Olfactory dysfunction in β-thalassemia major patients treated with iron-chelating agents

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Abstract

Ocular and ophthalmologic adverse effects may occur in patients with β-thalassemia major (BTM) treated regularly with blood transfusions and iron-chelating agents. We hypothesized that olfactory dysfunction may be present in this patient population. We aimed to investigate olfactory dysfunction in patients with BTM and to determine etiologic factors. A total of 43 patients with BTM were included in the study. Forty-three subjects without nasal complaints, history of facial trauma, or nasal surgery were included as the controls. All participants had nasal endoscopy. The use of iron-chelating agents by patients with BTM and their duration of use were recorded, as well as hemoglobin and ferritin levels. The Sniffin' Sticks test (SST) was used to assess olfactory function, comparing results between the BTM and control groups. The correlations of SST scores with the other study parameters were analyzed. Eight (18.6%) of 43 patients in the BTM group and none of the subjects in the control group had hyposmia ($p < 0.001$). Older age, low hemoglobin level, and longer use of deferoxamine were found to be correlated with olfactory dysfunction. Olfactory dysfunction can occur in patients with BTM treated with iron-chelating agents. The results suggest that screening for olfactory function should be part of the routine follow-up of patients with BTM.

Introduction

β-thalassemia major (BTM) is a congenital disease that starts in childhood and causes hypochromic-microcytic anemia. It develops as a result of defective synthesis of fibrinogen β-chain needed for formation of hemoglobin and specific mutations in the β-globin gene.[1] Regular blood transfusions are standard in patients with BTM, starting from childhood, to improve quality of life and to increase survival.[2] Regular blood transfusions, however, result in iron deposition (secondary chromatosis), which causes organ dysfunction such as hepatic fibrosis and cirrhosis, hyperpigmentation of skin, diabetes mellitus, hypogonadism, pulmonary dysfunction, and cardiac disorders.[3]

Iron-chelating agents are used to decrease the rate and severity of complications related to transfusion-induced hemochromatosis in patients with BTM. The first chelating agent used for this purpose was deferoxamine, which was introduced in 1962.[4] Life expectancy of patients with BTM increased from 20 years to approximately 50 years after the introduction of chelating agents. The adverse effects of deferoxamine were first described in the 1980s.[4] Its reported systemic adverse effects are flushing at the site of injection, urticaria, hypotension, reversible nephrotoxicity, hearing loss, and optic neuropathy.[5]

Deferasirox and deferiprone are new oral iron-chelating agents. Deferasirox was approved by the U.S. Food and Drug Administration (FDA) in 2005, and its use has increased in recent years. Its most frequent adverse effect is temporary mild or moderate gastrointestinal dysfunction; however, hearing loss has also been reported.[6] Deferiprone was approved by FDA in 2011. It may rarely cause severe adverse effects such as neutropenia and agranulocytosis, and therefore it is not used widely.[6]

Olfactory dysfunction has not been studied previously in patients with BTM who are treated regularly with iron-chelating agents. Olfactory dysfunction may lead to poor quality of life, inability to recognize smells of dangerous gases, and depression.[7] The Sniffin' Sticks Test (SST) is one of the most popular tests used to identify olfactory dysfunction.

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In this study, we aimed to investigate olfactory dysfunction in patients with BTM who were administered iron-chelating agents and to analyze the correlation between olfactory dysfunction and patients' characteristics and medications used.

Patients and methods

Patients. A total of 43 patients with a diagnosis of BTM who were followed in the Thalassemia Follow-up Center of Muğla Sıtkı Koçman University Medical Faculty were included in our study. Age, sex, complaints, comorbidities, and previous surgeries were recorded. Mean hemoglobin level in the previous 2 months and mean ferritin level in the previous 4 months were also recorded. The use of iron-chelating agents, the specific agents used, and their durations of use were recorded.

Deferoxamine was administered at 30 to 50 mg/kg/day subcutaneously, deferiprone at 75 to 100 mg/kg/day orally, and deferasirox at 20 to 40 mg/kg/day orally.

