

Does hereditary hemorrhagic telangiectasia affect olfactory or gustatory function?

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ABSTRACT

Background: The olfactory and gustatory functions of hereditary hemorrhagic telangiectasia (HHT) patients have not been documented by validated tests. Disorders of the nasal/oral cavity may interfere with the olfactory and gustatory functions. Fifty-four HHT patients were investigated by smell/taste tests.

Methods: HHT patients provided subjective ratings in areas such as ability to perceive smell/taste. "Sniffin' Sticks" were used for smell tests, and taste strips were used for taste tests.

Results: HHT patients rated their subjective olfactory and gustatory function on a visual analog scale from 0 (none) to 100 (high) as 65.3 ± 27.7 and 68.1 ± 25.1 , respectively. Comparison of smell test results of HHT patients with normative data of sex- and age-matched controls from Hummel et al. revealed that HHT patients had lower threshold values, whereas there was no difference in identification and discrimination values. HHT patients were hyposmic. In the case of taste qualities, all values (sweet, sour, salty, and bitter) in HHT patients were lower than those in normative data of Mueller et al. However, HHT patients were not hypogeusic. The duration of disease, extranasal manifestation, and treatments did not significantly correlate with smell/taste test values.

Conclusion: Compared with healthy people, HHT patients exhibit reduced olfactory and gustatory function; however, HHT patients are hyposmic and not hypogeusic. This chemosensory deficit may highlight an early sign of disease and has no correlation with disease severity. HHT patients should be informed about these potential disease manifestations, thus enabling them to improve their quality of life.

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Hereditary hemorrhagic telangiectasia (HHT), or Osler-Weber-Rendu syndrome, is a disorder of blood vessels that is inherited as an autosomal dominant trait. HHT is characterized by vascular dysplasia and excessive bleeding. The pathogenesis of HHT has been related to abnormal modulations of the transforming growth factor signaling pathway. HHT commonly results from mutations in *ENG* (the gene encoding endoglin [HHT type 1]) and *ACVRL1* (the gene encoding activin receptor-like kinase [ALK-1] [HHT type 2]), which are exclusively expressed on vascular endothelial cells, and rarely from *MADH4/SMAD4* gene mutations (HHT in association with juvenile polyposis).^{1–4} In addition, *HHT3* (mapped to chromosome 5q between D5S2011 and D5S2490) and *HHT4* (mapped to chromosome 7p between D7S2252 and D7S510) have been implicated in the development of classic HHT.^{4,5} These genetic mutations cause abnormal vascular structures ranging from dilated microvessels to large arteriovenous malformations.⁵ The abnormal blood vessels, identified as telangiectasias, are mostly found on the skin, nasal mucosa, buccal mucosa, lips, lungs, brain, liver, and anterior portion of the tongue.⁶ Most patients present with characteristically severe and recurrent nose bleeds (>90% of all patients) and with hemorrhage in the gastrointestinal tract (10–40% of all patients).^{5–7} Moreover, hepatic vascular malformations are detected in ~80% of patients, arteriovenous malformations of the lung in ~15–50% of patients, and cerebrovascular malformations in 5–27% of patients.^{6,7} Although the course of

HHT may be silent without any symptoms,⁸ some types of HHT may cause life-threatening complications, including severe anemia, ischemic or hemorrhagic cerebrovascular accident, deep venous thrombosis, liver diseases, severe pulmonary hypertension, and spinovascular accident.⁵ Because of their tendency of continuous growth and inherent health dangers, arteriovenous malformations require early diagnosis. Often, diminished olfactory and gustatory function indicates early stage of disease. In addition, disorders of the nose and oral cavity may interfere with their respective functions. Therefore, it is expected that smell and taste are affected in HHT. The potential effect of HHT on the olfactory nerve has not been reported previously; however, underlying vascular disorders may lead to recurrent nasal bleeds, chronic nasal irritation and crust formation, and altered nasal and oral mucosal integrity, which may in turn cause olfactory and gustatory dysfunction.

