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# Olfactory function and olfactory bulb volume in Wilson's disease

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## Abstract

**Purpose** To evaluate the olfactory function and the olfactory bulb (OB) volume changes in Wilson's Disease (WD) patients.
**Methods** A prospective, controlled, single-blinded study was planned. 12 patients with WD (Group 1) and 12 healthy subjects (Group 2) were included in the study. Connecticut Chemosensory Clinical Research Center (CCCRC) test was applied to evaluate olfactory functions. OB volumes were measured with a 1.5 T General Electric Signa Excite MRI scanner.
**Results** There was a significant difference between the CCCRC scores of the two groups ($p < 0.05$). The difference of the OB volumes of the two groups was insignificant ($p > 0.05$).
**Conclusions** WD patients are likely to experience olfactory dysfunction, so its assessment may be a useful tool to the follow-up care of these patients, although further studies are needed to evaluate correlations in WD evolution.

**Keywords** Wilson's disease · Olfactory dysfunction · Olfactory bulb · Olfaction

## Introduction

Wilson's disease (WD) is a rare autosomal recessive disorder characterized by excessive copper deposition in the body, mainly in the liver and the brain [1]. The diagnosis is usually based on the clinical and laboratory findings, including Kayser–Fleischer rings, neurological symptoms, low serum ceruloplasmin, increased urine and hepatic copper level [2]. There are many reports on sensory deficits in primary neurodegenerative disorders. Recent studies suggests that the olfactory deficit in Parkinson Disease is progressive and could correlate with other clinical markers [3]. This study was conducted to evaluate the olfactory function and the olfactory bulb (OB) volume changes in WD patients.

## Materials and methods

### Study design

A prospective, controlled, single-blinded study was planned.

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## Patient characteristics

A total of 12 patients with Wilson's disease (Group 1) and 12 healthy subjects (Group 2) with similar demographical characteristics were recruited in the study. Any patient with a condition that could cause olfactory dysfunction, such as septum deviation, nasal polyposis, congenital olfactory dysfunction, head trauma, chronic rhinosinusitis, allergic rhinitis, or neurological disorders other than WD were excluded from the study. Permission for the study was obtained from Bezmialem Vakif University Clinical Research Ethics Committee following the National Health and Medical Research guidelines and in accordance with the Declaration of Helsinki.

## Neurological examination

All patients were diagnosed as WD with neurological symptoms. Time since manifestation of the neurological disease ranged from 8 to 27 years (mean, 17.1 years). Five of the patients had resting and postural tremor and bradykinesia, another five of the patients had dystonia, one of them had ataxia and resting tremor and the last one had ataxia and bradykinesia as symptoms.

## Evaluation of olfactory function

The Connecticut Chemosensory Clinical Research Center (CCCRC) test was conducted as described previously [4, 5]. The CCCRC test is composed of *n*-butanol odor threshold test and odor identification test. Olfactory tests were scored out of 7 (0: worst, 7: best olfaction) and mean score was calculated as the total CCCRC test score. Test scores were categorized as anosmic, severely hyposmic, moderately hyposmic, mildly hyposmic or normosmic [4].

## Evaluation of olfactory bulb volume

OB volumes were measured with a 1.5 T General Electric Signa Excite MRI scanner. Each consecutive cross-section was taken with 2-mm slice thickness (gap = 0) and eight-channel head coil was used. Coronal, axial and sagittal slices were manually segmented and measured by an experienced radiologist (DG) on T2W TSE cross-sections for three-dimensional evaluation of OB volume(Figs. 1, 2). Measurements were done individually on the right and left olfactory bulbs in a single-blinded method, and the mean OB volume was calculated in cubic millimeters.