A total of 43 subjects who had no olfactory complaints; no complaints of nasal obstruction, chronic rhinitis, or rhinosinusitis; and no previous nasal surgery were included as controls.

Nasal examination and exclusion criteria. All patients and controls had endoscopic examination of the nose and nasopharynx. They were examined for findings suggestive of mucosal disease such as allergic rhinitis, nasal septal deviation causing severe nasal obstruction, nasal polyps, nasal masses, acute upper airway infection, and rhinosinusitis. They were excluded if any of the aforementioned disorders were detected on nasal endoscopy. People with a history of facial trauma or nasal surgery, neurologic disease, hypothyroidism, diabetes mellitus, chronic rhinosinusitis, nasal polyps, and/or smoking also were excluded.

Olfactory assessment. Olfactory function was analyzed using the three stages of the Sniffin' Sticks test (SST) (Burghart Messtechnik GmbH; Wedel, Germany), which is based on a pen-like odor-dispensing device.[8] Subjects were asked not to eat or drink anything except for water for 15 minutes before testing, and similarly were asked to refrain from smoking and chewing gum. The smell test room was silent and well ventilated. The test sequence was the threshold test followed by the discrimination test and, finally, the identification test, with 3-minute breaks between the tests.

In the odor threshold (OT) test (stage 1), OT was assessed using n-butanol as a single odorant. The smell threshold was determined in a so-called "staircase procedure." After determining the minimum concentration of odor (n-butanol) that could be perceived, the dilution step was identified as the concentration at which the odor could be distinguished from nonsmelling pens. The OTs were determined to be the mean of the last four from a total of seven staircase reversals.

In the odor discrimination (OD) test (stage 2), discrimination between two different odorants was assessed. The subject was presented with three pens; two contained the same odorant and one contained a different odorant. The subject's task was to discern the one that smelled different. This comparison was performed for 16 triplets. Presentation of triplets was separated by at least 30 seconds. The result was a sum score of correctly identified pens.

In the odor identification (OI) test (stage 3), the ability to identify everyday smells by means of a card with four choices was determined. The patient had to pick one of the four choices. A total of 16 odors were presented in the OI Test. Subjects were free to sample the odors as often as necessary to decide. The experimenter presented each odorant in intervals of at least 30 seconds to minimize olfactory desensitization. OI score was the sum score of the correctly identified odors.

The maximum score in each stage was 16 points, with a maximum possible total score of 48 points for the stages of threshold, discrimination, and identification combined (TDI). Subjects with a TDI score >30 were considered to have normal olfactory function (normosmia), subjects with a score of 15 to 30 were considered to have decreased olfactory function (hyposmia), and those with a score <15 were considered to have a loss of olfactory function (anosmia).[9]

OT, OD, OI, and TDI scores of the patients and controls were recorded.

Statistical analysis. Demographic characteristics and SST results including OT, OI, OD, and TDI scores were compared between the BTM and control groups. The ratios of hyposmic patients were also compared between the groups. In the study group, OT, OI, OD, and TDI scores were analyzed for correlations with age, sex, hemoglobin level, ferritin level, duration of deferoxamine use, and total use of the three iron-chelating agents.

Data analysis was made using the Statistical Package for the Social Sciences (SPSS), version 21 (SPSS, Inc.; Chicago). Means and standard deviations were used to describe continuous variables. The Student *t* test was used for continuous variables. The Mann-Whitney *U* test was used to compare the SST results between the study and the control groups. Correlations were analyzed using the Pearson's correlation test. *P* value for significance was set at <0.05.

Results

Demographic data and iron-chelating agents. Among 43 patients with BTM, 25 (58.1%) were males and 18 (41.9%) were females; the mean age was 24.76 ± 8.24 years. There were 21 (48.8%) males and 22 (51.2%) females in the control group, for a total of 43 subjects,

who had a mean age of 27.41 ± 8.94 years. BTM and control groups were similar for age and sex ($p = 0.157$ and $p = 0.393$, respectively). Demographic characteristics and mean hemoglobin and ferritin levels of the patients with BTM are presented in the table.