Olfactory and gustatory dysfunctions have important implications on human health and safety. Distorted olfaction may impair an individual's ability to detect smoke from a fire,⁹ to identify spoiled food, or to cook good-tasting food.¹⁰ Furthermore, distortion may result in reduced appetite and changed mood.¹⁰ Some patients lose weight due to distorted olfactory function, while some patients gain weight due to the addition of sweetening agents to improve taste.^{11,12} Thus, the objective of this study was to determine if patients with HHT have impaired taste and smell functions and to ensure whether they are adequately informed about how to overcome the deficits.

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PATIENTS AND METHODS

Patients

This is a case control study on 54 HHT patients. Positive diagnosis was based on a family history of HHT along with telangiectasia at the time of diagnosis and recurrent epistaxis. All patients provided written consent for their participation in the study. The study protocol was approved by the Ethics Committee of the Faculty of Medicine at the Philipps-University of Marburg, Germany.

Subjective Assessment

After undergoing an ear, nose, and throat examination to exclude nasal polyps and crust formation, the participants provided initial subjective ratings on topics such as appetite or ability to perceive smell and taste. The ratings were based on a visual analog scale (VAS) with the score for each variable ranging from 0 to 100 (0 represented complete loss of appetite and perception of smell or taste; 100 represented excellent appetite and perception of smell or taste).

Smell Testing

"Sniffin' Sticks" (Burghart Messtechnik GmbH, Wedel, Germany) were used in smell tests, which included tests for odor identification (ID), odor discrimination (DIS), and odor threshold (THR).^{13–15} Odors were presented using felt-tip pens; the cap was removed and the tip was positioned ~2 cm in front of patient's nostrils for 3 seconds. For the ID test, patients sniffed 16 pens of different, but familiar, odors separately. Patients were asked to select the source substance that matched the presented odor from four different items in a forced-choice procedure (four-alternative forced choices). The DIS test kit contains 48 pens arranged in 16 triplets; 2 of the pens in each triplet contained the same odor. Patients were asked to identify the pen with the different odor (three-alternative forced choice). The THR test kit contains 48 pens arranged in 16 triplets; 2 of the pens in each triplet were odorless and the third was impregnated with different concentrations of an *n*-butanol solution with a concentration range starting from 4%. The triplet sets were presented to the patients from the lowest to highest *n*-butanol concentrations and the patients were asked to identify the pen with *n*-butanol odor. After patients correctly recognized the pen with *n*-butanol in each triplet, the triplet pens were shuffled and presented again in a random order. If the patient was able to recognize the odor of the pen in each triplet the second time, then he/she was presented with the triplets in a reversed staircase (*i.e.*, highest to lowest concentrations) until he/she could no longer identify the pen with the odor of *n*-butanol. The THR value is represented as the mean of the last four of the seven total staircase reversal test values.

Thus, the range of values is 0–16 for ID and DIS and 1–16 for THR. The sum of the ID, DIS, and THR values is referred to as TDI (range, 1–48). Patients were blindfolded during the THR and DIS tests to avoid visual ID of the pens.

Taste Testing

Taste strips were used in the taste test. A total of 16 filter paper strips were impregnated at one end with one of the four types of taste (sweet, sour, salty, or bitter) in one of the following four concentrations: 0.05, 0.1, 0.2, or 0.4 g/mL of sucrose (sweet); 0.05, 0.09, 0.165, or 0.3 g/mL of citric acid (sour); 0.016, 0.04, 0.1, or 0.25 g/mL of sodium chloride (salty); or 0.0004, 0.0009, 0.0024, or 0.006 g/mL of quinine hydrochloride (bitter).¹⁶ The taste strips were placed on two sides of the patient's tongue ~1.5 cm from the tip. Patients were asked to identify the taste stimuli (*i.e.*, sweet, sour, salty, or bitter) by a forced-choice procedure. The patients were instructed to protrude their tongues during the tasting process. Correct ID of each taste was scored on a scale of 0–4, with a total of 16 points for one side of the tongue and 32 points for both sides of the tongue.

