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European Journal of Paediatric Neurology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

Association of pediatric idiopathic intracranial hypertension with olfactory performance

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ARTICLE INFO

Article history:
Received 16 February 2020
Received in revised form
19 September 2020
Accepted 22 September 2020

Keywords:
Pseudotumor cerebri
Olfactory dysfunction
Sniffin' sticks
Odor threshold
Odor identification
Headache

ABSTRACT

Objective: To assess the association between pediatric Idiopathic intracranial hypertension (IIH) and olfactory performance.
Methods: A cross-sectional comparative study was conducted including 17 patients under 18 years diagnosed with IIH at a tertiary hospital and 17 healthy age- and sex-matched subjects. All participants underwent the semi-objective chemosensory Sniffin' Sticks test for evaluation of odor threshold (OT), indicative of peripheral olfactory function, and odor identification (OI), reflecting higher cognitive olfactory processing. Scores were compared and referred to the updated normative values. Demographic, clinical, and neuroimaging data were collected from the medical files. The patients with IIH were reassessed for olfactory function and clinical state at the subsequent follow-up, under treatment.
Results: Compared to controls, the IIH group had a significantly lower mean OT score (6.41 ± 3.43 vs 10.21 ± 2.79, $p = 0.001$) and higher rate of OT score below the 10th percentile for age and sex according to the normative values (47.1% vs 0%, $p = 0.001$). There was no significant between-group difference in mean OI scores (9.82 ± 1.63, vs 10.59 ± 1.84, $p = 0.290$). OT scores were not associated with sex, age, body mass index, neuroimaging abnormalities, or lumbar puncture opening pressure. At the follow-up assessment, the OT scores were improved (9.36 ± 4.17 vs 6.7 ± 3.32, $p = 0.027$) whereas the OI scores were unchanged (9.88 ± 2.5 vs 9.69 ± 1.58, $p = 0.432$).
Conclusions: As reported in adults, children and adolescents with IIH appear to have a selective reversible deficit in olfactory detection threshold, which may imply a reduction in peripheral olfactory perceptual ability. Future studies should examine the predictive value of olfactory function for IIH.
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1. Introduction

Idiopathic intracranial hypertension (IIH), also known as Pseudotumor cerebri syndrome, is a neurological disorder of unknown etiology. IIH typically occurs in obese women of childbearing age but it can affect both obese and non-obese individuals, males and females, and all age groups. The demographic and clinical features differ between adults and prepubertal children, in whom IIH is less associated with obesity, with no sex predilection [1]. The annual incidence in the general population is 1–2 per 100,000 [2], and in the pediatric population, 0.71 per 100,000 [3].

IIH is characterized by increased intracranial pressure in the absence of intracranial pathology (hydrocephalus, mass, etc.) on

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; IIH, idiopathic intracranial hypertension; LPOP, lumbar puncture opening pressure; OI, odor identification; OT, odor threshold.

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https://doi.org/10.1016/j.ejpn.2020.09.006
1090-3798/© 2020 Published by Elsevier Ltd on behalf of European Paediatric Neurology Society.

Please cite this article as: M. Muhlbauer Avni, N. Yosha-Orpaz, O. Konen *et al.*, Association of pediatric idiopathic intracranial hypertension with olfactory performance, European Journal of Paediatric Neurology, https://doi.org/10.1016/j.ejpn.2020.09.006

neuroimaging or abnormalities in cerebrospinal fluid (CSF) composition. The symptoms and signs are heterogeneous; the most common are headache, papilledema, vision abnormalities, tinnitus, nausea and abducens nerve palsy. The most serious consequence is visual loss [4]. Since the intracranial pressure is evenly elevated in IIH, there is no neuroanatomic basis for preferential compression of the optic nerve [5]. In recent years, there have been reports of other cranial nerve [6] and auditory deficits [7] in addition to cognitive [8] and psychiatric disorders [9] in patients with IIH. This has led to a growing tendency to redefine IIH as a global neurologic syndrome [10].

Olfactory dysfunction has been associated with some neurological [11] and psychiatric disorders [12,13], and its evaluation has gained increasing interest with the development of novel quantitative standardized tools. Cumulative reports have suggested an association of IIH with olfactory dysfunction in adults [5,14–16], and some authors proposed that olfactory impairment might serve as a more sensitive predictor of IIH than other clinical features [5]. However, none of the studies conducted to date included patients younger than 18 years.

