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RHINOLOGY

Olfactory dysfunction and quality of life in patients with transfusion-dependent thalassemia

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Abstract Transfusion-dependent thalassemia (TDT) is a group of thalassemia syndromes that require regular blood transfusions for survival. It is unknown whether the sense of smell of patients with TDT is affected, and if so, whether smell loss has an adverse effect on quality of life (QOL). Olfactory thresholds were measured using Snap & Sniff® wands. QOL was assessed via the Short Form-36 (SF-36) questionnaire. Forty-two TDT patients from the Thalassemia Center in Istanbul Medical Faculty were tested (mean age 26.6 years), along with 42 healthy controls (mean age 28.0 years). Mean olfactory sensitivity was lower in the TDT patients than the controls ($p < 0.0001$). TDT was associated with lower mean QOL scores on the domains of physical function ($p < 0.0001$), physical role limitation ($p = 0.011$), and general health ($p < 0.0001$). Within the TDT group, significant correlations were present between the threshold scores and physical function, physical role limitation, emotional role limitation, and general health. Patients with TDT are less sensitive to odors than healthy controls and the lower olfactory test scores are related to lower quality of life, suggesting that decreased smell function is an additional complication of this disease.

Keywords Transfusion-dependent thalassemia · Olfactory dysfunction · Olfactory threshold · Psychophysics · SF-36 · Quality of life

Abbreviations

TDT	Transfusion dependent thalassemia
QOL	Quality of life
OF	Olfactory function
SF-36	Short form-36

Introduction

Thalassemia is an inherited chronic blood disorder in which an abnormal form of hemoglobin induces severe and life-threatening anemia. Based on the requirement for transfusions, thalassemia syndromes are classified as transfusion-dependent (TDT) and non-transfusion-dependent forms [1]. TDT is characterized by homozygotes and compound heterozygotes of thalassemia alleles.

In light of their severe anemia, patients with TDT require regular blood transfusions to survive. Besides the disease's symptoms, patients can also experience such transfusion complications as congestive heart failure, chronic liver disease, and neurocognitive deficits [2]. After the introduction of chelating agents in the 1950s, a reduction in the complications and a higher survival rate ensued [3]. However, as life spans lengthened, quality of life (QOL) became a major issue, with QOL scores falling below those of individuals within the general population [4]. The World Health Organization defines QOL as an

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individual's perceptions of their position in life in relation to their goals, expectations, standards, and concerns [5].

It is now well established that alterations in the sense of smell can significantly influence QOL. This primary sensory system largely determines the flavor of foods and beverages, influences nutrition, and, when deficient, compromises safety by decreasing the ability to detect spoiled foods, fire, leaking natural gas, and other environmental hazards [6]. In 2013–2014, olfactory testing was first employed in the National Health and Nutrition Examination Survey (NHANES). As a result of such employment, it was estimated that over 20 million adults in the United States experience smell and taste impairment [7]. Unfortunately, the function of this primary sensory system is commonly ignored and is rarely assessed in polyclinic settings.

To date, no studies have measured olfactory function in patients with thalassemia. In this study, we quantitatively assessed such function using a very sensitive detection threshold measure. Moreover, in light of the close association between olfactory function and QOL, we determined whether the olfactory test scores correlated with eight health-related quality-of-life domains within a standardized QOL questionnaire.

Materials and methods

Subjects

Twenty-three female and 19 male TDT patients [mean (SD) age = 26.6 (11.1) years; range 7–42 years], along with a healthy control group of 26 women and 16 men [mean (SD) age = 28.0 (9.2) years; range 8–49 years)], were tested between June and December of 2016. They were screened from a group of ~90 patients who visited the clinic during the study period on the basis of not having, at the time of recruitment, an acute infection (i.e., acute rhinitis, allergic rhinitis, upper or lower respiratory tract infection, urinary tract infection, and acute gastroenteritis) or any other evidence of rhinosinus disease. The mean (SD) disease duration was 25.3 (11.2) years. Forty percent ($n = 16$) had comorbidities such as diabetes mellitus (DM), hypothyroidism, hyperthyroidism, growth retardation, psychiatric disorders, osteoporosis, heart failure, and hypercholesterolemia. Although three patients reported a loss of appetite and one gustatory ageusia, none reported difficulties with their sense of smell. All patients received regular blood transfusions, with 80% receiving transfusions every 3–4 weeks. Seventy percent of patients used deferasirox (DFX) as an oral chelator, and 25% used deferiprone (DFP). The mean (SD) level of serum ferritin was 1601.8 (1010.7 ng/mL). While data from all subjects were available for the olfactory threshold test, three patients and one control failed to complete the Short Form 36 Questionnaire version 1.0 (SF-36) test (see below), resulting in a sample size for this test of 39 TDT patients and 41 controls.