Normative Data of Smell and Taste Tests

Hummel *et al.*¹⁵ published normative data for the Sniffin' Sticks test battery after investigating >3000 healthy individuals. To validate whether the study group's results are comparable with those of the cohort of healthy individuals examined by Hummel *et al.*,¹⁵ the group formed a representative cohort of 22 healthy female volunteers (age range, 36–55 years; mean age, 43.6 ± 5.9 years) and performed the Sniffin' Sticks test battery used in our HHT patients. No significant differences were noted in comparison with the results of Hummel *et*

*al.*¹⁵ (mean values: ID, 14.1 ± 1.4 ; DIS, 13.1 ± 1.4 ; and THR, 9.5 ± 1.9). Thus, the data from the Sniffin' Stick test performed on HHT patients (men and women considered separately in defined age groups) were compared with the normative data acquired by Hummel *et al.*¹⁵ In this data set, hyposmia was defined as the score of subjects aged 16–35 years in the 10th percentile. Thus, TDI scores of ≤ 30.5 in women and ≤ 29.5 in men, THR scores of ≤ 6.5 in women and ≤ 6.0 in men, DIS of ≤ 10 or women and men, and ID scores of ≤ 11 in women and men were suggestive of hyposmia (versus normosmia).¹⁵ Similarly, HHT patient data of the "taste strips" tests were compared with the normative data based on the mean results of 69 healthy subjects as described by Mueller *et al.*¹⁶ Using the bilateral taste strip test on the tongue, Landis *et al.*¹⁷ defined hypogeusia as the 10th percentile score in subjects aged 18–40 years, thus separating normogeusic from hypogeusic subjects. A patient was classified as normogeusic if the score was ≥ 19 in women and ≥ 17 in men (range, 0–32).¹⁷

Statistical Analysis

The data were coded, edited, and then statistically analyzed using SPSS software 19.0 and R 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria). Data were presented as mean $\pm$ SD or median (range). To compare different subgroups we used the exact Mann-Whitney *U* test. Relationships between two intervals or ordinal data were studied based on Spearman rank correlation coefficients r_s . Comparison with normative data was performed by using one- and two-sample *t*-tests. All statistical analyses were performed based on a two-sided 0.05 level of significance.

RESULTS

Patient Cohort

The distribution of gender, age, body mass index, disease duration, frequency of nose bleeds, most recent nose bleeding episode, septal perforation, extranasal manifestations, treatments, and smoking/alcohol habits is summarized in Table 1. No patient had hypo- or hyperactivity of the thyroid gland, diabetes, neurological disorders, or tumors.

Subjective Assessment of Smell and Taste

Table 2 summarizes the subjective assessment results of smell, taste, appetite, parosmia, and phantosmia on a VAS from 0 (none) to 100 (high).

Smell and Taste Test Results based on Age and Gender

A significant correlation was observed between the age of HHT patients and ID ($p = 0.02$; $r_s = -0.34$), DIS ($p = 0.04$; $r_s = -0.31$), THR ($p = 0.01$; $r_s = -0.36$), and TDI ($p < 0.01$; $r_s = -0.42$). However, no significant correlation was found between age and taste. Men exhibited lower values for ID, DIS, THR, TDI, and subjective assessment of smell than women, but the difference was significant only for the subjective assessment of smell ($p = 0.04$). In addition, all taste values were lower in men than in women, but the significant difference was limited to the total taste value (left side, $p = 0.03$; right side, $p = 0.01$) and the salty quality value (left side, $p = 0.03$; right side, $p = 0.02$).

