

OLFACTORY FUNCTION ASSESSMENT IN NEUROMYELITIS OPTICA AND COMPARISON WITH MULTIPLE SCLEROSIS

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Received on May 20, 2025

Presented by D. Damianov, Member of BAS, on July 29, 2025

Abstract

Olfactory dysfunction may be an occasional presymptomatic sign of demyelinating diseases such as multiple sclerosis (MS), and neuromyelitis optica spectrum disease (NMOSD). In our study, we aim to investigate and compare olfactory functions in NMOSD and MS patients using a validated olfactory test tool and to evaluate the association of olfaction with disease duration, severity, and according to the presence of antibodies.

This study was comprised of 16 NMOSD patients (9 women (56.2%), 7 men (43.8%)), 26 MS patients (17 women (65.4%), 9 men (34.6%)); 35 healthy volunteers (25 women (71.4%), 10 men (28.6%)) were included in the study as control group. The Connecticut Chemosensory Clinical Research Center olfactory test, developed for assessing orthonasal olfaction, was used.

The odour identification score, smell threshold, and mean olfactory combined scores of NMOSD patients were significantly lower than the healthy controls and MS patients. All odour scores in control group and MS group did not differ significantly ($p > 0.05$). There was no difference in olfaction scores of NMOSD population with regard to AQP4-IgG positivity/negativity status.

Our study suggests that olfactory dysfunction might be a part of clinical spectrum of NMOSD, so physicians treating patients with central nervous system demyelinating diseases should be aware of the potential for olfactory deficit and should counsel their patients accordingly.

Key words: olfactory dysfunction, neuromyelitis optica spectrum disease (NMOSD), multiple sclerosis (MS)

<https://doi.org/10.7546/CRABS.2025.09.15>

Introduction. Olfaction is initiated in the olfactory receptor cells in the olfactory mucosa of the nasal cavity and the signals are transmitted to the olfactory bulbs via olfactory nerves and processed in the primary olfactory cortex in the brain. Damage to either the olfactory receptor cells or the olfactory bulb and primary olfactory cortex may influence olfactory functioning. The olfactory mucosa is suggested to constitute a unique interface between the nervous and immune systems. A close link between neuroimmunological disorders and olfactory dysfunction has been reported in patients and animal models [1, 2]. Olfactory dysfunction may be an occasional presymptomatic sign of demyelinating diseases such as multiple sclerosis (MS), neuromyelitis optica spectrum disease (NMOSD), acute disseminated encephalomyelitis, systemic lupus erythematosus, etc. [1, 2].

NMOSD is a rare autoimmune disease of the central nervous system (CNS). Some NMOSD patients suffer from olfactory dysfunction associated with atrophy of olfactory-associated gray matter [3–5]. On autopsy of NMOSD brains, demyelination of the olfactory bulb and tracts has been reported occasionally [6]. In a review irrespective of the cause of CNS autoimmune diseases including NMOSD and MS [4], it is suggested that atrophy or/and demyelination of the olfactory system may be linked to olfactory dysfunction. Olfactory disturbance in MS and other CNS diseases where demyelination is a feature, such as NMOSD, has been relatively neglected in clinical and research studies. According to a functional evaluation, including the odour identification test, patients with MS suffer from loss of smell [7, 8].

In our study, we aim to investigate and compare the olfactory functions in NMOSD and MS patients using a validated olfactory test tool and to evaluate the association of olfaction with the disease duration, disease severity, and according to the presence of antibodies.

Methods. This study was comprised of 16 NMOSD patients (9 women (56.2%), 7 men (43.8%)), 26 MS patients (17 women (65.4%), 9 men (34.6%)) who were followed at Demiroglu Bilim University Medical Faculty Neurology Department Demyelinating Diseases outpatient/inpatient clinics. Thirty-five healthy volunteers (25 women (71.4%), 10 men (28.6%)) were included in the study as the control group. Baseline characteristics for each patient were recorded which included demographical data, gender, age at disease onset, clinical aspects, number of attacks, the disease duration, brain and spinal cord magnetic resonance imaging (MRI) findings, serum anti-AQP4 antibody status, drug history, Expanded Disability Status Scale (EDSS) scores. The patients with NMOSD fulfilled the 2006 WINGERCHUK diagnostic criteria, as well as the International Panel for NMOSD Diagnosis 2015 criteria [9, 10]. The patients with MS met the 2017 McDonald criteria [11]. No patients in the acute attack period were included in the study. Newly diagnosed patients were tested at the following visit at least one month after they were in remission. In patients with an older diagnosis, only patients in

