Reduced Suprathreshold Odor Identification in Patients with Pseudotumor Cerebri: A Non-Randomized Prospective Study

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ABSTRACT: **Background:** Recent evidence suggests that olfaction is impaired in patients with pseudotumor cerebri (PTC).

Objectives: To measure suprathreshold olfactory function by using the University of Pennsylvania Smell Identification Test (UPSIT), assessing its usefulness for routine clinical use.

Methods: Forty PTC patients underwent USPIT olfactory testing.

Results: Twenty-nine out of 40 (73%) PTC patients (36 women, 4 men; mean age 34 years) had reduced suprathreshold smell sensation according to UPSIT scores: 19 (47%) had mild microsmia, 9 (23%) had moderate microsmia, and one (3%) was classified as having severe microsmia. The mean UPSIT score of all patients was 32.4 (95% confidence interval 31.4–33.4). Multivariate regression analysis found that UPSIT scores were not related to disease activity, disease duration, initial intracranial pressure (ICP), or visual function.

Conclusions: Many PTC patients have reduced suprathreshold olfactory dysfunction that can be discovered by UPSIT, a rapidly administered smell test, which is suitable for clinical office use.

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KEY WORDS: idiopathic intracranial hypertension (IIH), pseudotumor cerebri (PTC), olfaction dysfunction, smelling dysfunction, hyposmia

Pseudotumor cerebri (PTC), or idiopathic intracranial hypertension (IIH), is a disorder of unknown etiology that results in elevated intracranial pressure (ICP) [1]. Headache, diplopia, transient visual obscurations, and tinnitus, typically associated with papilledema, are common presenting features [2]. Lack of localizing neurologic findings, except for abducens nerve palsy, is an important diagnostic criterion of PTC. Nevertheless, other cranial neuropathies involving the oculomotor, trochlear, trigeminal, and facial nerves are occasionally present in PTC patients [3-6]. Recent evidence suggests that the olfactory nerve may also be involved in this disorder [7-10].

Assessment of olfactory function can be a prolonged process, when investigations are performed using instruments such as the "Sniffin' Sticks" smell test (Burghart, Wedel, Germany), which includes testing of odor threshold, discrimination, and identification, usually conducted by a technician in an odorless laboratory [9]. A simpler commercially available olfactory test is the University of Pennsylvania Smell Identification Test (UPSIT), which is based on identification of 40 common odorants [11]. This test was previously used to demonstrate reduced olfactory performance in several neurological conditions including Parkinson's disease and cerebellar ataxia [12,13].

The aim of our study was to evaluate olfactory function of PTC patients using the UPSIT administered in a clinician's office to assess its usefulness for routine clinical use.

PATIENTS AND METHODS

This study was approved by the institutional review board of the Tel Aviv Sourasky Medical Center and was conducted in accordance with all of its rules and regulations. A written informed consent was received from all participants.

Consecutive adult patients (> 18 years of age) with an established diagnosis of PTC, according to modified Dandy criteria [14], who attended the neuro-ophthalmology clinic between November 2013 and February 2014, were included in this study. Exclusion criteria included allergic rhinitis, nasal polyps, acute or chronic sinusitis, upper respiratory tract infection, pregnancy, or history of brain or nose surgeries.

The following information was collected for each patient: age, gender, body mass index (BMI), disease duration and activity, cerebrospinal fluid opening pressure recorded on first lumbar puncture, history of smoking, and medical and surgical treatment. PTC was considered to be active if its diagnosis was within 3 months of inclusion in this study or there was evidence of clinical deterioration during a comparable time period including worsening papilledema, increased headache severity, or decreased vision. All participants underwent a complete neuro-ophthalmological examination including assessment of visual acuity using standard Snellen optotypes, Ishihara color vision test, pupillary responses, and dilated fundoscopy. Visual field testing was done by automatic perimetry using the Humphrey visual field analyzer (Carl Zeiss Meditec, Jena,

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Germany), 30/2 Swedish Interactive Test Analysis (SITA) protocol. The mean deviation was used as a measure of decreased visual field sensitivity. Presence of visual loss was defined when best-corrected visual acuity was 20/30 or lower and/or there was a visual field defect with a mean deviation of at least -5 decibels in either eye, which were not attributable to any other ophthalmic diseases such as cataract, corneal opacity, or retinopathy.