Smell and Taste Test Results based on Age-Matched Normative Data

To investigate olfactory and gustatory function in HHT patients, we compared sex- and age-matched normative data from Hummel *et al.*¹⁵ (Table 3) and normative data from Mueller *et al.*¹⁶ (Table 4). For both age groups (36–55 years and >55 years) and both sexes, the values of THR were lower in HHT patients compared with healthy controls. However, ID and DIS remained unchanged in women from

Table 1 HHT patient characteristics

	Patients, n (%) Total n = 54
Gender	
Female	27 (50)
Male	27 (50)
Mean Age (yr): 58.0 ± 12.8 (range, 28–82)	
Body mass index: 26.3 ± 4.2 (range, 19–34)	
Disease duration (yr): 22.5 ± 17.1 (range, 0.25–80)	
Frequency of nose bleeds (per wk): 6.0 ± 7.7 (range, 0.05–40)	
Most recent nose bleeding episode (in days): 2.7 ± 5.5 (range, 0–28)	
Septal perforation	14 (25.9)
Extranasal manifestations	19 (35.2)
Lung	7 (12.9)
Liver	4 (7.4)
Gastrointestinal	3 (5.5)
Kidney	1 (1.8)
Lung/liver	3 (5.5)
Lung/liver/brain	1 (1.8)
Treatments	
ACE-inhibitor	1 (1.8)
Antidepressive/oral cortisone	0 (0.0)
Iron	9 (16.7)
Laser treatment	35 (64.8)
Saunders-operation	3 (5.5)
Embolization	4 (7.4)
Electrocoagulation	16 (29.6)
Cigarettes (per day) 9.4 ± 6.8 (range, 1–18)	7 (12.9)
Alcohol consumption	
Occasionally in low amounts	54 (100)

ACE = angiotensin-converting enzyme; HHT = hereditary hemorrhagic telangiectasia.

both age groups and in men aged 36–55 years. Men aged ≥ 55 years had lower ID values compared with healthy controls, but no difference was observed with respect to DIS (Table 3). For taste, all values (sweet, sour, salty, bitter, and total taste) in HHT patients were lower compared with those in healthy controls. However, reduction in the sweet quality value was not significant (Table 4).

Smell and Taste Results in Relation to Hyposmia and Hypogeusia

Hummel *et al.*¹⁵ defined hyposmia as a 10th percentile score or less in subjects aged 16–35 years. For HHT patients, the ID and DIS values were higher than those of the 10th percentile. However, the THR value for female patients was 5.1 ± 2.7 and for all male patients was 4.7 ± 3.1 , which were lower than those in the 10th percentile for healthy women and men aged 16–35 years (6.5 and 6.0, respectively; women, $p = 0.02$; men, $p = 0.07$). Thus, HHT patients were considered hyposmic. To evaluate hypogeusia, normogeusic subjects (aged 18–40 years) were separated from hypogeusic subjects based on the 10th percentile score cut-off value from bilateral taste strip tests on the tongue.¹⁷ No significant differences were observed between HHT patient data (women, 20.6 ± 6.9 , $p = 0.26$; men, 16.7 ± 6.1 , $p = 0.32$) and the defined 10th percentile scores presented by Landis *et al.*¹⁷ (women, 19; men, 17).

Smell and Taste Test Results based on Subjective Assessment of Smell and Taste Based on VAS Scores

On comparison of the subjective assessment of smell based on VAS scores with ID, DIS, THR, and TDI values, a correlation was found for ID ($p < 0.01$; $r_s = 0.58$), THR ($p = 0.02$; $r_s = 0.35$), and TDI ($p < 0.01$; $r_s = 0.42$), but not for DIS. In addition, a correlation was evident between the subjective assessment of taste based on the VAS score and the total taste score (left side, $p < 0.01$, $r_s = 0.40$; right side, $p = 0.03$, $r_s = 0.33$) and the score for the sweet quality (left side, $p = 0.014$, $r_s = 0.36$; right side, $p = 0.017$, $r_s = 0.36$).