The aim of the present study was to assess the olfactory performance and clinical characteristics of children and adolescents with IIH. We hypothesized that like in adults, pediatric IIH is associated with impaired olfaction. Presuming that the olfactory dysfunction in IIH is caused by the increase in intracranial pressure, it is possible that it recovers when the CSF drainage normalizes.

2. Methods

2.1. Subjects

A cross-sectional comparative study design was used. The study group included 17 patients aged less than 18 years who were diagnosed with IIH at a tertiary university-affiliated pediatric medical center in 2014–2016. The control group consisted of an equal number of age- and sex-matched subjects without papilledema and without clinical symptoms or signs of elevated intracranial pressure who were referred to the pediatric ophthalmology clinic of the same medical center for a different indication. Exclusion criteria for the study were presence of other conditions that might cause olfactory impairment (congenital anosmia, sinusitis, allergic rhinitis, upper respiratory tract infection, brain tumors, multiple sclerosis, diabetes mellitus etc) [17] and use of medications known to affect olfaction (several types of antibiotics, antihypertensive drugs, antilipidemics, antihistamines, anti-allergenic agents) [18].

Demographic, clinical, and imaging data were derived from the electronic medical files. The patients underwent evaluation of olfactory function and clinical state after the diagnosis of IIH was established and again at the subsequent follow-up visit, under treatment. Data from the first visit were compared with findings in the healthy control group.

All subjects included in the study verbally agreed to participate, and in all cases, the parents provided written informed consent at enrollment. The study was approved by the institutional ethics committee.

2.2. Olfactory evaluation

Olfactory function was evaluated with the Sniffin' Sticks (Burghart Medical Technology GmbH, Wedel, Germany), a semi-objective chemosensory nasal performance test based on pen-like odor-dispensing devices. It is used worldwide in research and clinical practice. The test-retest reliability of the Sniffin' sticks has been established [19], and a recent study published updated normative values of the test based on a large-scale sample divided by age and sex, increasing its diagnostic validity [20]. To facilitate and standardize the application of the Sniffin Sticks test and to document the results, we used OLAF software 2014 version, developed at the Smell & Taste clinic of the Department of Otorhinolaryngology, University of Dresden Medical School [21].

Two subsets of the Sniffin' Sticks battery were used in the present study: odor identification (OI) and odor threshold (OT), each yielding a score between 0 and 16. Test instructions were strictly observed to ensure reliable results.

The OI subtest measures the ability of the responder to name or associate common odorants (orange, leather, cinnamon, peppermint, banana. Lemon, liquorice, turpentine, garlic, coffee, apple, clove, pineapple, rose, anise and fish). Responders are asked to identify odors presented at supra-threshold levels from a written list of four options. Supra-threshold odors activate more centrally located components of the olfactory system that use higher order processing, including semantic and episodic memory [22]. The score reflects the number of correct identifications. A higher score indicates better performance.

The odor threshold (OT) subtest measures the perception of responders to low concentrations of odorants. Graduated concentrations of rose-like phenyl-ethyl alcohol are presented to the blindfolded subject in a stepwise pattern, starting from the lowest concentration (stick number 16) in a 1:2 dilution. Responders are asked to distinguish the phenyl-ethyl alcohol rose-like odor stick from two odorless sticks. Two successive correct identifications or one incorrect identification triggers a reversal of the staircase. The OT score is defined as the mean of the last 4 of 7 staircase reversals. A high score reflects a lower sensory threshold (i.e., better perception of odors at low concentrations). The OT test is a more sensitive measure of the functionality of the peripheral olfactory structures relative to the OI score [23]. A previous study suggested that the olfactory threshold is the parameter most sensitive to changes in intracranial pressure [15].

2.3. Clinical evaluation

The medical files of the patients enrolled in the study were carefully reviewed to ensure that all diagnoses met the revised criteria of Friedman et al. [24].

The neuroophthalmological evaluation was performed by several ophthalmologists as part of the diagnosis of IIH, prior to the patients' recruitment to the study. Findings such as presence of papilledema were documented. The lumbar puncture opening pressure (LPOP) was recorded.

Prior to olfactory testing, patients were asked to report their symptoms such as headache, nausea, vomiting, and visual or auditory disturbances and to rate the current severity of their headaches on a visual analog scale (VAS).

They were also asked to categorize their usual sense of smell as normal, enhanced or diminished and to indicate whether they had experienced any recent changes in their sense of smell and/or taste.

Body mass index (BMI) percentiles were determined using the Centers for Disease Control and Prevention (CDC) growth charts. Overweight was defined as BMI at or above the 85th percentile. Obesity was defined as BMI at or above the 95th percentile.

