient to seek some other method for evaluation of their symptoms. While spontaneous return of smell and/or taste function has been reported in about 1% of these patients this did not occur in any patient we evaluated [20]. Indeed, all patients who presented to The Taste and Smell Clinic complained of persistent smell and taste dysfunction despite these multiple prior attempts at evaluation and treatment. Physical examination of the head and neck was within normal limits in each patient.

Smell Acuity Changes

Tests of loss of smell acuity in all patients following TBI were compared to results in normal subjects in Table 1. Mean DT and RT for all odorants were significantly higher (less sensitive) than in normal subjects. Mean values were measurable for these stimuli which indicate that neural function, per se, was intact in most patients but was inhibited following TBI. Mean ME for all odorants were measureable but significantly lower than comparable values in normal subjects consistent with their inability to judge odorant intensity due to diminution of odorant receptor number and function; however, their presence indicates that olfactory receptors albeit decreased in number are present [11]. H values for the unpleasant odors of pyridine and thiophene were significantly decreased (less unpleasant) whereas values for H for pleasant odors of nitrobenzene and amyl acetate are significantly lower and less pleasant than comparable values in normal subjects which indicate abnormalities related to the interactions between olfactory receptors and brain function.

Taste Acuity Changes

Loss of taste acuity in all patients following TBI, as measured by psychophysical techniques, compared to results in normal subjects is shown in Table 2. Mean DT and RT for all tastants were significantly higher (less sensitive) than in normal subjects. The presence of these thresholds indicate that while gustatory function has been inhibited following TBI the anatomical system upon which taste function is experienced has been preserved in most patients. Mean ME for all tastants were also significantly lower in most patients. These results are consistent with diminution of both receptor number and function after TBI. H values for the unpleasant tastants of HCl and urea were lower (less sensitive) in patients after TBI consistent with their inability to perceive tastants quality and intensity; H values for the pleasant tastant (sucrose) was also lower in most patients after TBI also consistent with their inability to perceive pleasant tastant quality and intensity after TBI as well as do normal subjects. Presence of these responses, albeit decreased from normal, is consistent with intact neural function of the tastant system in most patients.

Changes in smell and taste loss type are shown in Table 3. For smell, only four of the 90 patients (4%) could neither detect nor recognize any odor (anosmia) whereas 15 (17%) could detect but not recognize correctly any odors (type I hyposmia). Thus, 71 or 83% of patients could both detect and recognize most odors (types II and III hyposmia). For taste, only two or 2% of the patients could neither detect nor recognize tastants (ageusia) whereas the remainder could both detect and recognize all tastants (type II, III hypogeusia and normal perception).

Smell and taste distortions

Twenty-three patients (11 men, 12 women, aged 21-82y) who reported smell and taste distortions in addition to their sensory losses consisted of 15 patients (nine men, six women) who exhibited phantosmia and/or phantageusia. Phantosmia was described as torquosmic (burned or smoky) by six patients, metallic by two, chemical by two and sweet or flowery by one, cacosmic (rotten) by two and torquosmic (chemical) by one. Phantosmia reported by these 15 patients had an intensity which varied from 5% -100% [(54 ± 9%) mean ± SEM]. Phantageusia was reported by 17 patients. Its intensity varied from 10% -100% (70 ± 7%). Both phantosmia and phantageusia were present in 14 patients. Their intensity varied from 10% -100% (62 ± 6%). Seven patients (one man, six women) exhibited aliosmia and/or aliageusia. One patient (a man) exhibited both phantosmia and aliageusia. Aliosmia and/or aliageusia were described as chemical (torquosmic and torquegeusic, respectively) by five patients and rotten (cacosmic and cacogeusic, respectively) by two. Both aliosmia and aliageusia occurred in seven patients in addition to their phantosmia and/or phantageusia. Their presence, with distorted perception of many external odors or imbibed foods, had an intensity which varied from 50% -100% (72 ± 9%). The one patient with both phantosmia and aliageusia described both of these sensations as rotten.

Discussion

Results indicate that both smell and taste function was impaired in these patients after TBI but intact to some degree. Losses in acuity were usually reported as early as one day after TBI and reported in our study as persisting for as long as 55 years. A few patients recognized these changes days rather then immediately after TBI. Patients noted onset of dysosmia and/or dysgeusia usually days or even months after they noted onset of acuity loss.

Acuity and distortion changes were measured by use of quantitative techniques and reflect both early and persistent changes after TBI, changes which can identify these patients. Variations in results quantitate severity of sensory changes consistent with the range of sensory dysfunction.

Smell and taste acuity changes were among the earliest reported sensory changes after TBI. They were reported once the patient was stabilized after other acute changes of TBI (e.g., headache, hearing loss, nausea and vomiting) had been obviated or significantly lessened. Sensory changes in smell and taste function, although early symptoms of pathology after TBI, tend to persist and are among the longest lasting sensory changes after TBI [10,14].