The mean duration of deferoxamine use was 14.81 ± 7.02 years in the BTM group. The mean total duration of the three iron-chelating agents used was 23.68 ± 8.79 years.

Results of SST. *OT test (stage 1).* The mean OT score was 6.99 ± 2.14 (range: 1.5 to 11.25) in the BTM and 7.41 ± 1.75 (range: 3.25 to 11.75) in the control group. OT scores were not significantly different between BTM and control groups ($p = 0.328$).

OD test (stage 2). The mean OD scores were 12.95 ± 2.35 (range: 3 to 16) in the BTM group and 14.13 ± 1.40 (range: 11 to 16) in the control group. OD score was significantly lower in the BTM group compared with the control group ($p = 0.015$).

OI test (stage 3). The mean OI score was 13.23 ± 1.91 (range: 7 to 16) in the BTM group compared with 13.86 ± 1.39 (range: 11 to 16) in the control group. BTM and control groups were similar for OI scores ($p = 0.157$).

TDI score. TDI score was obtained by summing up the scores obtained in stages 1, 2, and 3. The mean TDI score was 33.19 ± 4.89 (range: 15 to 42.25) in the BTM group and 35.44 ± 2.39 (range: 31 to 41.5) in the control groups. TDI scores were significantly lower in the BTM group compared with the controls ($p = 0.012$).

Participants with hyposmia. In accordance with the normative values determined for SST, the ones with TDI scores between 15 and 30 were diagnosed with hyposmia. Eight patients (18.6%) in the BTM group and none in the control group had hyposmia. Comparison of the BTM and the control groups for the proportion of patients with hyposmia revealed that hyposmia was significantly more frequent in patients with BTM compared with controls ($p < 0.001$). None of the participants in the BTM or control groups had anosmia (TDI score <15).

The results indicated that olfactory dysfunction was significantly more common in patients with BTM who were administered iron-chelating agents compared with the control group.

Correlation of smell test results with age, hemoglobin and ferritin levels, sex, and use of iron-chelating agents. *Age.* A significant and negative correlation was observed between age and OT, OD, OI, and TDI ($p = 0.016$, $p = 0.019$, $p = 0.022$, and $p = 0.001$, respectively). The scores of the smell tests decreased as the age of the patient increased.

Hemoglobin level. Hemoglobin level was significantly correlated with OD, OI, and TDI scores ($p < 0.001$, $p = 0.001$, and $p < 0.001$, respectively). Smell test scores decreased as the hemoglobin level decreased. There was no correlation between hemoglobin level and OT ($p = 0.078$).

Ferritin level. Ferritin level was not correlated with OT, OD, OI or TDI scores ($p = 0.815$, $p = 0.510$, $p = 0.121$, and $p = 0.425$, respectively).

Sex. Sex was not correlated with OT, OD, OI, or TDI scores ($p = 0.058$, $p = 0.983$, $p = 0.976$, and $p = 0.435$, respectively).

Duration of deferoxamine use. Duration of deferoxamine use had significant negative correlations with OI and TDI scores ($p = 0.014$ and $p = 0.021$, respectively). OI and TDI scores decreased as duration of deferoxamine use increased. There were no correlations between duration of deferoxamine use and OT or OD scores ($p = 0.083$ and $p = 0.280$, respectively).

No significant correlations were observed between total duration of use of the three iron-chelating agents (deferoxamine, deferasirox, and deferiprone) and OT, OD, OI, or TDI scores ($p = 0.090$, $p = 0.290$, $p = 0.210$, and $p = 0.072$, respectively).

Table. Demographic characteristics and mean hemoglobin and ferritin levels of patients with β-thalassemia major (N = 43)

	Mean	Minimum	Maximum	Standard deviation
Age (yr)	24.76	14	50	8.24
Hemoglobin (g/dl)	9.10	6.62	9.93	0.55
Ferritin (ng/ml)	1510.5	201.56	5,619.43	1,171.99
Duration of deferoxamine use (yr)	14.81	0	30	7.02

Discussion

The results of this study indicate that hyposmia was more frequent in patients with BTM who were administered iron-chelating agents regularly compared with a control group. Older age, low hemoglobin level, and long-term use of deferoxamine negatively affected olfactory functions in patients with BTM.