2.4. Neuroimaging evaluation

A pediatric neuroradiologist blinded to the Sniffin' Sticks results re-evaluated the patients' magnetic resonance imaging scans taken at diagnosis for the subtle abnormalities that are suggestive (albeit not pathognomonic) for IIH: (a) flattening of the posterior sclera relative to the curvature of the globe; (b) distension of the perioptic

subarachnoid space; (c) intraocular protrusion of the prelaminar optic nerve into the vitreous cavities; (d) vertical tortuosity of the orbital optic nerve; (e) an empty sella and (f) venous narrowing. Studies have shown that the presence of 3 or more concurrent features is associated with an increased risk of elevated intracranial pressure [25]. Each abnormality was rated for severity from 0 (absent) to 4 (maximal). The analysis took both the number and severity of the pathologies into account.

2.5. Sample size calculation

On the basis of previous studies, we determined that with a sample size of 34 (17 individuals in each group), the study would have 80% power to detect a 1-unit difference with 1 standard deviation in the olfactory function tests (according to the expected range of 6 units) at a significance level of 5%.

2.6. Statistical analysis

All values were expressed as mean and standard deviation (SD). Statistical significance was set at a p-value of less than 0.05. Continuous variables were compared between groups with the Mann-Whitney U-test, and categorical variables (proportions), with the chi-square ($\chi 2$) test. Percentiles of OI and OT were calculated using the reported mean and standard deviation of the updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects [20]. Means were compared using analysis of variance (ANOVA). All statistical analyses were conducted with IBM-SPSS, version 22.0.

3. Results

The demographics, and olfactory data of the study participants are summarized in Table 1. The IIH and control groups each consisted of 14 females (82%) and 3 males (18%); mean age at the recruitment to the study was 12.94 and 13.15 years, respectively (range 7–17). We divided the subjects to two age groups according to the study that provided the updated normative values of the Sniffin' sticks [20]. The first age group (5–10 years) consisted of 3 children in each group. The second age group (11–18 years) consisted of 14 adolescents in each group.

According to the anthropometric measurements, 70% of the patients in the IIH group were overweight and 53% were obese; the mean BMI percentile was 86.9 ± 17.41. Among the controls, 12% were overweight and none were obese; the mean BMI percentile in this group was 42.71 ± 32.38.

The mean interval between the diagnosis of IIH and the first olfactory evaluation was 7 days. Fig. 1 shows the OT and OI subtest scores of the patients and control groups. Fig. 2 shows the calculated percentiles of these two groups according to the normative values. Mean OT scores were significantly lower in the patients with IIH than the control subjects (6.41 ± 3.43 vs. 10.21 ± 2.79, $p = 0.001$). There was no significant difference in mean OI scores between the groups (9.82 ± 1.63 and 10.59 ± 1.84, respectively, $p = 0.290$). Comparison of the OT and OI scores of the study participants with the updated Sniffin' Sticks normative data [20] yielded a significant difference in mean OT Z-scores between the IIH and control groups (0.33 ± 0.34 vs 0.66 ± 0.28, $p = 0.004$). The mean percentile was 33 in the patients with IIH and 66 in the control subjects. There was no significant difference in mean OI Z-scores between the two groups (0.12 ± 0.14 vs 0.20 ± 0.18, $p = 0.158$); the mean OI percentiles were 12 and 20, respectively. The percentage of patients scoring below the 10th percentile for age and sex was higher in the IIH than the control group on the OT test (8 patients, 47.1% vs 0 control subjects, $p = 0.001$), with no significant difference between the groups on the OI test (10 patients, 58.8% vs 7 control subjects, 41.2%; $p = 0.303$).

All patients with IIH reported at least one symptom, with a median of 3 per patient (IQR 3–5). All patients had headache during the IIH episode, and 9 (53%) also experienced headache during the examination itself. The median VAS grade for headache pain was 2 (0–6). Other symptoms in the IIH group were obscure vision (59%), nausea and/or vomiting (47%), dizziness (41%), phonophobia (29%), reduced school performance (24%), photophobia (18%), diplopia (12%), tinnitus (12%), decreased hearing (12%) and scotoma (6%). None of the patients reported a subjective reduction in olfactory function or any alterations in sense of smell or taste.

The clinical signs and findings of the patients with IIH are summarized in Table 2. Papilledema was documented in 76.47% of the patients. Papilledema was an exclusion criterion for the control group. Two patients (11.76%) had abducens nerve palsy. The mean LPOP in the patients with IIH was 41.85 ± 14.04 cm H_2O (range 28–75).