These changes indicate a quantitative reduction of smell acuity (hyposmia) and taste (hypogeusia) acuity in these patients but not a total loss of smell (anosmia) or taste (ageusia). These measurements indicate that while both smell and taste systems were impaired and all patients initially reported that they could neither smell nor taste, most patients were still able to both smell and taste to some degree which is inconsistent with the concept that an overall anatomical disruption of their neural or brain structures occurred to cause these changes. In our studies, there were no overarching specific abnormalities in olfactory brain anatomy discovered in any of these patients. Obtaining Computed Tomography (CT) scans of brain and Magnetic Resonance Imaging (MRI) of brain in these patients at the time of their evaluation at The Taste and Smell Clinic uniformly demonstrated presence of olfactory clefts, presence of normal rectus gyrus regions and presence of olfactory bulbs although there was occasional diminution of olfactory bulb diameter as noted previously by other investigators [19-21]. Lack of pathology in the olfactory region at the time of our studies is consistent with a lack of these changes reported earlier in these patients in which initial radiological studies included cerebral concussion, skull fracture, intracranial or subdural hemorrhage and regions of cerebral scarring which persisted in various brain regions but did not involve significant persistent cerebral changes in regions directly involved with the olfactory system. Indeed, measurements of intact smell function, albeit impaired, have been demonstrated by use of functional Magnetic Resonance Imaging (fMRI) of brain in patients with smell/taste loss after TBI [22]. While they have been previously related by many physicians to traumatic severing of the fila olfactoria by which these slender nerve fibers are torn from the cribriform plate assumed to lead to total loss of smell (anosmia) and also loss of subsequent flavor perception this concept cannot account for a simultaneous loss of both smell and taste function, per se, i.e., loss of smell and loss of taste for salt, sweet, sour or bitter. In addition, these diverse and severe changes in smell and taste function have been reported to occur after a mild or insignificant head injury with these patients reporting as severe a loss in smell and taste acuity as those in whom a severe TBI has occurred [10,14]. Thus, anatomical changes which putatively inhibited smell function cannot account for the associated changes in taste perception since anatomical damage to the taste system, per se, did not occur after TBI. However, while most patients did not exhibit anatomical changes to their olfactory system after TBI, in 4% as indicated by measurements of their anosmia, and in 2% as indicated by the measurement of their ageusia, the majority of these patients exhibited only some type of hyposmia and/or hypogeusia.

These results, if not anatomically but functionally related to TBI, raise the question of mechanism(s) by which these changes might occur. One answer could relate to presence of metabolic/biochemical changes in brain and/or receptor function by which smell and taste function following TBI are both impaired and do not involve shearing of fila olfactoria from the cribriform plate. Although there have been measurable changes in measurements of diameter of olfactory nerves and olfactory groove width after TBI olfactory nerves and olfactory grooves in our studies were always present and measurable [19-21]. These sensory changes are consistent with the presence of some other mechanism(s) than anatomical responsible for these dramatic early and persistent changes.

How can we account for the diverse changes demonstrated in both smell and taste function in these patients? Could there be some pathological phenomena, other than anatomical, responsible for these changes? Could there be biochemical or metabolic abnormalities by which these sensory impairments are dependent? Although not clearly defined there have been multiple hypotheses proposed to explain these symptoms. They have been related to changes in cerebral blood flow (hypo and/or hyperperfusion) [23,24], impairments of cerebrovascular autoregulation [25,26], apoptotic or necrotic cell death [27], cellular damage after blood-brain barrier damage with subsequent inflammatory responses [28], changes in cytokine secretion [29], cerebral edema [30], dynamic changes in local glucose utilization [31], free radical formation [32], glutamate release [33], increased release of TNF alpha [34,35] and many other reported pathological events [36].

We ourselves in our studies have hypothesized that metabolic/biochemical and functional brain changes not yet definitively defined are responsible for the sensory dysfunction abnormalities we have encountered among these patients. We have demonstrated that acuity changes are manifested by abnormalities in so-called growth or transcription factors secreted in both saliva and nasal mucus [37]. We propose that these abnormalities are manifested by abnormalities in secretion of these growth or transcription moieties which are necessary to initiate and perpetuate normal sensory function [37,38]. Decreased secretion of growth factors such as adenylyl cyclases and their downstream components cAMP and cGMP [38,39], decreased secretion of sonic hedgehog (Shh) [40] and increased secretion of TNF alpha have been reported [41]. Cyclic AMP, cGMP and Shh act by stimulating stem cells of both smell and taste receptors whereby olfactory and gustatory receptors grow and develop [37]. Increased secretion of TNF alpha inhibits smells and taste function due to its "cellular death" contributing character [41]. These complex interactions have been demonstrated to occur after TBI and could contribute to measurable early and persistent sensory changes after TBI [11,42]. These changes are particularly relevant since both smell and taste receptors do not contain blood vessels, lymphatics or exhibit mitosis yet turnover rapidly thereby demonstrating their need for continual stimulation of stem cells in each system to produce adequate receptor numbers [37]. Since most smell and taste receptors commonly turnover on a daily basis, receptors in both systems require continual stimulation; any inhibition of this stimulation would cause