Smell and Taste Test Results based on Disease Severity and in Relation to Treatment

The duration of disease, frequency of nose bleeds, extranasal manifestation, and treatments (embolization, electrocoagulation, or laser) showed no significant correlation with ID, DIS, THR, TDI, total taste, or individual taste values (sweet, sour, salty, or bitter) or with the values of the subjective assessment of smell and taste. Correlation was observed in the most recent nose bleeding episode and ID ($p = 0.02$; $r_s = -0.35$) and DIS values ($p = 0.045$; $r_s = -0.30$) but not with THR ($p = 0.08$; $r_s = -0.26$). In addition, there was significant correlation between the most recent nose bleeding episode and the total taste score (left side, $p < 0.01$, $r_s = -0.40$; right side, $p = 0.04$, $r_s = -0.30$) and the sweet quality score (left side, $p < 0.01$, $r_s = -0.46$; right side, $p = 0.04$, $r_s = -0.31$). HHT patients who experienced nasal septal perforation exhibited low values for ID, DIS, TDI, total taste, sweet taste, sour taste, and bitter taste and the subjective assessment of smell and taste (Table 5).

DISCUSSION

In this study, we used subjective assessment based on VAS scores and validated smell/taste tests to conduct the first investigation of olfactory and gustatory function in HHT patients. Female and male HHT patients exhibited a decreased odor THR compared with sex- and age-matched healthy controls. However, there were no significant differences among HHT patients with regard to odor ID and odor DIS, with the exception of men > 55 years, who exhibited lower ID values compared with age-matched healthy men. In addition, the THR values, and not ID or DIS values, in all HHT patients were lower than the 10th percentile score of healthy women and men aged 16–35 years.¹⁵ It is assumed that THR, in particular, is a measure of the peripheral olfactory function, whereas ID and DIS indicate high central nervous processing of odors.^{18–21} Thus, HHT patients exhibit reduced olfactory function compared with healthy people and are hyposmic. To validate the comparison of HHT patients and > 3000 healthy individuals tested by Hummel *et al.*,¹⁵ a representative cohort of 22 healthy female volunteers was investigated in this study with the same Sniffin' Sticks test battery that was used in HHT patients. There was no significant difference in ID, DIS, THR, and TDI values between the 22 female volunteers and the women tested by Hummel *et al.*¹⁵

In the case of taste tests, the sweet quality decreased and the sour, salty, and bitter qualities, as well as the total taste values, in HHT patients were significantly lower compared with those of healthy controls. However, the HHT patients were not hypogeusic.

When asked to rate their olfactory and taste function on a VAS from 0 (no perception of smell and taste) to 100 (excellent perception of smell and taste), the HHT patients scored 65.3 ± 27.7 for smell and 68.1 ± 25.1 for taste. Thus, a reduction in both chemosensory functions was evident. Fasunla *et al.*²² also assessed smell and taste on VAS using the same method used in this study and they reported values of 83.8 ± 10.4 for olfaction and 83.5 ± 10.4 for taste in 16 healthy people. Steinbach *et al.*²³ assessed smell and taste in 87 patients with gynecological tumors before the initiation of chemotherapy and obtained the values of 85.9 ± 10.6 for olfaction and $82.9 \pm$

Table 2 Subjective ratings of smell and taste in HHT patients based on VAS scores

Subjective Ratings VAS 0 (none), 100 (high)	Mean $\pm$ SD	Median	Range
Olfactory function	65.3 $\pm$ 27.7	75	0–100
Gustatory function	68.1 $\pm$ 25.1	70	0–100
Appetite	73.7 $\pm$ 25.8	80	0–100
Aversion to odors (parosmia)	17.5 $\pm$ 26.5	4	0–78
Things that smell differently (parosmia)	9.1 $\pm$ 14.3	2	0–55
Smelling of odors not present (phantosmia)	5.6 $\pm$ 17.7	0	0–53
Food is sweetened more	16.8 $\pm$ 25.8	4.3	0–83
More salt is used	19.8 $\pm$ 25.9	8	0–55
Preference for more fatty meals	20.0 $\pm$ 25.9	8	0–95
Preference for more bitter meals	16.4 $\pm$ 25.2	4.5	0–98
Preference for more sour meals	23.4 $\pm$ 28.3	8.5	0–96

HHT = hereditary hemorrhagic telangiectasia; VAS = visual analog scale.