No association was found in the IIH group between the degree of olfactory impairment on the OT subtest and sex, age, BMI percentile, LPOP, or number of reported symptoms. There was no statistically significant difference in olfactory performance within the IIH group between the patients with or without papilledema.

Table 1
Demographic, clinical characteristics and olfactory evaluation of the study participants – patients with IIH versus control subjects.

Characteristic	Patients with IIH (n = 17)	Control subjects (n = 17)	p value
Sex (F/M), n	14/3	14/3	1.0
Age (yr), mean ± SD	12.94 ± 2.99	13.15 ± 2.60	0.919
Age group- 5–10 years	3	3	
Age group- 11–18 years	14	14	
BMI (percentile), mean ± SD	86.94 ± 17.41	42.71 ± 32.38	**<0.001**
The subjective self-assessment of the participants' usual sense of smell			
Normal, n (%)	16 (94)	16 (94)	1.0
Enhanced, n (%)	1 (6)	1 (6)	1.0
Reduced, n (%)	0 (0)	0 (0)	1.0
Number of participants complained about recent change is sense of smell	0	0	1.0
Number of participants complained about recent change is sense of taste	0	0	1.0
Odor Threshold (OT) score, mean ± SD	6.41 ± 3.43	10.21 ± 2.79	**0.001**
Odor Identification (OI) score, mean ± SD	9.82 ± 1.63	10.59 ± 1.84	0.290
Odor threshold Z score, mean ± SD	0.33 ± 0.34	0.66 ± 0.28	**0.004**
Odor identification Z score, mean ± SD	0.12 ± 0.14	0.20 ± 0.18	0.158
Odor threshold score below 10th percentile, n (%)	8 (47.1)	0 (0)	**0.001**
Odor identification score below 10th percentile, n (%)	10 (58.8)	7 (41.2)	0.303

BMI, body mass index.

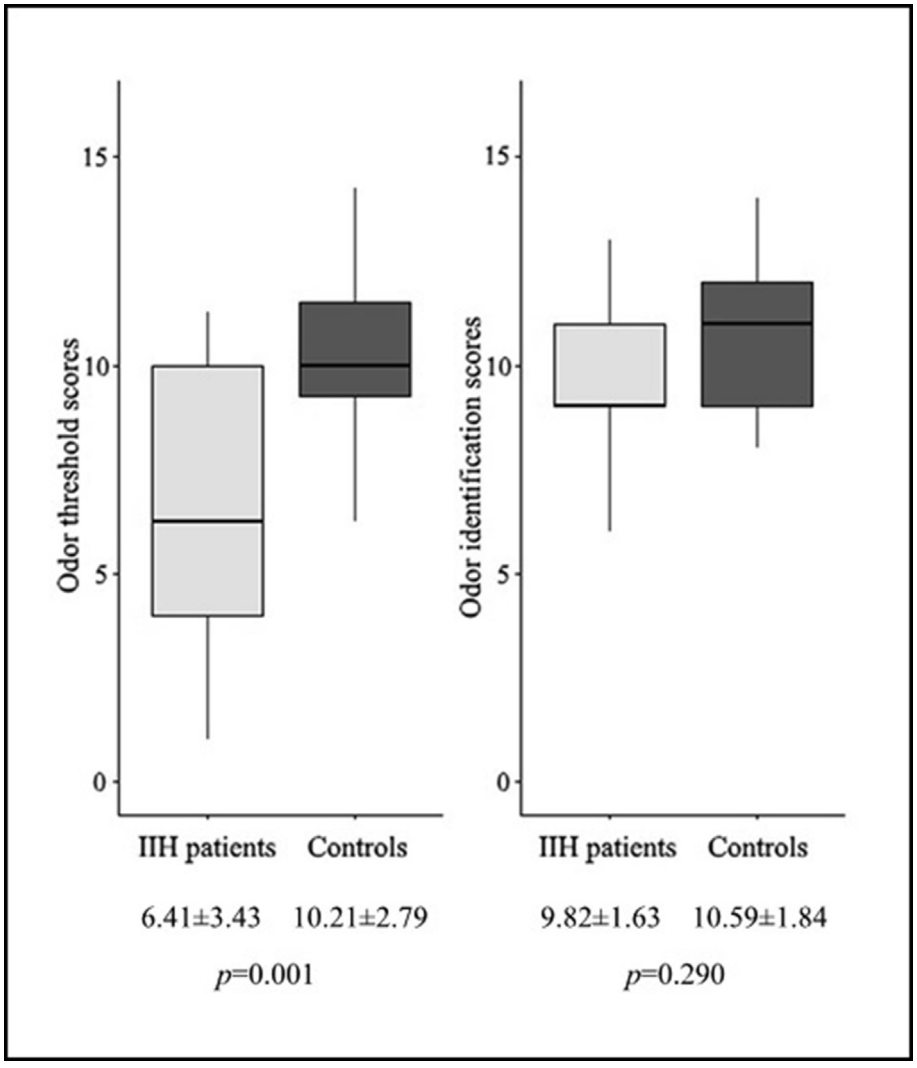

Fig. 1. Odor threshold and odor identification scores of patients with IIH versus controls.

