RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 2, pages: 212–218
DOI: 10.5603/PJNNS.a2023.0020

ISSN: 0028-3843, e-ISSN: 1897-4260

Olfactory dysfunction in patients with Wilson's Disease

Agnieszka Piechal[1, 2], Jan Bembenek[3], Anna Baranowska[1], Tomasz Litwin[1], Dagmara Mirowska-Guzel[2], Anna Członkowska[1]

[1]Second Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland
[2]Department of Experimental and Clinical Pharmacology, Centre for Preclinical Research and Technology, Medical University of Warsaw, Warsaw, Poland
[3]Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, Warsaw, Poland

ABSTRACT

Introduction. Many neurodegenerative disorders are associated with olfactory dysfunction (OD), but little is known about OD in Wilson's Disease (WD). We evaluated olfactory function in patients with WD.

Material and methods. OD was examined in 68 patients with WD and 70 sex- and age-matched healthy controls using subjective testing with 'Sniffin Sticks'. Threshold discrimination identification (TDI) score and its three components (odour detection threshold, discrimination, and identification) were assessed.

Results. Compared to controls, patients with WD had a significantly weaker sense of smell in terms of TDI ($p < 0.01$), odour discrimination ($p < 0.01$), and identification ($p < 0.01$), but not in terms of odour detection threshold ($p = 0.27$). Patients with predominantly neurological symptoms were characterised by greater OD by TDI ($p < 0.01$), odour detection threshold ($p = 0.01$), and discrimination ($p = 0.03$). The presence of pathological lesions ($p = 0.04$) in brain magnetic resonance imaging and generalised brain atrophy ($p = 0.02$) predisposed to worse TDI.

In the WD group, weak inverse correlations between age and TDI score ($r = –0.27$), odour detection threshold ($r = –0.3$), and discrimination ($r = –0.3$) were found. Male gender was a risk factor for abnormal TDI in both WD and controls (both $p = 0.02$).

Conclusions. Patients with WD, particularly older individuals, more frequently had OD than healthy volunteers. Predominantly neurological symptoms, and the presence of typical brain MRI changes, predisposed patients with WD to smell disorders.

Key words: Wilson's Disease, olfactory dysfunction, Sniffin Sticks, olfaction

(*Neurol Neurochir Pol 2023; 57 (2): 212–218*)

Introduction

Olfactory dysfunction (OD) is a frequently observed sensory symptom associated with various neurodegenerative disorders, including Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease and hereditary ataxia [1–4]. Recently, a link between OD and SARS-CoV-2 infection has been described [5]. Olfaction is transmitted by olfactory nerve fibres which pass the cribriform plate to enter the olfactory bulb, then proceed to the olfactory tract and olfactory striae to reach the olfactory cortex (piriform cortex, amygdala and entorhinal cortex). The olfactory cortex has numerous connections with the orbitofrontal cortex, insula, amygdala, and cerebellum, which are organised as an olfactory network [6].

Wilson's Disease (WD) is an autosomal recessive disorder of copper metabolism, caused by mutations in the copper transporting ATPase (ATP7B) that is responsible for excess copper excretion by hepatocytes. WD results in copper accumulation and subsequent clinical symptoms in various organs, but particularly in the liver and brain. Symptoms usually appear between the ages of five and 35. Most frequent is hepatic presentation (50–60% of cases) ranging from elevated

Address for correspondence: Jan Bembenek, Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, 9 Sobieskiego St., 02–957 Warsaw, Poland; e-mail: jbembenek@o2.pl

Received: 12.12.2022 Accepted: 15.02.2023 Early publication date: 20.03.2023

liver enzymes to liver cirrhosis and, rarely, acute liver failure. Neurological symptoms (up to 40% of patients) include movement disorders such as dystonia, tremor, bradykinesia, chorea associated with dysphagia, dysarthria, drooling, and gait and posture disturbances [7–9].

OD is of interest in many diseases, but there is little data regarding OD in WD. As early as the 1990s, patients with WD pointed out a possible olfactory deficit in a patients' newsletter [10]. Some patients, but not others, were unable to perceive certain bad odours. To date, only three studies have evaluated smell impairment [11, 12] or identification [13] in WD. Currently, smell dysfunction evaluation is based on functional assessment of global odour identification.