a remission state for the last 3 months were included. EDSS values were calculated in the remission phase of the patients. Patients with conditions with nasal septum deviation, nasal polyposis, allergic rhinitis, acute-chronic rhinosinusitis, previous nasal or paranasal surgery, or recent upper airway tract infections that could cause olfactory dysfunction were excluded. Patients with head trauma, psychiatric disorders (psychosis), other chronic degenerative neurological diseases (e.g., Parkinson's and Alzheimer's), congenital olfaction disorders, concomitant systemic diseases, patients treated with drugs that might affect olfactory function during the testing period, were also excluded. All patients were provided with information about the procedures, and informed consent was obtained from all participants prior to the study. The hospital's medical ethics committee approved the study.

Olfactory assessment. The Connecticut Chemosensory Clinical Research Center (CCCRC) olfactory test, developed for assessing orthonasal olfaction, was used. The CCCRC test defined by the CCCRC consists of smell detection threshold and smell identification test [12].

Smell threshold test. Different concentrations of butanol were used for testing, starting from the lowest concentration going on to the highest. Each nostril was tested separately. The strongest concentration of butanol contained 4% butanol in deionized water. Each subsequent dilution was a 1:3 deionized water dilution of the previous bottle's concentration. Possible scores ranged from 0 to 9, lower scores indicate worse olfactory function, but all scores 7 and higher were scored as 7, per the CCCRC test.

Smell identification test. Everyday items with characteristic odours (peanut butter, soap, mothballs, Vicks VapoRub[®], chocolate, coffee, cinnamon and baby powder) were used for the smell identification test. These eight substances were placed in separate dark glass bottles. Subjects were asked to sniff the odours and try to identify them. The ability to sense Vicks VapoRub[®] requires intact trigeminal nerve function, therefore it was not included in the final score. The total number of items that each person could recognize was calculated. Possible scores ranged from 0 to 7 for correctly identified items. Scores for both nostrils were averaged. The mean scores for the butanol threshold test and the identification test were calculated, and a composite score for olfactory function was obtained. Lower scores indicate worse, and higher scores indicate better olfactory function.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 27.0). The continuous variables were described by their mean and standard deviation. Categorical variables were presented as frequency. In the descriptive statistics of the data, mean, standard deviation, median, lowest, highest, frequency and ratio values were used. The distribution of variables was measured with the Kolmogorov–Smirnov test. Normality tests were based on the Kolmogorov–Smirnov test. ANOVA, Kruskal–Wallis, Mann–Whitney U test were used in the analysis of quantitative independent data. The Kruskal–Wallis

test was applied to test whether the means of two or more samples differ significantly. For the statistically significant ($p \leq 0.05$) results, Mann–Whitney U test was applied between each pairwise combination of subgroups to determine which groups the difference was between. Chi-square test was used in the analysis of qualitative independent data. Spearman correlation analysis was used for correlation analysis.

Results. There was no significant difference between the patient groups and control subjects according to gender and age. The disease duration did not differ significantly in the NMOSD and MS groups. The number of attacks were significantly higher in the NMOSD group than in the MS group ($p < 0.05$). EDSS values in NMOSD group and MS group did not differ significantly ($p > 0.05$) (Table 1).

We detected a statistically significant difference in olfactory functions between patients with NMOSD, MS and healthy controls. The odour identification score, smell threshold, and mean olfactory combined scores of the NMOSD patients were significantly lower than the healthy controls and MS patients. The difference was slightly more prominent in the smell identification score than the smell threshold. All the odour scores in the control group and the MS group did not differ significantly. The mean olfactory test scores are presented in Table 1.