Table 3 Comparison of the olfactory function between sex- and age-matched normative data and values of HHT patients

	Normative Data Female* (mean $\pm$ SD)	Patients Female	<i>p</i> Value	Normative Data Male* (mean $\pm$ SD)	Patients Male	<i>p</i> Value
Aged 16–35 yr		<i>n</i> = 3			<i>n</i> = 3	
Aged 36–55 yr		<i>n</i> = 6			<i>n</i> = 9	
TDI	35.16 $\pm$ 4.52	31.29 $\pm$ 3.19	0.04	33.2 $\pm$ 6.05	32.08 $\pm$ 9.37	0.73
ID	13.49 $\pm$ 1.56	13.33 $\pm$ 1.75	0.80	13.1 $\pm$ 1.88	13.11 $\pm$ 4.37	0.99
DIS	12.46 $\pm$ 1.96	11.67 $\pm$ 2.16	0.33	11.94 $\pm$ 2.24	13.11 $\pm$ 1.9	0.13
THR	9.08 $\pm$ 3.09	6.29 $\pm$ 3.4	0.03	8.43 $\pm$ 3.47	6.97 $\pm$ 3.4	0.22
Aged >55 yr		<i>n</i> = 18			<i>n</i> = 15	
TDI	29.83 $\pm$ 6.77	27.93 $\pm$ 4.15	0.13	29.81 $\pm$ 7.17	23.13 $\pm$ 6.79	<0.01
ID	12.06 $\pm$ 2.31	12.94 $\pm$ 1.77	0.14	12.2 $\pm$ 2.57	9.92 $\pm$ 3.42	<0.01
DIS	10.66 $\pm$ 2.50	10.25 $\pm$ 2.77	0.54	10.69 $\pm$ 2.77	9.75 $\pm$ 3.05	0.27
THR	7.44 $\pm$ 3.51	4.3 $\pm$ 2.58	<0.01	7.15 $\pm$ 3.59	3.42 $\pm$ 1.69	<0.01

*For reference, please see Ref. 15.

HHT = hereditary hemorrhagic telangiectasia; TDI = sum of ID, DIS, and THR; ID = odor identification; DIS = odor discrimination; THR = odor threshold.

Table 4 Comparison of the gustatory function between normative data and values of HHT patients

	Normative Data* (mean $\pm$ SD)	Patients	<i>p</i> Value
Total score			
Left side	12.4 $\pm$ 1.0	9.2 $\pm$ 3.4	<0.01
Right side	12.4 $\pm$ 1.0	9.0 $\pm$ 3.6	<0.01
Sweet			
Left side	3.3 $\pm$ 0.8	3.0 $\pm$ 1.2	0.17
Right side	3.3 $\pm$ 0.8	3.1 $\pm$ 1.0	0.33
Sour			
Left side	3.0 $\pm$ 0.8	1.8 $\pm$ 1.2	<0.01
Right side	3.0 $\pm$ 0.8	1.7 $\pm$ 1.2	<0.01
Salty			
Left side	3.1 $\pm$ 0.9	2.0 $\pm$ 1.2	<0.01
Right side	3.1 $\pm$ 0.9	2.0 $\pm$ 1.3	<0.01
Bitter			
Left side	3.0 $\pm$ 1.1	2.3 $\pm$ 1.4	<0.01
Right side	3.0 $\pm$ 1.1	2.1 $\pm$ 1.4	<0.01

For reference, Ref. 16.

HHT = hereditary hemorrhagic telangiectasia.