Identifying specific smells that are less perceived by patients with WD would allow for the development of more specific diagnostic olfactory tests for WD.

The aim of this study was to evaluate the sense of smell in patients with WD and in a comparable control group, including the odour detection threshold and the ability to identify and discriminate odours, and to define which smells are poorly identified by patients with WD.

Material and methods

Participants

Patients with WD plus sex- and age-matched healthy controls were prospectively enrolled in this study before the COVID-19 pandemic. All WD patients were treated at the Second Department of Neurology, Institute of Psychiatry and Neurology in Warsaw, Poland. Key eligibility criteria were: a confirmed diagnosis of WD (Leipzig score of 4 or more points) [14], signed informed consent, and the ability to participate in smell testing. WD patients were classified according to the predominant clinical symptoms (neurological or hepatic form) or the absence of clinical symptoms (asymptomatic or symptomatic) as described previously [15]. Data was also collected on patient demographics, the presence of Kayser-Fleischer rings, treatment type (i.e. d-penicillamine or zinc sulfate) and duration, smoking, and alcohol consumption. All participants were interviewed and physically examined to rule out any conditions that can cause OD, such as nasal polyposis, allergic rhinitis, acute or chronic rhinosinusitis, previous nasal or paranasal surgery, or recent upper airway tract infections. The control group comprised healthy volunteers with no history of neurological or hepatic diseases or smell problems.

Magnetic resonance imaging (MRI)

An MRI examination was performed in sagittal, frontal and transverse sections in spin echo (SE) and fast spin echo (FSE) sequences, with resulting T1-, T2-weighted and Flair images. The obtained MRI results were evaluated for the presence of hypointense or hyperintense focal lesions in T1- and T2-weighted sequences in typical WD structures including: globi pallidi, putamen, caudate nuclei, thalamus, cerebellum, and pons. The presence of atrophy dilation of lateral ventricles, dilation of cerebral sulci, and subarachnoid space) was assessed in the T1-weighted sequence.

Evaluation of olfactory function

Olfactory function assessment was performed using a 'Sniffin Sticks' subjective test (Heinrich Burghart GmbH, Germany) [16, 17], comprising an assessment of odour detection threshold, and the discrimination and identification of odours. The individually evaluated fragrances or odourless substances were placed in spongy buds in tightly closed plastic frames (the so-called 'sticks'). A 3–5-minute interval was maintained between the subsequent parts of the test. Fifteen minutes before the start of the test, the subjects refrained from consuming liquid or solid food, smoking cigarettes, or chewing gum.

Tests were performed as described previously [16]. In brief, the olfactory detection threshold test consisted of the determination of the fragrance threshold for phenylethyl alcohol (PEA) or butanol. Sixteen butanol solutions were used for this test. In each sample, three sticks ('triplets') were presented, one containing n-butanol, and the other two containing solvent. The triplets were presented at intervals of approximately 30 seconds. The results ranged from 1 to 16, where the higher the score, the lower (i.e. better) the olfactory threshold. The discrimination test consisted of distinguishing one stick with a different scent from two sticks with the same scent. Sixteen triplets were used for the test. The result of the test was the sum of all correctly differentiated smells, ranging from 0 to 16. The odour identification test involved identifying 16 common odours. After presenting the stick, the patient selected a fragrance from a list of four different fragrances. The sticks were presented at 30-second intervals. The test result was the sum of correctly identified smells and ranged from 0 to 16.

The threshold discrimination identification (TDI) score was the sum of the results of the odour detection threshold, plus the discrimination and identification tests. A TDI total score of 15 or below indicated anosmia, a score of 16–30 indicated hyposmia, and a score above 30 indicated normosmia [17]. The room in which the test was carried out was air-conditioned and quiet; the person tested had their eyes closed or covered for the duration of the test. During the test, the investigator used odourless disposable gloves.

This study was approved by the Bioethical Committee of the Institute of Psychiatry and Neurology, Warsaw, Poland.

Statistical analysis

Calculations were carried out using Statistica v.10 (Stat Soft Inc., Tulsa, OK, USA). Data was presented as numbers with percentages or means with standard deviations (SD).

