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CE ARTICLE

Longitudinal Olfactory Patterns in Multiple Sclerosis: A Scoping Review and Implication for Use in Management of Disease

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CE INFORMATION

ACTIVITY AVAILABLE ONLINE: To access the article and evaluation online, go to https://www.highmarksce.com/mscare.

TARGET AUDIENCE: The target audience for this activity is physicians, advanced practice clinicians, nursing professionals, and other health care providers involved in the management of patients with multiple sclerosis (MS).

LEARNING OBJECTIVE:
Identify the longitudinal patterns of olfactory dysfunction seen in various stages of multiple sclerosis disease course, as described in recent literature to better recognize olfaction as a dynamic, dependent variable of neurodegeneration that correlates with inflammation and clinical markers and may have a future role in recognizing and monitoring disease activity.

ACCREDITATION:

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Francois Bethoux, MD, editor in chief of the *International Journal of MS Care (IJMSC)*, and **Alissa Mary Willis, MD,** associate editor of *IJMSC*, have disclosed no relevant financial relationships. Author **Jennifer A. Villwock, MD,** has a patent pending for olfactory testing and training methods (AROMA, Affordable Rapid Olfaction Measurement Array). There is no product available for commercial sale. Authors **Sharon G. Lynch, MD; Lauren L. Todd, BS; Ram Sivakumar, BS; Jennifer H. Diebolt, MD;** and **Jacob White, MLS,** have disclosed no relevant financial relationships.

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ABSTRACT

BACKGROUND: Although studies regarding multiple sclerosis (MS) and olfactory dysfunction (OD) have been previously described and summarized, there is not a sole review of longitudinal studies regarding the matter. This review examines the existing literature investigating MS and its effect on olfaction. In addition, the role of OD in the diagnosis and prognosis of MS is explored.

METHODS: A scoping review of the literature was performed covering longitudinal studies investigating MS and OD. Systematic searches of PubMed, Google Scholar, Web of Science, Embase, PsycInfo, Cumulative Index to Nursing and Allied Health Literature, AgeLine, and MEDLINE were performed using terms that encompassed MS and olfaction. The aim of this review was to build on the existing literature by summarizing only findings that were demonstrated longitudinally.

RESULTS: Of 6938 articles identified from the search, 9 met the inclusion criteria: longitudinal observation of relapsing-remitting or progressive MS. Olfaction was measured and scored using various testing arrays, and these scores were then correlated with a multitude of clinical markers. Across all studies, patients with MS demonstrated increased OD. Longitudinally, 2 contrasting patterns were identified: (1) clinical markers of acute inflammation correlated with an increased odor threshold and (2) clinical markers of neurodegeneration, or progression of disease, correlated with a decreased ability to discriminate and identify odors.

CONCLUSIONS: These studies suggest that olfaction is a dynamic, dependent variable of neurodegeneration, correlating with inflammation and clinical markers. This opens the door for future exploration of olfaction's relationship with MS diagnosis, characterization, and therapeutic response.

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Multiple sclerosis (MS) is an autoimmune, neurologic, degenerative disease that is associated with olfactory dysfunction (OD).[1] Many sources have investigated the connection between olfaction and MS using metrics such as the University of Pennsylvania Smell Identification Test (UPSIT)[1,2] and the Connecticut Chemosensory Clinical Research Center olfactory test[3] to better understand the extent of the deficit. Studies usually compare olfaction in patients with MS vs controls or between patients with MS with different disease durations. Although these studies do connect MS and OD, most do so only via cross-sectional methods. Because MS is a disease with multiple progressive patterns—relapsing-remitting (RRMS), primary progressive, and secondary progressive[4]—the level of OD can be drastically different over time. For example, patients with early-stage MS can have minimal to no loss of olfactory identification or discrimination.[5] Identifying studies that use longitudinal methods of tracking olfaction will not only provide more clarity about the progression of OD but may also reveal a connection between the pattern of OD and various MS biomarkers, such as plaque burden. There may also be a place for olfaction in disease detection and surveillance. Olfactory testing is simple, inexpensive, and can be performed during a normal clinic visit.[6] Olfactory monitoring in patients with MS could serve as a useful marker for early intervention, tracking progression, and response to therapy.

METHODS

This scoping review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. As a scoping review, it was not eligible for registration on PROSPERO, an international prospective register of systematic reviews. The purpose of this scoping review was to evaluate the current literature base rather than to collect and analyze the data from these sources.

Eligibility Criteria

Studies were eligible if they were longitudinal in design with the primary discussion involving OD and diagnosis of MS (**FIGURE S1**, available online at IJMSC.org).