BTM is a life-threatening, autosomal recessive disease, and regular blood transfusions and iron-chelating agents form the mainstay of treatment.[10] The prevalence of thalassemia is high in the Mediterranean region.[11] Its prevalence is high in Turkey and in Muğla, located at the Mediterranean coast.[11] Regular blood transfusions and use of iron-chelating agents increases the life expectancy of patients with BTM; however, long survival increases the prevalence of complications of the disease in the organs.[10]

Deferoxamine is one of the first and most effective iron-chelating agents used in pa-

tients who undergo regular blood transfusions.[4] It has been used since the 1960s. Deferoxamine does not have an oral form; it is administered by subcutaneous injection. Deferiprone and deferasirox may be taken orally.

Deferoxamine has been considered as a minimally toxic agent with mild to moderate adverse effects.[5] The adverse effects related to deferoxamine treatment are ophthalmic and auditory neurotoxicity, sensorimotor neuropathy, renal toxicity, pulmonary syndrome, growth retardation and bone abnormalities, local irritation at the subcutaneous injection site, and allergic reactions.[3]

Ophthalmic and auditory adverse effects with deferoxamine have been studied extensively. Reduced peripheral vision, abnormal color vision, deteriorated dark adaptation, thinning of the retinal vessels, decreased visual acuity, and retinal stippling have been reported as adverse effects.[3,12,13]

Auditory toxic effects of deferoxamine emerge as high- frequency sensorineural hearing loss.[4] Chen et al demonstrated a ≥25-dB high-frequency sensorineural hearing loss in 20% of 30 patients treated with deferoxamine.[4] Shamsian et al found sensorineural hearing loss at 2,000 to 4,000 Hz in 7.4% of 67 patients.[2] Karimi et al studied the auditory adverse effects of deferoxamine and reported that deferoxamine ototoxicity was determined not only by the total amount of the drug given but also by its maximal plasma concentration; they suggested periodic audiologic check-ups for prompt diagnosis of audiologic complications and a low dosage of deferoxamine (<50 mg/kg/day) given on at least 5 days per week for prevention of such complications.[3]

The pathophysiology of the neurotoxic effects of deferoxamine is not yet clear. Davies et al suggest that deferoxamine reacts with superoxide free radicals to form more stable nitroxide free radicals, and that those react with methionine, cysteine, glutathione, vitamin C, and alcohol dehydrogenase to decrease enzymatic activity.[14] The neurotoxic effects of deferoxamine might cause olfactory dysfunction.

To the best of our knowledge, our study is the first to investigate olfactory function in patients with BTM who are on regular treatment with iron-chelating agents and to compare the results with a control group.

Olfactory dysfunction is not rare. It is evident in 1 to 2% of the population younger than 65 years, and its prevalence may be as high as 50% in those 65 years and older.[15] Approximately 20 easy-to-use and commercially available olfactory tests have been described in recent years.[15] SST is one the most frequently used. Test-retest reliability and validation studies of SST have been performed, and it has been used in more than 50 clinics worldwide.[16]

The most frequent causes of olfactory dysfunction are chronic rhinosinusitis, postinfectious anosmia, and post-traumatic anosmia.[7] Neurologic diseases (i.e., Alzheimer disease), nasal and intracranial tumors, Cushing disease, exposure to toxic substances such as some metals and solvents, and use of some antimicrobial, chemotherapeutic, and antithyroid agents may result in olfactory dysfunction. No studies to date have reported olfactory dysfunction related to BTM or use of iron-chelating agents.

In the present study, we found hyposmia in 18.6% of the BTM group treated with iron-chelating agents, and this rate was found to be significantly higher than in the control group. The pathophysiology of neurotoxic side effects such as high-frequency sensorineural hearing loss and retinal neurotoxicity is not yet clear in patients with BTM who are taking iron-chelating agents. However, olfactory dysfunction may share the same pathophysiologic mechanism.