The preliminary correlation analysis was carried out by examining the significance of differences in mean or median values for individual parameters in the WD group and the healthy volunteer group. For factors measured on continuous

scales and to assess the differences in the impact of the factors, the Wilcoxon rank sum test was applied. For factors measured on nominal scales, the relationship between the variables was tested in the system of contingency tables, using the chi-square test, or Fisher's exact test. Analysis of the correlations between TDI, odour detection threshold and odour discrimination parameters and clinical parameters were performed using the Spearman's rank correlation coefficient. For multiple comparisons, hypothesis testing was performed using the Bonferroni correction (the p-value divided by the total number of pairwise comparisons) to correct for the possibility that in multiple comparisons the null hypothesis would be rejected by chance. $P < 0.05$ was considered to be statistically significant.

Results

In total, 68 patients with WD were enrolled, including 35 women and 33 men. The control group consisted of 70 age- and gender-matched healthy volunteers. The demographics of the evaluated groups are set out in Table 1.

The average age of the WD patients at the time of study recruitment was 29.1 ± 9.4 years, and the age at diagnosis of WD was 27.0 ± 8.9 years. The presence of Kayser-Fleischer rings was confirmed in 46 (68%) patients. None of the patients reported smell problems. However, this was not verified by objective methods.

Neurological examination and MRI

At the time of the olfactory examination, 36 (51.5%) patients had no significant deviations from the normal state in the neurological examination; 32 (47%) had neurological symptoms; and one (1.5%) was asymptomatic. Among neurological forms, rigidity was diagnosed in four (13%) patients, tremor in 15 (48%), rigidity-tremor in seven (22.5%), and dystonic form in five (16%) patients.

MRI was performed on 63 patients. In 27 (42.9%) patients, no focal pathological lesions were found. In 9 (14.3%) patients, lesions were found in only one structure, while 27 (42.9%) patients had pathological lesions in at least two brain structures.

Evaluation of smell in WD patients and healthy volunteers

Statistically significant differences were found between the tested groups, with reduced TDI, discrimination, and identification in WD patients compared to controls (all $p < 0.01$), but there was no significant difference in odour detection threshold (Table 2).

A comparison of correct answers (%) in the identification test between the study groups is set out in Table 3. Significant differences were noted between the groups for the target fragrances of banana, lemon, turpentine, cloves, pineapple, rose, and aniseed, with reduced identification in the WD *vs.* controls in each case. The least frequently identified fragrance in both groups was the smell of apples.

Patients with predominantly neurological symptoms were identified by greater smell disorders in terms of TDI ($p < 0.01$), odour detection threshold ($p = 0.01$), and discrimination ($p = 0.03$) compared to patients with predominantly liver-related symptoms (data not shown).

Table 1. Demographic and clinical characteristics of patient and control groups

	Wilson's Disease (n = 68)	Healthy volunteers (n = 70)	P-value*
Gender, female, n (%)	35 (51.47%)	45 (64.29%)	0.71
Age at study recruitment, mean ± SD (years)	35.1 ± 12.0	34.7 ± 10.6	0.95
Latency between disease onset and smell test, mean ± SD (years)	8.1 ± 9.8	–	
Latency between WD diagnosis and smell test, mean ± SD (years)	6.1 ± 9.8	–	
Treatment			
Treatment duration, median (95% CI), years	6.06 (8.38–11.79)	–	
D-penicillamine, n (%)	36 (53%)	–	
Zinc sulfate, n (%)	32 (47%)	–	
Use of tobacco and alcohol			
Smoking, n (%)	17 (25%)	11 (15.71%)	0.17
Alcohol consumption, n (%)	7 (10.61%)	20 (29.85%)	0.01
Clinical symptoms of WD at study recruitment			
Hepatic symptoms, n (%)	35 (51.47%)	–	
Neurological symptoms, n (%)	32 (47.05%)	–	
Asymptomatic, n (%)	1 (1.47%)	–	
Kayser-Fleischer ring, n (%)	46 (68%)	–	

CI — confidence interval; SD — standard deviation; WD — Wilson's Disease
*P-value was calculated using chi-square test for comparisons of number of correct answers between Wilson's Disease patients and healthy volunteers

Table 2. Values of total result of olfactory test (threshold detection identification) and its individual components in study groups (scores)