Smell identification testing was performed using the UPSIT (Sensomics, NJ, USA). This test is comprised of booklets containing 40 encapsulated odorants. After scratching each item with a pencil tip, the examinee samples the smell and is asked to match it with one of four given choices. A response is required for all 40 items in the test even when no odor is perceived. The test score is the total number of correctly identified items. The interpretation of a given subject's test score is made by its comparison with age and gender matched population norms provided in the test manual categorizing it as normosmia, mild to severe microsmia, anosmia, or probable malingering.

Statistical analysis was performed using GraphPad Prism Software version 6.0 for Mac (GraphPad, La Jolla, CA, USA), and Minitab release 14 for Windows (Minitab Inc., State College, PA, USA). Statistical significance was defined at an alpha level of 5% and all tests conducted were two tailed. Unpaired *t*-test was used to analyze UPSIT scores according to gender, disease activity, medical treatment, and disease duration. A multivariate regression analysis was conducted between UPSIT scores and disease activity, disease duration, initial ICP, and visual function.

RESULTS

Forty patients (36 women and 4 men, mean age 34 years) with PTC were enrolled in this study. Mean disease duration was 4.7 years (95% confidence interval [95%CI] 3.6–5.8 years). Twenty -five percent of patients (n=10) had an active disease, and 55% percent (n=22) were under medical therapy with either acetazolamide or topiramate. Characteristics and demographics of participants are summarized in Table 1.

Mean UPSIT score of all patients was 32.4 (95%CI 31.4–33.4). Interpretation based on population norms established that 11 patients (27%) had normosmia, 19 (47%) had mild microsmia, 9 (23%) had moderate microsmia, and one patient (3%) was classified as having severe microsmia [Figure 1]. None of the patients tested was diagnosed as having complete anosmia. Even though 29/40 (73%) of patients were found to have some degree of reduced smell sensation, only 12% (n=5) were aware of their dysfunction.

There was no difference in mean scores of female patients (32.6, 95%CI 31.6–33.6) compared with males (30.5, 95%CI 23.8–37.2, $P = 0.205$). Mean test scores of patients with active disease (32.3, 95%CI 30.2–34.4) were not statistically different from patients with inactive disease (32.4, 95%CI 31.2–33.6, $P = 0.930$). Similar test scores were recorded in patients who were medically treated (mean 32.1, 95%CI 30.8–33.5) and those who were not (mean 32.6, 95%CI 31.1–34.3, $P = 0.596$). Mean UPSIT score of patients with less than 1 year of disease duration (30.5, 95%CI 27.7–33.3) was lower than that of patient with a longer disease duration (32.8, 95%CI 31.8–33.9); however, this difference was not statistically significant ($P = 0.054$). Eleven patients smoked cigarettes; however, mean test scores of smokers (31.7, 95%CI 29.8–33.6) was not significantly different than non-smokers (32.6, 95%CI 31.3–33.9, $P = 0.434$)

Multivariate regression analysis found that UPSIT smell scores were not related to disease activity, disease duration,

Table 1. Demographic and clinical characteristics of participants

	IIH Patients*
Age (years)	34.2 (30.2–38.1)
Gender (female)	36 (90%)
Disease duration (years)	4.7 (3.6–5.8)
Initial ICP	33.9 (31.6–36.2)
BMI (kg/m^2)	32.7 (30.7–34.7)
Active disease	10/40 (25%)
Headache	10/40 (25%)
Papilledema	20/40 (50%)
Visual loss‡	9/40 (23%)
Smoking	9/38§ (24%)
Medical therapy	22/40 (55%)