Several studies have been performed to identify factors related to hearing loss and retinal adverse effects. Those studies found no correlation between ferritin level and neurotoxicity.[2-4,10,16] In our study, we also found no correlation between ferritin level and olfactory dysfunction. Karimi et al reported no correlation between the neurotoxic effects of deferoxamine and mean hemoglobin concentration over the previous 3 months.[3] In our study, however, low mean hemoglobin levels in the previous 2 months showed correlation with olfactory dysfunction.

Chen et al reported that deferoxamine could be used safely at doses <50 mg/kg.[4] In our study, we could not perform a correlation analysis since different deferoxamine doses were administered in accordance with ferritin levels. Shamsian et al reported that the total duration of deferoxamine use was not correlated with adverse effects.[2] In contrast, we found that olfactory dysfunction increased as the duration of deferoxamine use increased.

Aging has been reported to increase olfactory dysfunction, but sex has had no effect on it.[16] As in previous studies, we found no correlation between sex and olfactory dysfunction. We did, however, find a correlation between older age and olfactory dysfunction. In patients with BTM, aging coincides with an increased duration of deferoxamine use; therefore, we suppose that both conditions cause olfactory dysfunction in these patients. The correlation study we performed indicated that older age, longer use of deferoxamine, and low hemoglobin levels were correlated with olfactory dysfunction.

Deferasirox and deferiprone are the other iron-chelating agents used in the treatment of BTM. These two agents are preferred in some patients since they have oral forms.[17,18] Ocular and auditory side effects of deferasirox and deferiprone are rare.[6,19] Some patients included in our study took deferasirox and deferiprone because of intolerance to subcutaneous injections. Some patients used one or both for different periods and for a short time, so we could not perform statistical analysis for deferasirox and deferiprone.

We calculated the duration of deferoxamine use and total duration of use for all three agents and analyzed their correlations with other variables. We found a correlation between duration of deferoxamine use and olfactory dysfunction, but no correlation between the total duration of use for all three agents and olfactory dysfunction. We suppose that the lack of correlation between olfactory dysfunction and duration of use of all three drugs may be related to minimal neurotoxic effects of the agents other than deferoxamine.

Studies on olfactory function have investigated subscores of SST, namely OT, OD, and OI, in addition to TDI.[20-22] Fu et al reported that OT was correlated with age.[20] It was reported that all subscores were affected in patients with idiopathic inflammatory myopathy, but OT and OD were affected in patients with systemic lupus erythematosus.[21,22] In our study, we found correlations of age with all SST subscores. Among the subscores, however, we found that only OD was smaller in the BTM group compared with the control group.

Study limitations

Our sample size is relatively small; therefore, further studies should be performed in a larger patient population. Another limitation is that all patients with BTM used iron-chelating agents. A third limitation is that we could not compare the patients who used deferiprone and deferasirox with the ones that used deferoxamine. Further studies on a larger sample size may enable comparison of olfactory dysfunction according to use of each of the three iron-chelating agents.

Conclusion

We found a significantly higher rate of hyposmia in patients with BTM who were treated with iron-chelating agents. TDI score and OD score were significantly smaller in the BTM group compared with the control group. Olfactory dysfunction was significantly correlated with age, low hemoglobin levels, and duration of deferoxamine use. Clinicians must keep in mind that olfactory dysfunction may be present in patients with BTM. Routine follow-up of patients with BTM to assess olfactory function may be warranted if further studies support our findings.