Parameter (mean ± SD)	Wilson's Disease (n = 68)	Healthy volunteers (n = 70)	P-value*
Threshold detection identification	28.41 ± 4.42	32.91 ± 2.80	0.00
Odour detection threshold	5.80 ± 1.59	6.04 ± 1.61	0.27 (NS)
Odour discrimination	11.23 ± 2.60	13.60 ± 1.34	0.00
Odour identification	11.37 ± 2.13	13.27 ± 1.31	0.00

NS — not significant; SD — standard deviation
After Bonferroni correction, all except odour detection threshold were statistically significant
*P-value was calculated using chi-square test for comparisons of number of correct answers between Wilson's Disease patients and healthy volunteers

Table 3. Comparison of correct answers (%) in identification test in study groups

Target fragrance	Other fragrances "to choose"	Wilson's Disease, n (%)	Healthy volunteers, n (%)	P-value*	P-value* after Bonferroni correction
Orange	Blackberry, strawberry, pineapple	57 (83.8)	62 (88.6)	0.42	NS
Skin	Smoke, glue, grass	39 (57.4)	49 (70.0)	0.12	NS
Cinnamon	Honey, vanilla, chocolate	39 (57.4)	54 (77.1)	0.13	NS
Mint	Chives, fir, onion	65 (95.6)	68 (97.1)	0.62	NS
Banana	Coconut, walnut, cherry	51 (75.0)	67 (95.7)	0.00	0.008
Lemon	Peach, apple, grapefruit	27 (39.7)	40 (57.1)	0.04	NS
Liquorice	Cherry, green mint, cake	53 (77.9)	55 (78.6)	0.15	NS
Turpentine	Mustard, rubber, menthol	27 (39.7)	44 (62.9)	0.01	NS
Garlic	Onions, sauerkraut, carrots	62 (91.2)	69 (98.6)	0.05	NS
Coffee	Paper, wine, smoke	67 (98.5)	68 (97.1)	0.58	NS
Apple	Melon, peach, orange	20 (29.4)	29 (41.4)	0.14	NS
Cloves	Pepper, cinnamon, mustard	54 (79.4)	65 (92.9)	0.02	NS
Pineapple	Pear, plum, peach	40 (58.8)	57 (81.4)	0.04	NS
Rose	Camomile, raspberry, cherry	52 (76.5)	66 (94.3)	0.003	0.048
Aniseed	Rum, honey, fir	46 (67.6)	66 (94.3)	0.00	0.002
Fish	Bread, cheese, ham	67 (98.5)	70 (100)	0.31	NS

*P-value was calculated using chi-square test for comparisons of number of correct answers between Wilson's Disease patients and healthy volunteers

Relation between demographic and clinical data and occurrence of olfactory disorders

In the group of WD patients, there was a weak inversely proportional correlation between the age of the patient and the TDI result ($r = -0.27$), their odour detection threshold ($r = -0.3$), and their odour discrimination ($r = -0.3$) (all $p < 0.05$). This relationship was not observed in the group of healthy volunteers.

Worse results were obtained in men *vs.* women in both groups. Among men *vs.* women with WD, there were statistically significantly worse TDI results ($p = 0.02$), odour detection threshold results ($p = 0.03$), and a trend towards worse odour identification ($p = 0.087$). Similarly, in the group of healthy volunteers, men obtained a statistically significantly lower TDI result ($p = 0.02$), and were less able to identify smells than women ($p = 0.003$).

There was no statistically significant correlation between the presence of Kayser-Fleischer rings and the occurrence of OD in TDI ($p = 0.5$) and its components [olfactory threshold ($p = 0.98$), discrimination ($p = 0.31$), and identification ($p = 0.86$)].

Abnormal brain MRI with the presence of pathological lesions ($p = 0.04$) characteristic for WD, including the globus pallidus ($p = 0.02$) and/or the putamen ($p = 0.048$), and generalised brain atrophy ($p = 0.02$) predisposed to a worse TDI.

There was no effect of the type of treatment (d-penicillamine *vs.* zinc sulfate) on the TDI score ($p = 0.4$) or on the individual components of the olfactory test [olfactory threshold ($p = 0.16$), discrimination ($p = 0.91$), and identification ($p = 0.45$)].