T a b l e 1

The mean olfactory test scores and demographical characteristics of study groups

	NMOSD Group ($n = 16$)	MS Group ($n = 26$)	Control Group ($n = 35$)	p -value
Age (Mean $\pm$ SD)	47.1 $\pm$ 18.2	39.8 $\pm$ 11.4	41 $\pm$ 13.6	NS
Female (n , %)	9 (56.3%)	17 (65.4%)	25 (71.4%)	NS
Male (n , %)	7 (43.8%)	9 (34.6%)	10 (28.6%)	NS
Smell threshold (Mean $\pm$ SD)	6.1 $\pm$ 1.0	6.8 $\pm$ 0.5	6.6 $\pm$ 0.5	0.005
Odour identification score (Mean $\pm$ SD)	4.0 $\pm$ 2.4	5.5 $\pm$ 1.5	6.1 $\pm$ 1.0	0.004
Mean olfactory combined score (Mean $\pm$ SD)	10.1 $\pm$ 2.9	12.3 $\pm$ 1.5	12.8 $\pm$ 1.1	0.002
Disease duration (months) (Mean $\pm$ SD)	6.1 $\pm$ 4.3	9.2 $\pm$ 7.3	–	NS
Number of attacks (Mean $\pm$ SD)	2.9 $\pm$ 1.8	2.2 $\pm$ 1.0	–	0.000
EDSS (Mean $\pm$ SD)	3.9 $\pm$ 2.64	2.6 $\pm$ 1.5	–	NS

NS: Not significant, SD: Standard deviation

Correlation analyses were performed separately for the NMOSD and MS groups and compared with each other and controls. Pairwise comparison of the olfactory test scores are mentioned in Table 2. There was no significant correlation between the olfactory threshold score and the duration of the disease, the

T a b l e 2

Pairwise comparison of the olfactory test scores between groups

	Control Group/ NMOSD Group	Control Group/ MS Group	NMOSD Group/ MS Group	<i>p</i> -value
Smell threshold (<i>p</i> -value)	0.066	0.036	0.002	0.005
Odour identification score (<i>p</i> -value)	0.002	0.081	0.052	0.004
Mean olfactory combined score (<i>p</i> -value)	0.001	0.293	0.010	0.002

number of attacks, and the EDSS value. Also, there was no significant correlation between the odour identification, mean olfactory combined scores, and the duration of the disease. But on the contrary, a significant negative correlation was observed between the mean olfactory combined scores ($p = 0.005$, $r = -0.424$), the odour identification ($p = 0.016$, $r = -0.369$) and the degree of disability measured by EDSS. These scores were diminished in patients with higher EDSS values. Also, we observed that the number of attacks and smell identification ($p = 0.024$, $r = -0.315$), and mean olfactory scores ($p = 0.028$, $r = -0.309$) were inversely correlated, thus the CCCRC scores were lower in patients with more frequent NMOSD and MS attacks.

The presence of Aquaporin-4 Immunoglobulin G (AQP4-IgG) antibody positivity was not associated with olfactory dysfunction. From the NMOSD patients 8 were AQP4-IgG positive and 8 were negative. There was no difference in the olfaction scores of NMOSD population with regard to the AQP4-IgG status (Table 3).

T a b l e 3

The olfaction scores of NMOSD population according to Aquaporin 4 IgG status

	Aquaporin 4 IgG positive (+) ($n = 8$)	Aquaporin 4 IgG negative (-) ($n = 8$)	<i>p</i> -value
Smell threshold (Mean $\pm$ SD)	6.3 ± 1.1	6.1 ± 0.8	NS
Odour identification score (Mean $\pm$ SD)	4.2 ± 2.7	4.3 ± 2.1	NS
Mean olfactory combined score (Mean $\pm$ SD)	10.5 ± 3.5	10.4 ± 2.3	NS

Discussion. Olfactory dysfunction is recognised across a spectrum of neuropsychiatric conditions including CNS demyelinating diseases such as MS and NMOSD [13]. According to recent studies, about 11.1–40% of patients with MS [14] and 50–53% of patients with NMOSD [3, 5] present olfactory dysfunction. In our study, we detected olfactory dysfunction only in NMOSD patients. No significant difference was observed in odour tests when MS patients were compared with healthy controls. In the study of Li et al. [4], patients with NMOSD seemed

to present worse olfactory recognition function than patients with MS, though the difference was not statistically significant. These results may partially support the results of our study.