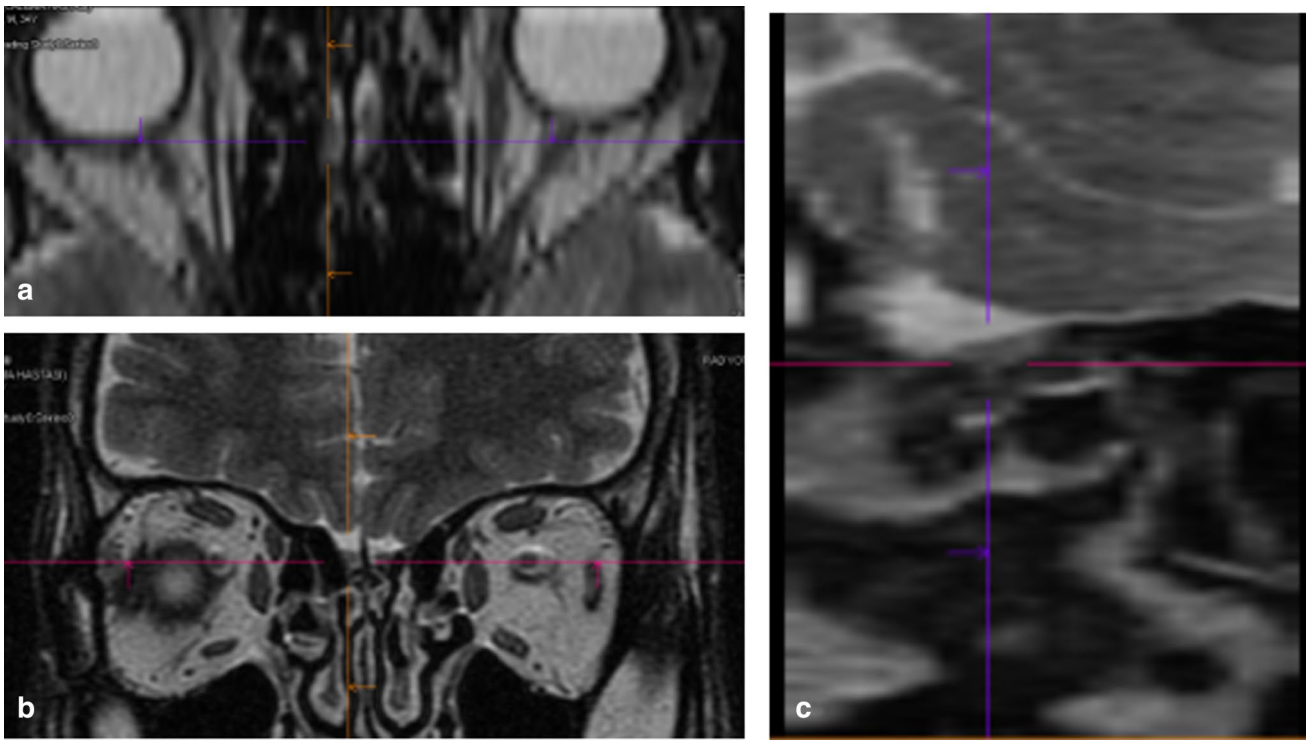


**Fig. 1** Cross-sectional images; axial (**a**), coronal (**b**), sagittal (**c**) views showing volume measurement of right olfactory bulb of a patient with Wilson's disease

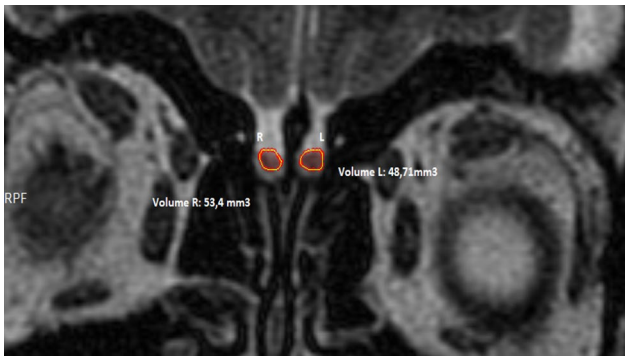


**Fig. 2** Coronal T2-weighted magnetic resonance imaging of a patient with Wilson's disease showing right and left olfactory bulb volumes

### Statistical analysis

Descriptive statistics were presented as mean and standard deviation. Mann–Whitney *U* Test was used to compare the two groups. Statistical analyses were conducted with the IBM SSPS 22.0 program. Significance level was set at 0.05 for all tests.

## Results

The mean age of the Group 1 was 30.9 ± 4.1 years; five were women and seven were men. Mean age of the Group 2 was 34.8 ± 5.5 years; seven were women and five were men. There was no statistical significance in terms of age between the two groups ($p < 0.05$).

The mean CCCRC score was 5.9 for the Group 1, whereas the CCCRC score of Group 2 was 6.3 and there was a significant difference between the two groups ($p < 0.05$). Detailed *n*-butanol odor threshold and odor identification scores were presented in Table 1. According to the CCCRC scores, ten patients were classified as normal, two as mildly hyposmic in Group 1. Group 2 consisted of 11/12 normosmic patients; only one patient was mildly hyposmic.