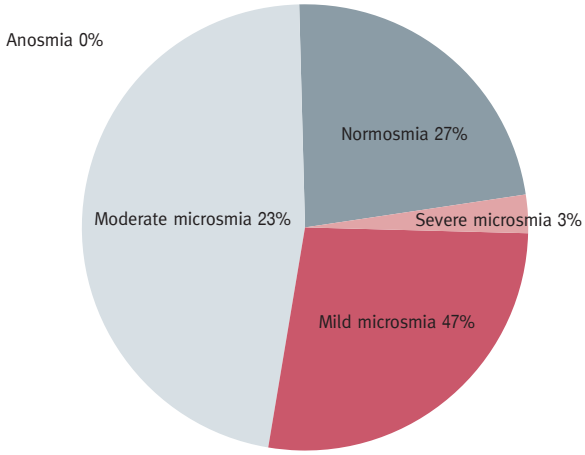
IIH = idiopathic intracranial hypertension, ICP = intracranial pressure, BMI = body mass index, CSF = cerebrospinal fluid

*data are means (95% confidence interval) or numbers (percentages)

‡visual loss defined as visual acuity of 6/9 or worse and/or visual field defect in the worst seeing eye

§missing data for two patients

Figure 1. UPSIT test scores of 40 PTC patients compared to age- and gender-matched population norms



UPSIT = University of Pennsylvania Smell Identification Test, PTC = pseudotumor cerebri

initial ICP, or visual function [Table 2]. Subgroup analysis of non-smoker patients reached similar results, except for a stronger correlation of test scores with disease duration [Table 3].

DISCUSSION

Our study established that many PTC patients have reduced smell sensation when tested by UPSIT, ranging from mild to severe microsmia.

Recent evidence suggests that PTC is often associated with reduced smell sensation, and an ICP reduction after lumbar puncture can improve this dysfunction [10]. Our study provides additional support, finding that 73% of PTC patients had some degree of smelling dysfunction. However, we also found that most of them were unaware of their disability. Even patients who had UPSIT score of moderate or severe microsmia frequently self-reported having normal smelling sensation.

The importance of reduced olfaction in PTC cannot be compared to that of vision loss; however, its significance should not be ignored all together. Women with reduced smelling sensation are at increased risk for developing depression, anxiety, social isolation, and relationship difficulties [15]. PTC patients are already at risk for having psychological difficulties as a result of their disease, and reduced smell sensation can add additional hardship [16].

Two previous studies described smelling dysfunction in PTC patients. Kunte and co-authors [8] performed the "Sniffin' Sticks" test in 17 PTC patients and found lower olfaction scores, especially in patients with new-onset disease or recent clinical deterioration. Bershad and co-authors [9] used the same procedure in addition to UPSIT in 19 PTC patients, and found marked smelling impairment, mostly in olfactory threshold levels. However, their analysis was conducted under unusual head positions, in a laboratory environment simulating conditions encountered by astronauts in outer space. In contrast, our study was performed in a clinician's office under normal conditions typical for a neuro-ophthalmology clinic. The mean UPSIT score of 32.4 measured in our cohort of 40 PTC patients was comparable to that of Bershad et al. In contrast to previous studies that found reduced smelling scores in patients with new onset disease or recent clinical deterioration [8]. In our study, we did not find reduced olfactory performance in PTC patients with new-onset or active disease. Even though we found a lower UPSIT score in patients who had PTC for less than 1 year, our study was underpowered for finding differences in smelling scores related to disease duration. We also found that smelling function was not correlated with initial ICP on presentation or visual function.