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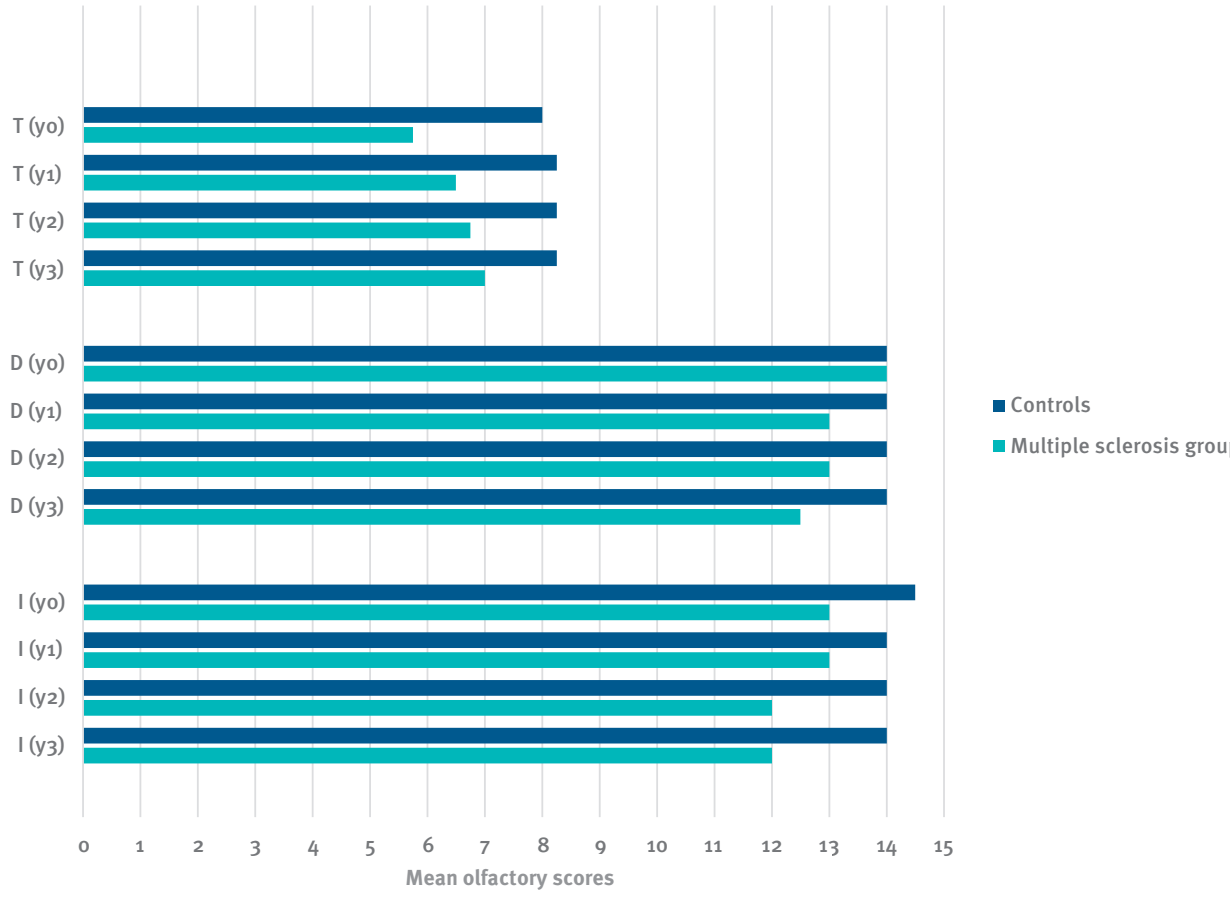
Note: Supplementary material for this article is available at IJMSC.org.

FIGURE. Mean Olfactory Scores Over Time



T, Threshold; D, Discrimination; I, Identification

Note: Data were compiled by and adapted from Bsteh G, Hegen H, Ladstätter F, et al. Change of olfactory function as a marker of inflammatory activity and disability progression in MS. *Mult Scler*. 2019;25(2):267-274. doi:10.1177/1352458517745724

Data Collection

Data extraction was performed by 2 authors (L.L.T., R.S.) using the databases and search terms listed in **TABLE S1**. A shared EndNote database was used to manage the citations. All disagreements were discussed between the 2 authors to arrive at a consensus. Data collected included author, year, journal, title, abstract. After the citations were filtered, they received a full-text review.