There were no significant differences in the result of the TDI score ($p = 0.39$) and its components [olfactory threshold ($p = 0.82$), discrimination ($p = 0.27$), and identification ($p = 0.21$)] between smokers and non-smokers.

Only seven (10.61%) patients with WD and 20 (29.85%) from the control group declared alcohol consumption. Due to these small numbers, we were unable to reliably assess the influence of alcohol consumption on olfactory parameters.

Discussion

In this relatively large cohort of patients with WD and healthy volunteers, WD was associated with OD, particularly as related to odour discrimination and identification. The exact mechanism of OD in WD is unclear, but it is possible that copper deposits may impair the structural, regulatory, and catalytic functions of the enzymes, receptors, transporters, and other proteins [18]. In WD, there is neuronal loss and atrophy in the thalamus and lenticular nucleus (structures involved in odour processing), as well as in the other parts of the basal ganglia [19].

Although patients with a neurological presentation of WD typically develop extrapyramidal symptoms [8], other subclinical abnormalities have also been reported in motor-evoked potentials reflecting pyramidal tracts damage [20], somatosensory, auditory and visually-evoked potentials [21], visual pathways [22] and blink reflex [23]. Our study supports other reports which have suggested that, additionally, olfactory tracts may be affected in WD patients [11–13].

Our results are consistent with the findings of Mueller et al., who observed a significant decrease in olfactory function in 24 WD patients compared to a control group in a study using Sniffin Sticks [11]. Similarly, a study by Chen et al., using a simplified Chinese version of the University of Pennsylvania Smell Identification Test, demonstrated that patients with WD had lower smell identification skills compared to a control group [12]. Obtained average values of the odour discrimination and identification test in the studied control group were comparable to the standards adopted for many European and Asian countries [17, 24, 25].

Comparing the ability to identify smells by WD patients and healthy volunteers in the studied group, the most visible deficiencies in the WD group concerned the identification of aniseed, banana, pineapple, rose, turpentine, lemon, and cloves. These results are partly consistent with those presented in an abstract by Carvalho et al. [13]. When assessing the identification of smells using Sniffin Sticks in 64 patients with WD and 60 people from a control group, they found the most significant differences between the groups concerned the identification of mint, banana, lemon, aniseed, and fish [13].

However, in our study, the smells of fish, coffee and mint were equally well identified by both groups. In our work, the least frequently identified fragrance in both the group of patients and the healthy control group was apples, which is consistent with reports from Turkish [26], German [1], and Belgian populations [27].

In our study, patients with dominant neurological symptoms scored much worse in TDI, odour detection threshold and odour discrimination compared to patients with dominant hepatic symptoms. Similar results were published by Mueller et al., where 13 WD patients with neurological symptoms obtained much worse olfactory results compared to 11 patients with WD-induced liver damage only [11]. Similarly to our results, the greatest differences concerned the odour detection threshold and odour discrimination, with no differences found in the ability to identify odours.

In our cohort, the presence of brain MRI changes typical for WD (in globi pallidi, putamen and generalised brain atrophy) resulted in poorer olfactory function in WD patients. This is not consistent with Mueller et al., who did not find significant correlations between OD and the presence of lesions by MRI (n = 24) or abnormalities of glucose metabolism by positron emission tomography (n = 21) [11]. In men with the neurological form, cerebellar atrophy and a trend indicating cerebral atrophy have been found to be more common [28]. However, to date, these differences have not been linked to OD.

Analysing the influence of age on the sense of smell in WD patients, we found a slight inverse proportional correlation with TDI, olfactory threshold score, and discrimination. No such relationship was found in the control group. Structural changes within the olfactory tract must be mentioned when discussing the reasons for age-related olfactory impairment, beginning with changes in the olfactory epithelium along with a decrease in the number of olfactory receptors [29], through the olfactory bulb, and ending with weaker age-dependent olfactory cortex activation [30].

According to most authors, the odour detection threshold increases with age [16, 31], although other authors [32] have recorded comparable odour detection thresholds between young people and healthy elderly people without cognitive impairment. Similarly, it has been found that the ability to discriminate odours is weaker in older people, and particularly so in males [33].