19.2 for taste. The results of subjective assessment of olfactory and gustatory function in HHT patients yielded values that were comparable with subjective assessments in patients with Wegener's granulomatosis.²²

Surprisingly, the results of subjective assessment of smell in HHT patients correlated significantly with their ID, THR, and TDI values. In addition, the subjective assessment of taste correlated significantly with the total taste and sweet quality. This result suggests the importance of using Sniffin' Sticks or taste strips to measure ID, THR, and the total taste in HHT patients. These two tests are noninvasive and can be easily performed. Especially in HHT patients assuming a decreased chemosensory function smell and taste test results may be poor. These patients should be tested frequently. Reduced olfactory and gustatory function can have a strong effect on the quality of life and may even be life-threatening (e.g., inability to smell smoke in a fire).²⁴ HHT patients should be aware of their reduced olfactory and gustatory function. To improve their quality of life, HHT patients with reduced smell and taste function may be advised to add more herbs and spices to their food or low amounts of glutamate and other flavors.^{25–28}

Based on a literature review, liver and kidney diseases appear to influence olfactory function.²⁹ Thus, HHT patients with extranasal manifestations may exhibit lower olfactory function than patients without lung, liver, kidney, or gastrointestinal tract involvement. However, we were unable to confirm this assumption. In addition, there was no significant correlation between smell and taste test scores and disease duration or frequency of nose bleeds. Early diagnosis of HHT is important because of its continuous growth and inherent dangers. In this study, reduced olfactory and gustatory function in HHT patients did not appear to depend on disease severity (e.g., extranasal manifestation and frequency of nose bleeds), thereby indicating that the reduced function is an early symptom or

Table 5 Olfactory and gustatory function of HHT patients with and without nasal septal perforation

	Septal Perforation Mean $\pm$ SD (median, range)	No Septal Perforation Mean $\pm$ SD (median, range)	<i>p</i> Value
TDI	25.4 $\pm$ 5.9 (25.7, 13–32)	29.9 $\pm$ 5.9 (29.5, 16–44)	0.04
ID	10.6 $\pm$ 3.5 (12.0, 2–14)	13.4 $\pm$ 1.9 (13.0, 8–16)	<0.01
DIS	9.7 $\pm$ 2.6 (9.0, 4–13)	11.5 $\pm$ 2.6 (12.0, 6–16)	0.05
THR	4.7 $\pm$ 2.8 (4.5, 2–12)	5.3 $\pm$ 2.9 (4.7, 1–12)	0.48
Subjective assessment of smell (VAS)	51 $\pm$ 28 (49, 10–90)	74 $\pm$ 20 (79, 30–100)	<0.01
Total taste score			
Left side	8.1 $\pm$ 3.3 (8, 3–15)	9.9 $\pm$ 3.3 (9, 4–16)	0.10
Right side	7.3 $\pm$ 3.5 (7.5, 2–15)	9.6 $\pm$ 3.6 (9, 3–16)	0.07
Sweet			
Left side	2.3 $\pm$ 1.2 (3, 0–4)	3.3 $\pm$ 0.9 (4, 1–4)	<0.01
Right side	2.5 $\pm$ 1.1 (2.5, 0–4)	3.3 $\pm$ 0.9 (4, 1–4)	0.014
Sour			
Left side	1.3 $\pm$ 1.1 (1, 0–3)	2.2 $\pm$ 1.1 (2, 0–4)	0.025
Right side	1.2 $\pm$ 1.0 (1, 0–3)	1.9 $\pm$ 1.2 (2, 0–4)	0.05
Salty			
Left side	2.6 $\pm$ 1.0 (3, 1–4)	1.8 $\pm$ 1.4 (2, 0–4)	0.08
Right side	1.8 $\pm$ 0.9 (2, 1–4)	2.0 $\pm$ 1.4 (2, 0–4)	0.73
Bitter			
Left side	1.9 $\pm$ 1.4 (2, 0–4)	2.6 $\pm$ 1.4 (3, 0–4)	0.14
Right side	1.8 $\pm$ 1.6 (1.5, 0–4)	2.3 $\pm$ 1.3 (2, 0–4)	0.30
Subjective assessment of taste (VAS)	57 $\pm$ 17 (56, 30–90)	74 $\pm$ 24 (80, 20–100)	0.02