The mechanism responsible for smelling loss in PTC is not fully known; however, two explanatory theories exist. Recently, an important cerebrospinal fluid (CSF) outflow pathway across the cribriform plate was discovered, connecting the subarachnoid space and nasal lympathic channels [18,19]. An outflow dysfunction that may exist in PTC patients potentially leads to CSF accumulation in these channels, exerting local pressure on the olfactory bulbs, which lie in close anatomical proximity [7]. Support for this theory was provided by Schmidt and co-authors [20] who identified decreased olfactory bulb volume on brain magnetic resonance imaging of PTC patients compared with matched controls. Evidence that this anatomical abnormality is associated with poor olfactory function was recently provided by Podlesek and colleagues [21]. The second explanation for olfactory dysfunction in PTC is based on the anatomical resemblance of the meningeal sheaths surrounding the optic nerve and the olfactory nerve. It is possible that increased ICP compresses the olfactory axons in a similar fashion to that on the optic nerve [7,20].

In our study we used the UPSIT, which is a rapidly administered clinical smell test, providing information only on suprathreshold odor identification. Other smell tests, such as the "Sniffin's Sticks" test, offer a more extensive assessment of smelling function including olfactory threshold, discrimination and identification; however, they are usually conducted in a laboratory by a technician, taking much more time to complete, thus limiting their applicability for every day clinical use. In our opinion, UPSIT is more suitable for routine clinical use, whereas the "Sniffin's Sticks" procedure may be preferable when more detailed information concerning olfaction is required, much like the Ishihara booklet is commonly used for a rapid assessment of color vision compared to the more detailed Farnsworth–Munsell color vision test.

Table 2. Multivariate regression analysis correlating UPSIT scores with disease activity, disease duration, initial ICP, and vision loss

Predictor	Correlation coefficient	*P* value
Disease activity	0.572	0.653
Disease duration	0.209	0.210
Initial ICP	0.006	0.393
Vision loss	-0.359	0.769

ICP = intracranial pressure, UPSIT = University of Pennsylvania Smell Identification Test

Table 3. Multivariate regression analysis correlating UPSIT scores of non-smokers PTC patients with disease activity, disease duration, initial ICP, and vision loss

Predictor	Correlation coefficient	*P* value
Disease activity	0.879	0.554
Disease duration	0.555	0.021*
Initial ICP	0.007	0.374
Vision loss	-0.228	0.872

ICP = intracranial pressure, UPSIT = University of Pennsylvania Smell Identification Test, PTC = pseudotumor cerebri

*statistically significant results

To the best of our knowledge this work constitutes the largest prospective study to date evaluating olfaction in PTC patients; nevertheless, it was underpowered for identifying predictors of smelling dysfunction. Since our study group included more patients with longer than 1 year disease duration, it was impossible for us to determine whether loss of smell function occurs early or late during the course of PTC disease. A prospective study evaluating smelling function at the time of initial presentation would permit better clarification regarding the timing of smelling loss in this condition.

CONCLUSIONS

In conclusion, many PTC patients have reduced smell function even though they are often unaware of their dysfunction. UPSIT, which can be easily administered in a physician's office, can be used for rapid identification of PTC related smelling loss.