The percent of current smokers, past smokers, and nonsmokers did not differ between the patient and control groups (respective patient percentages: 22.5, 12.5, and 65.0%; respective control percentages: 23.8, 4.8, and 71.4%; Fisher exact probability = 0.498). The same was true for exercise, with 12.5% of patients reporting regular exercise and 14.3% of the controls doing so (Fisher exact probability = 0.535). In general, a greater number of patients than controls reported sleeping more than 8 h per night (respective percentages 32.5 and 9.5%, Fisher exact probability = 0.014).

Test procedures

This study was approved by the Institutional Review Board (Istanbul University, Istanbul Medical Faculty Clinical Research Ethics Committee) (No. 2016/807). Upon acceptance into the study and following signed informed consent, each subject was administered the Short Form 36 Questionnaire version 1.0 (SF-36) [8]. This 36-item questionnaire assesses eight health-related quality-of-life domains: physical functioning (PF), social functioning (SF), physical role limitation (PRL), emotional role limitation (ERL), mental health (MH), energy/vitality (VT), bodily pain (BP), and general health status (GH). SF-36 was translated into Turkish and validation studies of Turkish version of SF-36 were performed in patient groups in 1999 and 2005 [9, 10]. For each quality-of-life domain tested, item scores were coded 0 (worst) to 100 (best) using the standard SF-36 scoring algorithms and summed within each subgroup [11].

Olfactory sensitivity was tested using an odor detection threshold test that employed the odorant phenyl ethyl alcohol (PEA), a rose-like smelling odorant with minimal intranasal trigeminal (CN V) neural activity [12]. The stimuli were presented using the Snap & Sniff® olfactory threshold test kit wands [13]. Liquids, per se, are not present in the wands; the odorants are embedded in an absorbent material, which is exposed to the air when the collar on the outside of the wand is moved forward. Procedurally, a single initially ascending staircase procedure was employed. The staircase began at the −6.00 log concentration step of a half-log step (vol/vol) dilution series extending from –9.00 log concentration to −2.00 log concentration. At each concentration, the subject was required to report which of two stimulus presentations, an odorant or a blank, smells strongest. The order of the presentation of the wand containing the odor and the wand

containing only the diluent was randomly determined. The odorant concentration was increased in full log steps until correct detection occurred on five sets of consecutive trials at a given concentration. When an incorrect response was given on any trial, the staircase was moved upward one full log step. When a correct response was made on all five trials, the staircase was reversed and subsequently moved up or down in 0.50 log increments or decrements, depending upon the subject's performance on two pairs of trials at each concentration step. The mean of the last four of seven staircase reversals was used as the threshold estimate. A reliable threshold can be obtained in 10–12 min [14].

Data analyses

Analyses of covariance (ANCOVA) with group and sex as between subject factors and age as a covariate were performed on the olfactory threshold test scores as well as individually on each of the SF-36 subscales. A separate ANCOVA was performed to examine whether chelation type influenced olfactory test scores. Pearson correlations were computed separately for the TDT and control groups among the test scores and the QOL measures to determine whether associations were present.

Results

The TDT group was less sensitive, i.e., had higher detection thresholds, than the control group [respective adjusted means (SEMs) = −5.13 (0.17) and −6.03 (0.17); $F(1, 79) = 14.18$, $p < 0.0001$; values log vol/vol]. Neither gender nor its interaction with subject group was significant ($p > 0.55$). The age covariate was also non-significant ($p = 0.385$). No significant difference between chelation types was found ($p = 0.82$). The olfactory sensitivity of patients with comorbidities did not differ from that of patients without comorbidities ($p = 0.173$).

Lower QOL indices were found for the TDT than for the controls for the domains of Physical Function [respective means (SEMs) = 81.28 (1.85) and 96.35 (1.84); $p < 0.0001$], Physical Role Limitation [respective means (SEMs) = 73.72 (4.91) and 91.46 (4.78); $p = 0.016$] and General Health [respective means (SEMs) = 60.38 (3.15) and 75.12 (2.05); $p < 0.0001$] (Table 1). Irrespective of subject group, women had lower QOL scores than men for the domains of vitality [M and F means (SEMs) = 69.96 (2.96) and 61.58 (2.55); $p = 0.035$], mental health [71.78 (2.58) and 63.96 (3.15); $p = 0.024$], and social function [87.58 (3.36) and 77.82 (2.90); $p = 0.031$].

For the TDT group, the correlation between the olfactory threshold test scores and the ferritin levels was not significant ($p = 0.974$). However, for this group, significant correlations were present between the threshold scores and the physical function ($r = -0.29$, $p = 0.008$), physical role limitation (PRL) ($r = -0.42$, $p < 0.0001$), emotional role limitation (ERL) ($r = -0.23$, $p = 0.041$), and general health ($r = -0.30$, $p = 0.007$). Note that larger negative numbers on the olfactory threshold test mean higher sensitivity. No significant correlations were present within the control group between the threshold values and scores on any of the domain scales.