Women may have a better ability overall to identify odours. A meta-analysis by Sorokowski et al. [34] demonstrated that in every analysed aspect of olfactory function, i.e. odour detection threshold, discrimination and identification, women performed better than men. Similarly, in our study, women were less likely to present with OD than men. Additionally, there were more women in the control group, which may explain why smell appeared to be better in the control group. According to the literature review by Doty and Cameron, sex hormones are not the only factors determining the differences in smell sensation between women and men [35]. Other factors affecting smell may include those concerning the impact of the monthly cycle and pregnancy on the sense of smell, and whether the neuroendocrine changes are specific and concern only selected types of smells. Another meta-analysis of 13 studies found that the odour detection threshold is significantly lower in the fertile phase compared to the non-fertile phase of the monthly cycle [36]. However, we did not investigate the effects of the menstrual cycle or the use of contraceptives on the sense of smell.

We did not find a relationship between the tested olfactory parameters and cigarette smoking, either in WD patients or healthy volunteers. Results of studies assessing the impact of cigarette smoking on smell sensation are inconsistent. A meta-analysis of 11 studies showed a higher risk of OD in

current but not former smokers [37]. Çengel Kurnaz et al. [38] demonstrated that olfactory functions were affected by both active and passive smoking. Smoking had the greatest impact on the odour detection threshold, followed by identification and discrimination [38].

Finally, our study was conducted before the COVID-19 pandemic. The prevalence of olfactory deficits worldwide in COVID-19 patients has been estimated to be 22.2% [39]. A similar study to ours, being conducted currently, may have been biased by the effects of COVID-19 on WD patients, or patients who suffered from COVID-19 would have to have been disqualified from participating. This also limits the usefulness of performing routine smell testing in WD patients. Moreover, this would not change the methods of routine diagnosis and treatment in this group of patients.

Limitations of study

The main limitation of our study is that not all patients, and none of the healthy volunteers, had a brain MRI. Hence, we cannot exclude any potential subclinical/preclinical lesions. Moreover, olfactory tracts in the central nervous system involve multiple anatomical structures and functional connectivity, and these complex interrelations and connections make it difficult to define the observed OD to any specific brain structures.

Conclusions

Patients with WD, particularly males and older individuals, often experience OD even if they are unaware of it. Predominant neurological symptoms and the presence of typical brain MRI changes may predispose WD patients to smell disorders.