References

1. Cunningham MJ, Sankaran VJ, Nathan DG, Orkin SH. The thalassemias. In: Orkin SH, Nathan DG, Ginsburg D, et al (eds). Nathan and Oski's Hematology of Infancy and Childhood. 7th ed. Philadelphia: Saunder/Elsevier; 2009:1015-108.
2. Shamsian BS, Aminasnafi A, Moghadassian H, et al. Sensory neural hearing loss in beta-thalassemia major patients treated with deferoxamine. Pediatr Hematol Oncol 2008;25(6):502-8.
3. Karimi M, Asadi-Pooya AA, Khademi B, et al. Evaluation of the incidence of sensorineural hearing loss in beta-thalassemia major patients under regular chelation therapy with desferrioxamine. Acta Haematol 2002;108(2):79-83.
4. Chen SH, Liang DC, Lin HC, et al. Auditory and visual toxicity during deferoxamine therapy in transfusion-dependent patients. J Pediatr Hematol Oncol 2005;27(12):651-3.
5. Pinna A, Corda L, Carta F. Rapid recovery with oral zinc sulphate in deferoxamine-induced presumed optic neuropathy and hearing loss. J Neuroophthalmol 2001;21(1):32-3.
6. Chaudhary P, Pullarkat V. Deferasirox: Appraisal of safety and efficacy in long-term therapy. J Blood Med 2013;4:101-10.
7. Huart C, Eloy P, Rombaux P. Olfaction. In: Onerci TM (ed). *Nasal Physiology and Pathophysiology of Nasal Disorders*. 1st ed. Berlin: Springer-Verlag; 2013:113-8.
8. Hummel T, Sekinger B, Wolf SR, et al. "Sniffin' sticks": Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses 1997;22(1):39–52.
9. Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: An upgrade based on a group of more than 3,000 subjects. Eur Arch Otorhinolaryngol 2007;264(3):237–43.
10. Ambrosetti U, Dondè E, Piatti G, Cappellini MD. Audiological evaluation in adult beta-thalassemia major patients under regular chelation treatment. Pharmacol Res 2000;42(5):485-7.
11. Topal Y, Topal H, Ceyhan MN, et al. The prevalence of hemoglobinopathies in young adolescents in the province of Muğla in Turkey: Results of a screening program. Hemoglobin 2015; 39(4):247-50.
12. Cohen A, Martin M, Mizanin J, et al. Vision and hearing during deferoxamine therapy. J Pediatr 1990;117(2 Pt 1):326-30.
13. Mehta AM, Engstrom RE Jr, Kreiger AE. Deferoxamine-associated retinopathy after subcutaneous injection. Am J Ophthalmol 1994;118(2):260-2.
14. Davies MJ, Donkor R, Dunster CA, et al. Desferrioxamine (Desferal) and superoxide free radicals. Formation of an enzyme-damaging nitroxide. Biochem J 1987;246(3):725-9.
15. Doty RL. Assessment of olfaction. In: Brewer W, Castle D, Pantelis C (eds). *Olfaction and the Brain*. 1st ed. New York: Cambridge University Press; 2006:235-58.
16. Kobal G, Klimek L, Wolfensberger M, et al. Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. Eur Arch Otorhinolaryngol 2000;257(4):205-11.
17. Ejaz MS, Baloch S, Arif F. Efficacy and adverse effects of oral chelating therapy (deferasirox) in multi-transfused Pakistani children with β-thalassemia major. Pak J Med Sci 2015;31(3):621-5.
18. Yadav M, Yadav J, Sood SS, et al. Effect of iron chelating agents desferrioxamine, deferiprone and their combination on brainstem auditory evoked potential (BAEP). JK Practitioner 2012;17(4):29-34.
19. Meerpohl JJ, Schell LK, Rücker G, et al. Deferasirox for managing iron overload in people with myelodysplastic syndrome. Cochrane Database Syst Rev 2014;10:CD007461.
20. Fu D, Pinto JM, Wang L, et al. The effect of nasal structure on olfactory function in patients with OSA. Eur Arch Otorhinolaryngol 2015;272(2):357-62.
21. Iaccarino L, Shoenfeld N, Rampudda M, et al. The olfactory function is impaired in patients with idiopathic inflammatory myopathies. Immunol Res 2014;60(2-3):247-52.
22. Shoenfeld N, Agmon-Levin N, Flitman-Katzevman I, et al. The sense of smell in systemic lupus erythematosus. Arthritis Rheum 2009;60(5):1484–7.