HHT = hereditary hemorrhagic telangiectasia; VAS = visual analog scale.

sign of a disorder. One may speculate that decreased olfactory and gustatory functions occur in individuals with altered nasal and oral mucosal integrity because of an underlying vascular disorder. Nose bleeds and their associated therapy may irritate nasal mucosa and result in crust formation. Assuming that THR is a better measure of the peripheral olfactory function when compared with ID and DIS,^{18,19} the most recent episode of nasal bleeding may mainly influence THR. However, in this study, we observed a significant correlation between ID and DIS and the most recent episode of nasal bleeding, but not between THR and the most recent nasal bleeding episode. Perhaps, HHT patients who have experienced an episode of nose bleeding shortly before the smell tests may have experienced more difficulties in focusing during the smell test, and therefore they might find it more difficult to identify odors (ID and DIS). In addition, values for total taste and sweet quality correlated significantly with the most recent episode of nose bleeding, which did not correspond to nasal crust formation and irritation of the nasal mucosa. In our study, a comparison of HHT patients who had undergone nasal treatments (e.g., intranasal electrocoagulation or laser therapy) with those who did not undergo nasal treatments did not reveal any differences in smell and taste values or in the subjective assessment of smell and taste. Most published studies on olfactory outcomes during and after laser treatment or radiofrequency that were performed to reduce hypertrophic inferior turbinate showed an increase in olfactory function after treatment.^{30,31} In HHT, blood vessels are shaped like spots, loops, spiders, or cluster of raspberries. The blood vessels may be found in the anterior nasal cavity as well as on the middle turbinates, floor of the nose, valve area, around septal perforation edges, in profound portions of the nasal cavity, and in the nasopharynx.³² Human olfactory neuroepithelium may be located on the roof of the nasal cavity or olfactory cleft, middle turbinates, and upper nasal septum.^{33,34} Thus, intranasal manipulations may potentially disturb the olfactory neuroepithelium. However, we did not observe any difference between olfactory function in HHT patients who had undergone or who did not undergo intranasal treatments. This information may be helpful for the treatment of HHT patients.

HHT patients often suffer from nasal septal perforation. For the study of nasal aerodynamics, computational fluid dynamics has been

adopted. Thus, it is known that high velocity airflow and shear stress to the wall cause desiccation and mucosal damage at the nasal septal perforation.³⁵ However, there is less information on olfactory and gustatory function in patients with nasal septal perforation. In this study, the smell and taste test values in HHT patients with nasal septal perforation were lower than those in patients without nasal septal perforation. However, the reduction was only significant for values of ID, DIS, and sweet and sour taste qualities as well as subjectively assessed smell and taste function. We speculate that HHT patients with nasal septal perforation may identify odors relatively poorly because of their own perceptions of the nasal septal perforation. This possibility requires further investigation.

With regard to olfactory or gustatory function and age or gender in our study, the results of HHT patients were within an expected range. The values for ID, DIS, and THR are known to decline with age.^{15,36} Taste function also decreases with age, but the loss of gustatory function is much less pronounced than the loss of olfactory function.^{37–39} In addition, the results of olfactory and gustatory tests in women were better than those in men.^{15,17}

In conclusion, HHT patients exhibited decreased olfactory and gustatory function compared with sex- and age-matched healthy controls; however, HHT patients are hyposmic and not hypogeusic. This chemosensory deficit may highlight an early sign of disease and is not correlated to disease severity. HHT patients should be informed about these potential disease manifestations and thus encouraged to improve their quality of life.

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