Of the 15 patients with IIH (88.2%) who underwent magnetic resonance imaging, 7 (46.67%) had at least one abnormal finding suggestive of the disease. Only one patient had more than 3 abnormal findings. The highest grade of abnormal neuroimaging was 2 (out of 4). There were no statistically significant differences in olfactory performance between patients with and without neuroimaging features of IIH.

Fifteen patients were treated with acetazolamide and one patient was switched from acetazolamide to topiramate because of an allergic reaction. The remaining patient showed marked clinical improvement following lumbar puncture and was on surveillance only, without any drug treatment.

Sixteen of the seventeen patients in the IIH group were re-evaluated on follow-up. The mean interval between evaluations was 97 days. The findings on the two evaluations are compared in Table 3. Fig. 3 illustrates the Sniffin' sticks scores of the first and second evaluations of the IIH patients compared with the scores of the healthy controls. Significantly fewer symptoms were reported at the second than at the first evaluation, with only six patients (35%) still experiencing headache. The median VAS grade of the second evaluation was 0 (0–3).

The mean OT score at the second evaluation was significantly higher than the mean OT score at the first evaluation (9.36 ± 4.17 vs 6.70 ± 3.32; $p = 0.027$) to the mean OT score of the healthy controls (9.36 ± 4.17 vs 10.21 ± 2.79; $p = 0.432$). The mean odor threshold Z score of the second evaluation was 0.59 ± 0.33 in comparison to 0.35 ± 0.34 of the first evaluation ($p = 0.026$) and 0.66 ± 0.28 of the healthy controls. Only two patients (12.5%) still had OT scores below the 10th percentile at the second evaluation compared to seven (43.8%) at the first evaluation ($p = 0.025$). The mean OI score was unchanged (9.88 ± 2.50 vs 9.69 ± 1.58, $p = 0.0756$), with no significant difference from the control score (9.88 ± 2.50 vs 10.59 ± 1.84, $p = 0.305$). The mean odor identification z-score was 0.18 ± 0.22 compared with 0.11 ± 0.13 ($p = 0.269$) at the first evaluation and 0.20 ± 0.18 of the healthy controls. Nine patients (56.3%) still had OI scores bellow the 10th percentile at the second evaluation compared to 10 (62.5%) at the first evaluation ($p = 0.705$).

4. Discussion

This study sought to determine if there is an association between olfactory function and pediatric IIH. Our results, in agreement with previous reports, showed that compared to healthy control subjects, children and adolescents with IIH had a significantly lower olfactory detection threshold as measured by OT score,