The mean of right and left OB volume in the Group 1 was 57.5 (range, 22.2–100.3) $mm^3$. The mean of right and left OB volume in the Group 2 was 58.6 (range, 39–88.5) $mm^3$ (Table 1). The difference between the two groups was insignificant ($p > 0.05$) (Fig. 3).

## Discussion

Olfactory dysfunction, can occured because of conductive or sensorineural problems [6]. Conductive dysfunction can be the result of nasal pathologies. The participants in our study underwent a detailed nasal examination and conductive etiology was discarded. Sensorineural olfactory dysfunction is due to defects in the olfactory nerve fibers, receptors, olfactory bulb and orbitofrontal cortex [6]. Olfactory sensory neurons extend their axons solely to the olfactory bulb. OB is the most important link connecting the peripheral and cortical structures, and it reflects afferent neural activity of the olfactory system, which preserves its plasticity [7]. In healthy subjects, OB volume was found to correlate to the measured olfactory function and to vary as a function of age [8].

It is suggested that impaired olfaction in old age is a result of the accumulation of neurofibrillar pathology in central olfactory system. The level of neurofibrillar pathology in central olfactory regions is moderately correlated with levels

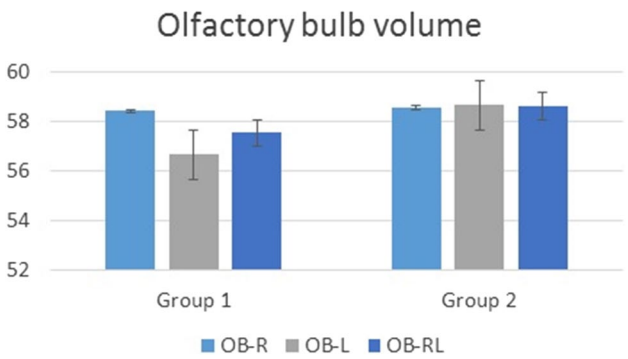


**Fig. 3** Mean olfactory bulb volume measurements of the two groups (*OB-R* Right olfactory bulb, *OB-L* Left olfactory bulb, *OB-RL* Right and left olfactory bulb)

**Table 1** Olfactory bulb volume measurements and olfactory function tests' results

| | *n* | OB-R volume ($mm^3$) | OB-L volume ($mm^3$) | OB-RL volume ($mm^3$) | CCCRC total score | *N*-butanol odor threshold score | Odor identification score |
|---|---|---|---|---|---|---|---|
| Group 1 | 12 | 58.4 ± 29.7 | 56.6 ± 21.9 | 57.5 ± 24.4 | 5.9 ± 0.2* | 5.8 ± 0.5 | 6.08 ± 0.6 |
| Group 2 | 12 | 58.5 ± 15.2 | 58.6 ± 13.1 | 58.6 ± 13.7 | 6.3 ± 0.3 | 6.2 ± 0.3 | 6.58 ± 0.6 |

Olfactory evaluation (0: worst, 7: best olfaction), Olfactory volume measured in $mm^3$

*OB-R* Right olfactory bulb, *OB-L* Left olfactory bulb, *OB-RL* Right and left olfactory bulbs

*Statistically significant difference ($p < 0.05$)

of neurofibrillar pathology elsewhere in the brain [9]. In WD, it is suggested that the degeneration in the basal ganglia and neuronal loss in association with an increase of the copper content in this brain region play a role in olfactory deficit [2].

It was shown that WD patients with neurological symptoms had a significant olfactory dysfunction compared to hepatic-type patients [2]. Results from the present study revealed that WD patients had olfactory dysfunction compared to the healthy subjects. It was also found that WD patients' olfactory function did not correlate significantly with the presence of MRI-visible lesions in the basal ganglia or with any regional glucose metabolism as measured by [18]FFDG-PET [2]. The present study compared the OB volumes of the WD patients and the healthy subjects and the difference was insignificant.

The other possible cause of olfactory dysfunction in WD patients is the side effect of the medical treatment. But it was shown that there was no significant effect of different medical treatment protocols (D-penicillamine, trientine/zinc combination, zinc only) on olfactory function. There were no differences between the three types of treatment in terms of olfactory function [2].

## Conclusion

In this study we observed that WD patients are likely to experience olfactory dysfunction, so its assessment may be a useful tool for the follow-up care of these patients, although further studies are needed to evaluate correlations in WD evolution.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical standards** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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