Discussion

This study demonstrates, for the first time, that patients with TDT experience decrements in their ability to smell, as measured by a sensitive detection threshold test. The deficit was present in both men and women and did not differ between chelation types or those with or without comorbidities. Moreover, the threshold test scores were not related to ferritin levels. Importantly, the olfactory threshold test scores were related to some QOL indices. Thus, TDT subjects, relative to controls, had lower scores on the physical function, physical role limitation (PRL), and general health domains. Moreover, the olfactory test scores were significantly correlated with the physical function, PRL, ERL and general health domain scores.

The finding that more olfactory dysfunction in the TDT subjects was associated with reported greater difficulties in physical activities (e.g., walking, running, bending, and climbing) and limitations in everyday life (e.g., accomplishing less or have difficult performing work), emotion role limitations (e.g., decreased work because of emotional issues), and feelings of general health (e.g., good, poor, worse, or the same as a year ago) is important. This implies that the sensitivity of the olfactory system is intimately associated overall health, including cognitive and motor function in this disease. Previous studies have established, in the general population, that the sense of smell is critical to both safety and optimal quality of life [6]. For example, one study found that one-third of those with olfactory impairment had experienced at least one olfactory-related hazardous event during adulthood [15], the most common being cooking-related incidents (45%), followed by ingestion of spoiled food (25%), the inability to detect a natural gas leak (23%), and the inability to smell a fire (7%). More recently, a longitudinal study of 1,162 non-demented older persons found that, over a 4-year period, those with the lowest baseline olfactory test scores had a 45% mortality rate, as compared to an 18% mortality rate in those with the highest test scores [16].

The physiological basis for the lower olfactory test scores in the TDT group is not clear. It is conceivable that

Table 1 Mean (SEM) short form-36 scores and Snap & Sniff® olfactory threshold test scores for the thalassemia and healthy controls

	Thalassemia group	Healthy group	*p* value
Snap & Sniff® olfactory threshold	−5.13 (0.17)	−6.03 (0.17)	<0.0001
SF-36 domains			
Physical functioning	81.50 (1.87)	96.19 (1.87)	<0.0001
Physical role limitation	73.72 (4.91)	91.46 (4.78)	0.011
Emotional role limitation	76.92 (5.78)	78.05 (5.64)	0.889
Vitality	66.78 (2.93)	63.54 (2.86)	0.428
Mental health	67.31 (2.49)	67.61 (2.43)	0.931
Social functioning	80.13 (3.17)	83.84 (3.09)	0.405
Pain	81.35 (2.90)	84.45 (2.83)	0.445
General health	60.38 (3.15)	75.12 (2.05)	<0.0001

For the threshold test, sample size is 42 in each subject group. For the other measures, sample size is 39 for the thalassemia group and 41 for the controls. Adjusted means and *p* values are from analyses of covariance in which group and sex served as a between subject factors and age served as the covariate. Greater negative threshold values reflect higher sensitivity (see text for details)

these patients have accumulations of iron in brain areas involved in olfactory function. Iron overload, along with increased intestinal iron absorption, is a major complication of TDT. Transfusional iron loading can lead to major pathologies, resulting in morbidity and, in some cases, mortality [17, 18]. It has been shown in experimental models that iron deposits can cause cellular damage and gliosis in the piriform and entorhinal cortexes, main components of the olfactory cortex [19]. Unfortunately, presently, there are no human studies that have sought to determine whether excessive iron is present in the olfactory cortex or olfactory specific brain areas. In light of the present findings, such research is sorely needed. Genetic factors must be also considered, since it is known that the b-globin gene cluster is surrounded by a large cluster of olfactory receptor genes (ORG) [20, 21]. In addition, homozygous deletion of six olfactory receptor genes has been found in patients with beta thalassemia [22]. Research is needed to determine whether this deletion adversely influences olfactory function.

Conclusion

This study assessed the sense of smell in TDT patients and demonstrated reduced olfactory sensitivity in these patients relative to controls. No meaningful correlation was noted between the olfactory threshold test scores and ferritin levels. In addition, it found that patients with TDT have decreased QOL, as measured by several SF-36 domains. Thus, significant correlations were present between the threshold scores and the physical function, physical role limitation, emotional role limitation, and general health domain scores in the TDT group, but not in the controls. This work strongly suggests that olfactory dysfunction is an element of TDT and that such dysfunction may contribute to the overall quality of life of TDT patients.

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Compliance with ethical standards

Ethical approval Institutional Review Board (Istanbul University Istanbul Medical Faculty Clinical Research Ethic Committee) approval was obtained for this study (No. 2016/807).

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Conflict of interest Yasin Yilmaz, Zeynep Karakas, Büsra Uzun, Cömert Sen, Senol Comoglu, Selime Aydogdu, Ayse Ozkan Karagenc, Deniz Tugcu, Serap Karaman, Kadir Serkan Orhan, and Crystal Wylie declare that they have no conflict of interest. Richard L. Doty is the President of Sensonics International, the manufacturer and distributor of the olfactory threshold test system employed in this study.

Informed consent Informed consent was obtained from all patients for being included in the study.

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