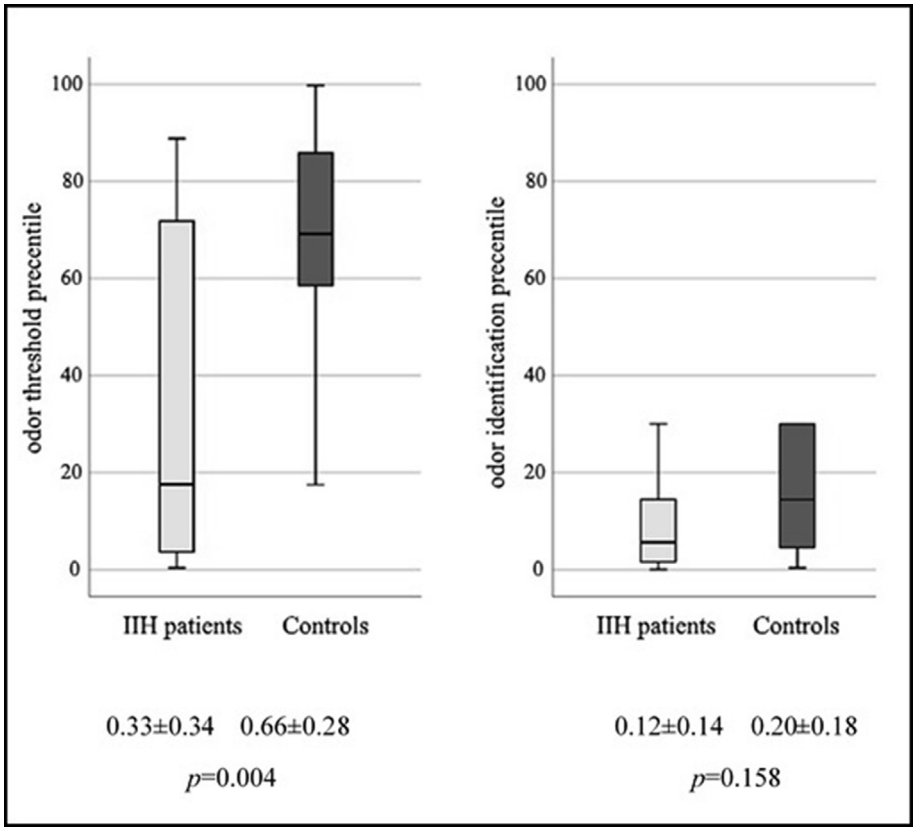

Fig. 2. Odor threshold and odor identification percentiles of patients with IIH versus controls according to normative value.

Table 2
Clinical findings of the patients with IIH.

Papilledema, n (%)	13 (76.47)
Abducens nerve palsy, n (%)	2 (11.76%)
LPOP (mmH2O), mean ± SD	41.85 ± 14.04
Patients underwent magnetic resonance imaging (MRI), n (%)	15 (88%)
flattening of the posterior sclera relative to the curvature of the globe, n (%)	4 (27%)
mean degree between 0 and 4	1.5
distension of the perioptic subarachnoid space, n (%)	2 (13%)
mean degree between 0 and 4	1.5
intraocular protrusion of the prelaminar optic nerve into the vitreous cavities, n (%)	3 (20%)
mean degree between 0 and 4	1.33
vertical tortuosity of the orbital optic nerve, n (%)	2 (13%)
mean degree between 0 and 4	1.5
empty sella, n (%)	1 (7%)
mean degree between 0 and 4	2
venous narrowing, n (%)	0

LPOP, lumbar puncture opening pressure.

and a significantly higher prevalence of low olfactory sensitivity, as measured by percent of OT scores below the 10th percentile.

Since all previous studies were performed on adults and the characteristics of children with IIH differ from those of adults with IIH, before this study we could not extend the conclusions of previous studies to the pediatric population.

The impairment in olfactory function in patients with IIH often goes unnoticed [14]. Accordingly, none of our patients reported a symptomatic change in their sense of smell. Therefore, self-reports of olfactory ability are not conclusive, and a non-subjective measurement is necessary. The Sniffin' Sticks test used in the present study is a simple, easy to use, low-cost quantitative test of olfactory function, and valid normative values based upon a large-scale sample are available [20].

Two pathophysiological mechanisms may potentially be responsible for the diminished olfactory function in IIH: compression of the olfactory nerve sheath by the elevated intracranial pressure, or local pressure on the peripheral olfactory structures arising from increased drainage of CSF through the lymphatic network that crosses the cribriform plate along the meningeal sheath of the olfactory nerve. The second mechanism is related to the increased resistance to CSF drainage characteristic of IIH [14]. Since both presumed mechanisms involve the peripheral olfactory structures and not higher cognitive centers, and since the OT test is known to be more sensitive to peripheral olfactory function than the OI test, it is not surprising that we found a significantly lower OT score in our study group compared to controls. The selective deficit in olfactory detection threshold sensitivity in children with

Table 3
Comparison of the symptoms and olfactory function between the two evaluations of the patients with IIH.