Conflicts of interest: *None.*
Funding: *None.*

References

1. Boesveldt S, Verbaan D, Knol DL, et al. Odour identification and discrimination in Dutch adults over 45 years. Rhinology. 2008; 46(2): 131–136, indexed in Pubmed: 18575015.
2. Doty RL. Age-Related Deficits in Taste and Smell. Otolaryngol Clin North Am. 2018; 51(4): 815–825, doi: 10.1016/j.otc.2018.03.014, indexed in Pubmed: 30001793.
3. Fernandez-Ruiz J, Díaz R, Hall-Haro C, et al. Olfactory dysfunction in hereditary ataxia and basal ganglia disorders. Neuroreport. 2003; 14(10): 1339–1341, doi: 10.1097/01.wnr.0000077551.91466.d3, indexed in Pubmed: 12876469.
4. Barrios F, Gonzalez L, Favila R, et al. Olfaction and neurodegeneration in HD. NeuroReport. 2007; 18(1): 73–76, doi: 10.1097/wnr.0b013e3280102302.
5. Karamali K, Elliott M, Hopkins C. COVID-19 related olfactory dysfunction. Curr Opin Otolaryngol Head Neck Surg. 2022; 30(1): 19–25, doi: 10.1097/MOO.0000000000000783, indexed in Pubmed: 34889850.
6. Hawkes CH, Doty RL. Smell and taste disorders. Cambridge University Press : 2018.
7. Roberts EA, Schilsky ML. American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. Hepatology. 2008; 47(6): 2089–2111, doi: 10.1002/hep.22261, indexed in Pubmed: 18506894.
8. Członkowska A, Litwin T, Dusek P, et al. Wilson disease. Nat Rev Dis Primers. 2018; 4(1): 21, doi: 10.1038/s41572-018-0018-3, indexed in Pubmed: 30190489.
9. Litwin T, Dusek P, Szafrański T, et al. Psychiatric manifestations in Wilson's disease: possibilities and difficulties for treatment. Ther Adv Psychopharmacol. 2018; 8(7): 199–211, doi: 10.1177/2045125318759461, indexed in Pubmed: 29977520.
10. Ruiz DV. Wilson's disease and skunks? The copper connection. Wilson's Disease Association Newsletter 1997.
11. Mueller A, Reuner U, Landis B, et al. Extrapyramidal symptoms in Wilson's disease are associated with olfactory dysfunction. Mov Disord. 2006; 21(9): 1311–1316, doi: 10.1002/mds.20989, indexed in Pubmed: 16763975.
12. Chen L, Wang X, Doty RL, et al. Olfactory impairment in Wilson's disease. Brain Behav. 2021; 11(3): e02022, doi: 10.1002/brb3.2022, indexed in Pubmed: 33415839.
13. Carvalho MJ, Machado AA, Barbosa ER. Analysis of smell in Wilson's disease patients. Abstracts of the Sixteenth International Congress of Parkinson's Disease and Movement Disorders. June 17-21, 2012. Mov Disord. 2012; 27(Suppl 1), doi: 10.1002/mds.25051, indexed in Pubmed: 22714688.
14. Ferenci P, Caca K, Loudianos G, et al. Diagnosis and phenotypic classification of Wilson disease. Liver Int. 2003; 23(3): 139–142, doi: 10.1034/j.1600-0676.2003.00824.x, indexed in Pubmed: 12955875.
15. Członkowska A, Litwin T, Dzieżyc K, et al. Characteristics of a newly diagnosed Polish cohort of patients with neurological manifestations of Wilson disease evaluated with the Unified Wilson's Disease Rating Scale. BMC Neurol. 2018; 18(1): 34, doi: 10.1186/s12883-018-1039-y, indexed in Pubmed: 29621974.
16. Hummel T, Kobal G, Gudziol H, et al. 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): 237–243, doi: 10.1007/s00405-006-0173-0, indexed in Pubmed: 17021776.
17. 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): 205–211, doi: 10.1007/s004050050223, indexed in Pubmed: 10867835.
18. Mezzaroba L, Alfieri DF, Colado Simão AN, et al. The role of zinc, copper, manganese and iron in neurodegenerative diseases. Neurotoxicology. 2019; 74: 230–241, doi: 10.1016/j.neuro.2019.07.007, indexed in Pubmed: 31377220.
19. Meenakshi-Sundaram S, Mahadevan A, Taly AB, et al. Wilson's disease: a clinico-neuropathological autopsy study. J Clin Neurosci. 2008; 15(4): 409–417, doi: 10.1016/j.jocn.2006.07.017, indexed in Pubmed: 18242093.
20. Bembenek JP, Kurczych K, Członkowska A. TMS-induced motor evoked potentials in Wilson's disease: a systematic literature review. Bioelectromagnetics. 2015; 36(4): 255–266, doi: 10.1002/bem.21909, indexed in Pubmed: 25808411.