The differences in the results between these two groups of patients might be due to the different underlying mechanisms of olfactory deficits in NMOSD and MS. In keeping with this hypothesis, LIU et al. [15] showed that early parahippocampal gyrus atrophy might be a key feature distinguishing MS from NMOSD. On the other hand, demyelination, a common pathogenic feature of both diseases, is frequently seen also in the olfactory bulb and/or tract [6]. SCHMIDT et al. [3] reported a relation between the lesion load in the olfactory cortex and the volume of the olfactory bulb and olfactory brain. However, a correlation between lesions in olfactory-related areas and olfactory impairment was not found in a study by ROLET et al. [14]. It has been previously demonstrated that reduced gray matter volume is correlated with olfactory dysfunction in patients with NMOSD or MS [3,5]. Given that gray matter lesions distinct from those in MS are found in NMOSD [16], the mechanism underlying the decreased gray matter volume seems to differ between NMOSD and MS.

However, comparisons of olfactory deficits and olfactory-related gray matter atrophy between NMOSD and MS have not been reported. The small sample size of our cohort, limited our research of the relevant pathophysiological mechanisms underlying the disease. Moreover, further studies to better understand the difference in olfactory impairment and olfactory-related areas in NMOSD and MS could be of considerable importance both clinically and scientifically.

In the study of SØRBØ et al. [17] it is indicated that AQP4 is strongly expressed in the glomerulus, the synaptic unit of the olfactory bulb, suggesting a role for AQP4 in olfactory function. They report that, in the nasal epithelium AQP4 is upregulated as early as in the brain. In the study conducted by Schmidt et al. [3] the occurrence of olfactory dysfunction was explained by tissue damage in olfactory structures with AQP4 expression. In another study it is mentioned that the specific loss of AQP4 immunoreactivity, one of the pathological hallmarks of NMOSD [18], would replicate the pattern of gray matter atrophy described above [19]. As a different point of view, JOSEPH and DELUCA [13] concluded that the loss of AQP4 in NMOSD lesions within the olfactory bulb/tract was consistent with the pattern seen in NMOSD lesions elsewhere in the nervous system. Similarly, ROEMER et al. [20] indicated in their research that in NMOSD, olfactory bulb/tract lesions demonstrated selective loss of aquaporin-4 reflecting the established role of antibodies directed against this water channel in NMO pathogenesis. On the other hand, the fact that there was no difference regarding the seropositivity for AQP4-IgG, in the olfaction scores of NMOSD population in our study, made us think about the presence of different antibodies that should be investigated. In the study of ZHANG et al., [5] in NMO, the association of both anti-AQP4 seropositivity and radiological abnormalities within the olfactory bulb

and cortex with olfactory dysfunction is explained by the diffuse expression of AQP4 throughout the olfactory system [5]. Thus, we appreciate that both neuropathological and MRI studies together are required to demonstrate lesions in olfactory structures to detect the supposed link between NMOSD and olfactory dysfunctions in patients.

The shift of olfactory disturbance between early and late disease stages raises the question that whether different olfactory structures are affected at different disease stages in CNS demyelinating diseases. In the study of DELUCA et al. [6] MS and NMOSD cases, demonstrated olfactory bulb and tract pathology in autopsy within few months of disease onset, suggesting early involvement of these structures. The fact that olfactory pathology in CNS demyelinating diseases may be frequent, can occur early, raises questions about the role of the olfactory system in the initiation and propagation of these diseases.

However, in our study, there was no significant correlation between the olfactory scores and the duration of the disease in NMOSD and MS patient groups. These results suggest that the olfaction was affected independent of the disease duration but dependent on number of attacks and the degree of disability. Another limitation of our study is the lack of longitudinal follow-up. Future studies should also search the changes in olfactory function and olfactory-related structures in patients with NMOSD and MS over time, and at different states of disease progression.

Conclusion. In conclusion, our results suggest that olfactory dysfunction might be a part of clinical spectrum of NMOSD, so physicians treating patients with CNS demyelinating diseases should be aware of the potential for olfactory deficit and should counsel their patients accordingly. Whether the olfactory system plays a role in the pathogenesis of CNS demyelinating diseases remains uncertain, but our findings support its further research with multicentre studies on the frequency, extent and underlying mechanisms of olfactory dysfunction.

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