Characteristic	1st evaluation	2nd evaluation	p value
Median number of symptoms (IQR)	3 (3–5)	0 (0–2)	**p < 0.01**
Headache, n (%	17 (100%)	6 (35%)	**p < 0.001**
Suffered from Headache during the test, n (%)	9 (53%)	6 (35%)	0.315
Median Headache VAS	2 (0–6)	0 (0–3)	0.05
Obscure vision, n (%)	10 (59%)	2 (12%)	0.01
Nausea and vomiting, n (%)	8 (47%)	2 (12%)	0.027
dizziness, n (%)	7 (41%)	1 (6%)	0.018
Phonophobia, n (%)	5 (29%)	0	0.019
Reduced school performance, n (%)	4 (24%)	0	0.045
Photophobia, n (%)	3 (18%)	0	0.104
Diplopia, n (%)	2 (12%)	0	0.229
Tinnitus, n (%)	2 (12%)	0	0.229
decreased hearing, n (%)	2 (12%)	0	0.229
Scotoma, n (%)	1 (6%)	0	0.486
Odor threshold score, mean ± SD	6.70 ± 3.32[a]	9.36 ± 4.17	**0.027**
Odor identification score, mean ± SD	9.69 ± 1.58	9.88 ± 2.50	0.756
odor threshold z-score, mean ± SD	0.35 ± 0.34	0.59 ± 0.33	**0.026**
odor identification z-score, mean ± SD	0.11 ± 0.13	0.18 ± 0.22	0.269
Odor threshold score below 10th percentile, n (%)	7 (43.8)	2 (12.5)	**0.025**
Odor identification score below 10th percentile, n (%)	10 (62.5)[a]	9 (56.3)	0.705

LPOP, lumbar puncture opening pressure; VAS, visual analog scale; IQR, interquartile range.
[a] For paired comparisons, one case was omitted due to missing second measurement.

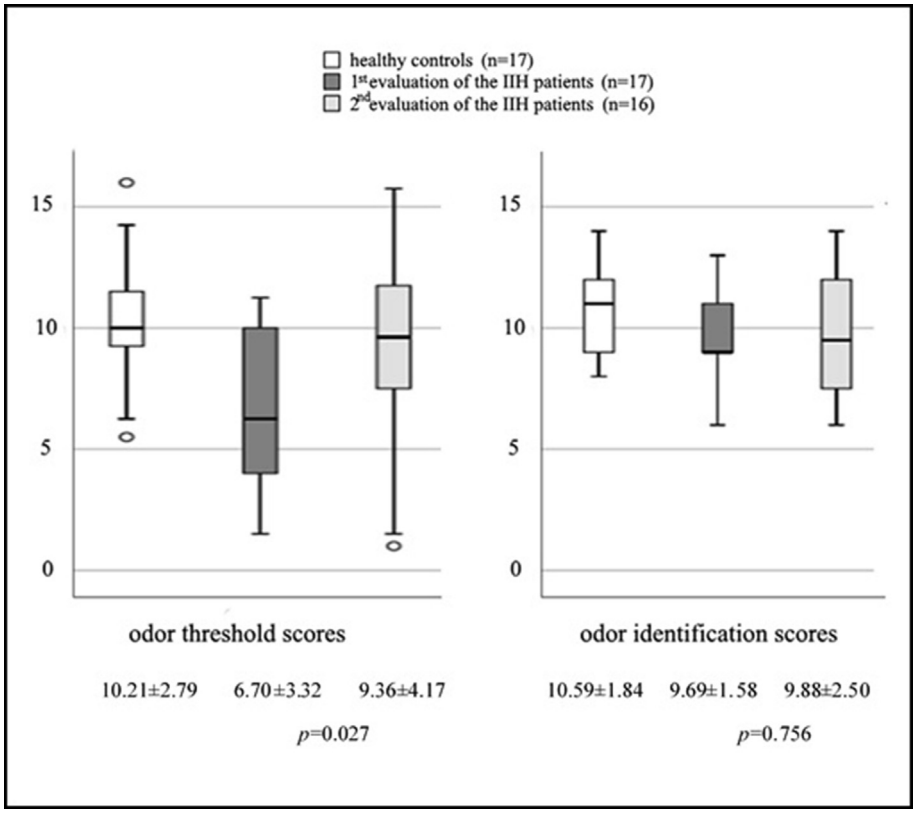

Fig. 3. Odor threshold and odor identification scores of the healthy controls compared to the scores of the IIH patients on the first and second evaluations.

IIH is probably attributable to reduced peripheral olfactory perceptual ability secondary to damage to peripheral olfactory areas. Indeed, a recent case report showed that the olfactory dysfunction may be reversed when the cranial pressure is reduced by drainage of the spinal fluid during lumber puncture [23]. The odor threshold score in that study went from below the 5th percentile to above the 75th percentile after intra-cranial pressure dropped from 50 cm H2O to 15 cm H2O [23]. In our cohort, the detection sensitivity increased at the second evaluation, after treatment and clinical improvement. Together, these findings support the suggestion that the olfactory threshold is more sensitive to changes in intracranial pressure than to other clinical factors [5].