21. Ecevit C, Ozgenç F, Gökçay F, et al. The diagnostic value of multimodal evoked potentials in the determination of subclinical neurological involvement of Wilson's disease. Eur J Gastroenterol Hepatol. 2012; 24(6): 627–632, doi: 10.1097/MEG.0b013e3283526f81, indexed in Pubmed: 22433793.
22. Langwińska-Wośko E, Litwin T, Szulborski K, et al. Optical coherence tomography and electrophysiology of retinal and visual pathways in Wilson's disease. Metab Brain Dis. 2016; 31(2): 405–415, doi: 10.1007/s11011-015-9776-8, indexed in Pubmed: 26686677.
23. Bembenek JP, Kiryluk K, Inglot E, et al. Blink reflex in newly diagnosed and treated patients with Wilson's disease. J Neural Transm (Vienna). 2021; 128(12): 1873–1880, doi: 10.1007/s00702-021-02432-x, indexed in Pubmed: 34669020.
24. Hummel T, Welge-Lüssen A. Assessment of olfactory function. Adv Otorhinolaryngol. 2006; 63: 84–98, doi: 10.1159/000093752, indexed in Pubmed: 16733334.
25. Shu CH, Yuan BC, Lin SH, et al. Cross-cultural application of the „Sniffin' Sticks" odor identification test. Am J Rhinol. 2007; 21(5): 570–573, doi: 10.2500/ajr.2007.21.3075, indexed in Pubmed: 17999792.
26. Tekeli H, Altundağ A, Salihoğlu M, et al. The applicability of the „Sniffin' Sticks" olfactory test in a Turkish population. Med Sci Monit. 2013; 19: 1221–1226, doi: 10.12659/MSM.889838, indexed in Pubmed: 24382345.
27. Baert F, Vlaemynck G, Maselyne J, et al. Odor Identification by Parkinson's Disease Patients Tested by Using Sniffin' Sticks versus Natural Spices. Parkinsons Dis. 2022; 2022: 2272691, doi: 10.1155/2022/2272691, indexed in Pubmed: 35529474.
28. Litwin T, Gromadzka G, Szpak GM, et al. Brain metal accumulation in Wilson's disease. J Neurol Sci. 2013; 329(1-2): 55–58, doi: 10.1016/j.jns.2013.03.021, indexed in Pubmed: 23597670.
29. Rawson NE. Olfactory loss in aging. Sci Aging Knowledge Environ. 2006; 2006(5): pe6, doi: 10.1126/sageke.2006.5.pe6, indexed in Pubmed: 16469731.
30. Wang J, Eslinger PJ, Smith MB, et al. Functional magnetic resonance imaging study of human olfaction and normal aging. J Gerontol A Biol Sci Med Sci. 2005; 60(4): 510–514, doi: 10.1093/gerona/60.4.510, indexed in Pubmed: 15933393.
31. Larsson M, Finkel D, Pedersen NL. Odor identification: influences of age, gender, cognition, and personality. J Gerontol B Psychol Sci Soc Sci. 2000; 55(5): P304–P310, doi: 10.1093/geronb/55.5.p304, indexed in Pubmed: 10985295.
32. Nordin S, Monsch AU, Murphy C. Unawareness of smell loss in normal aging and Alzheimer's disease: discrepancy between self-reported and diagnosed smell sensitivity. J Gerontol B Psychol Sci Soc Sci. 1995; 50(4): P187–P192, doi: 10.1093/geronb/50b.4.p187, indexed in Pubmed: 7606530.
33. Kondo K, Kikuta S, Ueha R, et al. Age-Related Olfactory Dysfunction: Epidemiology, Pathophysiology, and Clinical Management. Front Aging Neurosci. 2020; 12: 208, doi: 10.3389/fnagi.2020.00208, indexed in Pubmed: 32733233.
34. Sorokowski P, Karwowski M, Misiak M, et al. Sex Differences in Human Olfaction: A Meta-Analysis. Front Psychol. 2019; 10: 242, doi: 10.3389/fpsyg.2019.00242, indexed in Pubmed: 30814965.
35. Doty RL, Cameron EL. Sex differences and reproductive hormone influences on human odor perception. Physiol Behav. 2009; 97(2): 213–228, doi: 10.1016/j.physbeh.2009.02.032, indexed in Pubmed: 19272398.
36. Nováková LM, Havlíček J, Roberts S. Olfactory processing and odor specificity: a meta-analysis of menstrual cycle variation in olfactory sensitivity. Anthropological Review. 2014; 77(3): 331–345, doi: 10.2478/anre-2014-0024.
37. Ajmani GS, Suh HH, Wroblewski KE, et al. Smoking and olfactory dysfunction: A systematic literature review and meta-analysis. Laryngoscope. 2017; 127(8): 1753–1761, doi: 10.1002/lary.26558, indexed in Pubmed: 28561327.
38. Çengel Kurnaz S, Tahir E, Kavaz E. Olfactory dysfunction in passive vs active smoking. Laryngoscope Investig Otolaryngol. 2021; 6(5): 932–939, doi: 10.1002/lio2.671, indexed in Pubmed: 34692999.
39. Desiato VM, Levy DA, Byun YJ, et al. The Prevalence of Olfactory Dysfunction in the General Population: A Systematic Review and Meta-analysis. Am J Rhinol Allergy. 2021; 35(2): 195–205, doi: 10.1177/1945892420946254, indexed in Pubmed: 32746612.