a rapid and persistent inhibition of both smell and taste function. The metabolic/biochemical changes we have found occur rapidly consistent with early perceptions of loss and eventual distortion of smell and taste function. Pathological changes in saliva and nasal mucus have been modified and improved by increasing secretion of these growth factors in saliva and nasal mucus (cAMP, cGMP [38,39] and Shh [40]) and decreasing TNF alpha with subsequent improvement in both taste and smell function as previously reported although not the subject of this report [11,41,42].

Biochemical mechanisms by which changes in sensory acuity occur may also relate to onset of sensory distortions. We have studied these distortion phenomena in detail in these patients first by use of functional Magnetic Resonance Imaging (fMRI [22]) and then by use of Magnetic Resonance Spectroscopy (MRS) [43,44]. By use of fMRI, placing patients in the MRI scanner and requesting them to imagine their distortions, a significant global brain activation occurred not only in regions related to smell and/or taste function but also to multiple brain regions not directly related to smell and taste function [44,45]. By use of MRS, we measured lowered levels of brain Gamma-Aminobutyric Acid (GABA) in these same brain regions [43,44]. Others have associated these phenomena with alterations in astrocyte function [46]. These results emphasize the importance of several biochemical changes in brain function which could initiate sensory abnormalities we measured in patients after TBI.

There are also significant relationships between the putative biochemical changes which initiate sensory acuity changes and those which initiate sensory distortions. The GABA receptor is negatively coupled to adenylate cyclase in various brain regions [47]. GABA receptor agonists potentiate GABA response in brain and regulate cGMP brain signaling [48,49]. Cyclic AMP-dependent protein kinase facilitates GABA receptor coupling [50]. TNF alpha, a pro-inflammatory cytokine increased in patients after TBI, has been shown to inhibit brain GABA [51]. Indeed, TNF alpha mediates GABA receptor trafficking in spinal cord neurons whereas increases in cellular GABA reduces release of TNF alpha [51,52]. Sonic hedgehog secretion has been shown to promote survival of neuronal GABA [53].

This study has several limitations. Following TBI, patients exhibit a wide spectrum of physiological and sensory changes. Some patients are so handicapped that their ability to function in a normal setting is impossible. We did not deal with these patients.

Another set of limitations requires physicians to measure smell and taste function systematically using psychophysical techniques which are not well-known to them but are necessary to measure these sensory changes. However, once these quantitative psychophysical techniques are learned and practiced, these objective measurements can be used to define these early and persistent sensory abnormalities. Physicians are also required to deal with sensory phenomena with which they had not previously been acquainted such that dysosmia and dysgeusia need to be characterized and defined quantitatively including use of fMRI techniques. These techniques add additional components to the diagnostic armamentarium by which to diagnose TBI. In addition, measurements of biochemical moieties in saliva and nasal mucus are not familiar to many physicians who deal with these patients. In order to understand the pathology which underlies TBI it is necessary to make these measurements. We wish to expand testing techniques available to physicians so that they can critically evaluate these patients and guide their diagnosis and eventual treatment of their condition.

Measurements of changes in sensory function were obtained at various times after TBI in these patients based upon the timing of their appearance at The Taste and Smell Clinic. Obtaining these measurements immediately after TBI and at various specific time periods following TBI in a prospective study would be helpful to confirm these observations of diminished sensory acuity and subsequent onset of sensory distortions. Obtaining these timed measurements in these patients or in a larger group of patients with undefined TBI was not the subject matter of this work. Indeed, defined incidence of smell and taste dysfunction in a general TBI population is unknown.

The clinical history in each patient is consistent with a rapid change in both smell and taste acuity with subsequent onset of sensory distortions. These results confirm both the initial and persistent aspects of these sensory changes. Changes we report in smell and taste function and in changes in growth factor secretion in saliva and nasal mucus reflect measurable changes in both smell and taste function which can also serve as useful quantitative markers of pathology among these patients. These findings have not been commonly considered before these data were assembled but can now serve as useful objective quantitative measurements by which these patients can be identified and followed clinically.

Conclusions

Abnormalities of both smell and taste function has been measured in patients after TBI by quantitative means. These measurements can be used as markers by which patients with TBI can be identified and followed clinically. While mechanism(s) responsible for these changes are not immediately apparent these results indicate that the time honored term “anosmia” and its associated mechanism of severing of the fila olfactoria as the overarching cause of these sensory changes is no longer clinically tenable.

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