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References

1. Kosmorsky GS. Idiopathic intracranial hypertension: pseudotumor cerebri. *Headache* 2014, 54: 389-93.
2. Wakerley B, Tan M, Ting E. Idiopathic intracranial hypertension. *Cephalalgia* 2015; 35 (3): 248-61.
3. Brackmann DE, Doherty JK. Facial palsy and fallopian canal expansion associated with idiopathic intracranial hypertension. *Otol Neurotol* 2007; 28: 715-18.
4. Bruce BB, Newman NJ, Biousse V. Ophthalmoparesis in idiopathic intracranial hypertension. *Am J Ophthalmol* 2006; 142: 878-80.
5. Davenport RJ, Will RG, Galloway PJ. Isolated intracranial hypertension presenting with trigeminal neuropathy. *J Neurol Neurosurg Psychiatry* 1994; 57: 381.
6. Lee AG. Fourth nerve palsy in pseudotumor cerebri. *Strabismus* 1995; 3: 57-9.
7. Kapoor KG. Do patients with idiopathic intracranial hypertension suffer from hyposmia? *Med Hypotheses* 2008; 71: 816-17.
8. Kunte H, Schmidt F, Kronenberg G, et al. Olfactory dysfunction in patients with idiopathic intracranial hypertension. *Neurology* 2013; 81: 379-82.
9. Bershad EM, Urfy MZ, Calvillo E, et al. Marked olfactory impairment in idiopathic intracranial hypertension. *J Neurol Neurosurg Psychiatry* 2014; 85: 959-64.
10. Becker N, Kronenberg G, Harms L, et al. Rapid improvement of olfaction after lumbar puncture in a patient with idiopathic intracranial hypertension. *Headache* 2016; 56 (5): 890-2.
11. Cameron EL. Measures of human olfactory perception during pregnancy. *Chem Senses* 2007; 32: 775-82.
12. Picillo M, Pellecchia MT, Erro R, et al. The use of University of Pennsylvania Smell Identification Test in the diagnosis of Parkinson's disease in Italy. *Neurol Sci* 2014; 35: 379-83.
13. Galvez V, Diaz R, Hernandez-Castillo CR, Campos-Romo A, Fernandez-Ruiz J. Olfactory performance in spinocerebellar ataxia type 7 patients. *Parkinsonism Relat Disord* 2014; 20: 499-502.
14. Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. *Neurology* 2002; 59: 1492-5.
15. Philpott CM, Boak D. The impact of olfactory disorders in the United Kingdom. *Chem Senses* 2014; 39: 711-18.
16. Kesler A, Mosek A, Fithlicher N, Gidron Y. Psychological correlates of idiopathic intracranial hypertension. *IMAJ* 2005; 7: 627-30.
17. Ogihara H, Kobayashi M, Nishida K, Kitano M, Takeuchi K. Applicability of the cross-culturally modified University of Pennsylvania Smell Identification Test in a Japanese population. *Am J Rhinol Allergy* 2011; 25: 404-10.
18. Johnston M. The importance of lymphatics in cerebrospinal fluid transport. *Lymphat Res Biol* 2003; 1: 41-4.
19. Johnston M, Zakharov A, Papaiconomou C, Salmasi G, Armstrong D. Evidence of connections between cerebrospinal fluid and nasal lymphatic vessels in humans, non-human primates and other mammalian species. *Cerebrospinal Fluid Res* 2004; 1: 2.
20. Schmidt C, Wiener E, Hoffmann J, et al. Structural olfactory nerve changes in patients suffering from idiopathic intracranial hypertension. *PLoS One* 2012; 7: e35221.
21. Podlesek D, Leimert M, Schuster B, et al. Olfactory bulb volume in patients with idiopathic normal pressure hydrocephalus. *Neuroradiology* 2012; 54: 1229-33.

Capsule

A single-cell survey of the small intestinal epithelium

Intestinal epithelial cells absorb nutrients, respond to microbes, function as a barrier, and help to coordinate immune responses. **Haber** and co-authors reported profiling 53,193 individual epithelial cells from the small intestine and organoids of mice, which enabled the identification and characterization of previously unknown subtypes of intestinal epithelial cell and their gene signatures. The authors found unexpected diversity in hormone-secreting enteroendocrine cells and constructed the taxonomy of newly identified subtypes. They distinguished between two subtypes of tuft cell, one of which expresses the epithelial cytokine Tslp and the pan-immune marker CD45, which was not previously associated with non-hematopoietic cells. They also characterized the ways in which cell-intrinsic states and the proportions of different cell types respond to bacterial and helminth infections: *Salmonella* infection caused an increase in the abundance of Paneth cells and enterocytes, and broad activation of an antimicrobial program; *Heligmosomoides polygyrus* caused an increase in the abundance of goblet and tuft cells. This survey highlights previously unidentified markers and programs, associates sensory molecules with cell types, and uncovers principles of gut homeostasis and response to pathogens.

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