Since the OI scores were not significantly different between our two groups, and they did not change during the follow up period we conclude that pediatric IIH does not influence the ability of the

cognitive processing system to identify odors at supra-threshold levels. The mean OI score percentiles in both groups were in the lower range of normal. A Few recent studies suggested that the Sniffin' Sticks odor identification test is not optimal for use in children because it is strongly dependent on familiarity with the odorants and cognitive and linguistic sophistication, and it is subject to cultural influences [26,27]. This emphasizes the need for an age-appropriate and cross-cultural olfactory test.

An article published after the beginning of our study presented a modified "Sniffin' Kids" test comprise of 14 items, excluding 2 odorants (apple, turpentine) which were significantly less often correctly identified by children compared to the other odors (as noted in our cohort as well). The authors provided normative data for three age groups based on a large sample [28].

Others recently developed a new odor identification test (U-Sniff) for children including 12 odorants that proved highly recognizable based on average scores obtained in many countries. Participants were presented with descriptors of the odors (in pictures and words) before being asked to identify them and they were allowed to smell each odor up to 3 times. The U-Sniff test was internationally validated in a multicenter study [29]. Normative data have been provided [30] and test-retest reliability was evaluated [31]. Nevertheless, the odor identification scores differed significantly across some countries [29], thus, additional comparison of the odor identification scores to scores of a local control group may be useful.

Currently, the diagnosis of IIH poses a major clinical challenge [2] mainly because of the substantial limitations of current diagnostic tools. For example, the ophthalmoscopic examination is examiner-dependent [32], and the absence of ophthalmic findings does not exclude the diagnosis of IIH; the cutoff for normal CSF opening pressure is arbitrary; and the measurement of CSF opening pressure may be influenced by many factors [33]. Accordingly, overdiagnosis of IIH is common, often leading to unnecessary and sometimes extensive evaluations and inappropriate treatments [32]. It has been suggested that olfactory impairment might serve as a sensitive predictor of IIH given the dominant contribution of the olfactory perineurial sheath to CSF drainage [5]. We suggest that future studies investigate the value of olfactory testing for the diagnosis, management and prognosis of IIH in larger cohorts, with repeated follow-up olfactory tests and concurrent lumbar punctures in addition to clinical evaluations and neuro-ophthalmologic tests such as orbital sonography, with comparison to healthy children matched for age, sex, and BMI.

It may be interesting to study and evaluate the association between olfactory function and other pediatric diseases besides IIH, such as Bardet-Biedl syndrome, Kallmann syndrome, Multiple sclerosis, and Covid-19. We suggest that olfactory evaluation, which is often neglected in pediatric neurological examinations, should be an integral part of the clinical evaluation, and it may serve as a common and useful clinical tool.

The diagnosis of olfactory dysfunction has additional significance: It is important to overall patient well-being. Olfaction plays a key role in human daily life. The correct detection of odors alerts us to certain dangers (fires, spoiled food, etc.), influences food intake, and affects interpersonal relations. Left untreated, olfactory dysfunction can decrease quality of life [34] and increase the risk of depression [35].

4.1. Study limitations

Our study has several limitations. First, the sample size was small, although the comparison of the participants' Sniffin' Sticks scores to the updated normative values allowed us to generalize our conclusions.

Second, the IIH group was comprised mostly of adolescents with few pre-pubertal children. Hence, their clinical characteristics were more similar to adult IIH in terms of female predominance and association with higher BMI. We matched our study groups for age and sex, but they differed significantly in BMI percentiles. The data on whether obesity is a confounder in olfactory impairment are conflicting. Some studies showed an association between obesity and reduced olfaction [36,37] whereas a more recent study found that adolescents with a high BMI had significantly greater olfactory sensitivity than normal-weight adolescents [38]. Interestingly, we found no association between BMI percentiles and olfactory performance, suggesting that IIH itself may have an independent effect on olfactory function regardless of BMI. Further studies are required to precisely determine the size of the effect of obesity on olfactory function in patients with IIH.

5. Conclusion

This study provides new evidence that olfaction is impaired in pediatric IIH. This finding is presumably due to disease-induced alteration of the peripheral structures of the olfactory system. Olfactory testing should be an integral part of the clinical evaluation of patients with IIH. Future studies should evaluate impaired olfactory sensitivity as a predictor of IIH so it might serve as an early diagnostic and prognostic tool.

Declaration of competing interest

None.

Acknowledgements

We thank Gloria Ginzach, professional medical editor, Rabin Medical Center, who edited the manuscript for non-intellectual content.

We thank Prof. Gabriel Hudik, Head of the Epidemiology and Database Research department, in MaccabiTech and associate Professor at the School of Public Health in Tel Aviv University who conducted the statistical analysis and interpretation.

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