RESULTS

The initial search identified 6938 published manuscripts. After duplicates were removed, 5170 manuscripts remained. After titles and abstracts were reviewed, 9 studies met the inclusion criteria and underwent full-text review. The 9 studies observed patients with MS at varying stages over a longitudinal time frame, from 24 weeks to 10 years. Olfactory function was measured in 6 studies using the Sniffin' Sticks protocol, in 1 study using the UPSIT, and in 1 study using the Brief Smell Identification Test. A ninth study monitored brain activity during olfaction to measure function. Specific study qualities are listed in **TABLE S2**. Note that of the 9 selected studies, the 5 authored by Bsteh included patients from a single study group.

Many of the studies correlated these results with clinical markers such as Expanded Disability Status Scale score, serum neurofilament light chain (sNfL) level, disease duration, and death, which are presented in **TABLE S3**.

MS and OD

Participants in the study by Bsteh et al[7] exhibited lower scores in all measures of olfaction/olfactory function (threshold, discrimination, and identification) at every point compared with controls. The difference between discrimination (−0.5; IQR, −1.0, 0.0; $P = .43$) and identification (−1.0; IQR, −1.5, −0.5; $P = .002$) scores from baseline to year 3 showed significant decay. Threshold scores did not decline with increased duration of disease. The evolution of scores between patients and controls is presented in the **FIGURE**.

TABLE 1. Baseline Participant Characteristics

Author	Clinical marker of acute inflammation	Clinical marker of neurodegeneration and progression of disease
Doty et al[9]		Increased plaque numbers in those with decreased UPSIT scores (identification). Subsequent increase in UPSIT score as plaques healed.
Bsteh et al[7,8,12-14]	Increased INL thickness/volume and decreased threshold scores in patients with acute relapse compared with patients who had not relapsed. Significance of this finding decreased as time drew further from relapse.[7,12,13]	Statistically profound correlation between decreased DI scores and decreased gray matter concentration in patients with MS.[8] Increased sNfL levels on 2 occasions correlated with larger decreases in DI scores.[14]
Ciurleo et al[10]	Absent OERPs at baseline were a significant predictor of increased TNR ($r_{pb} = -0.34$; $P = .08$) and increased disability (EDSS) ($r_{pb} = -0.48$; $P = .009$).	
da Silva et al[15]		Lower BSIT scores at baseline correlated with higher increases in MSSS, ARMSSS, and HRs of death.
Uecker et al[11]		Significant correlation between lower odor discrimination scores in patients with higher rates of relapse.

ARMSSS, Age-Related Multiple Sclerosis Severity Score; BSIT, Brief Identification Smell Test; DI, discrimination and identification; EDSS, Expanded Disability Status Scale; INL, inner nuclear layer; MS, multiple sclerosis; MSSS, Multiple Sclerosis Severity Score; OERP, olfactory event-related potential; sNfL, serum neurofilament light chain; TNR, total number of relapses; UPSIT, University of Pennsylvania Smell Identification Test.

Two studies used neurologic imaging to investigate olfaction.[8,9] In both instances, olfaction was consistently impaired in patients with a more severe degree of change on imaging. Specific findings are listed in **TABLE 1**. Of note, threshold scores were not affected by changes seen on MRI.

Brain activity relating to olfaction was measured using evoked potentials (olfactory event-related potentials [OERPs]) in individuals with disease vs controls.[10] As seen in Table 1, a blunted degree of brain activity at baseline was predictive of a higher number of relapses and furthered disability in those with RRMS. Only 1 group of patients with RRMS had stable, albeit decreased, levels of olfaction over the course of 3 years.[11]

Relapsing-Remitting MS

Two studies of individuals with only RRMS looked at markers of acute inflammation, presence of acute relapse, and increased retinal inner nuclear layer thickness to track disease activity against olfaction.[12,13] Both inflammatory markers dynamically correlated with threshold score (Table 1).

Another clinical marker—sNfL level, a marker of axonal injury—measured higher in individuals with RRMS than in controls. Those with a sustained increase in sNfL measurements displayed a significantly steeper decline in discrimination and identification scores from baseline.[14]

Progressive MS

Only 1 study investigated olfaction in people with progressive MS using degree of disability and length of life.[15] A more severe loss of olfaction correlated with increased disability over time, as measured using the Multiple Sclerosis Severity Score and the Age-Related Multiple Sclerosis Severity Score. Impaired baseline olfaction scores were also correlated with higher rates of death in those with progressive MS after 10 years (Table 1).

DISCUSSION

This scoping review sought to identify, review, and interpret the emerging literature on the longitudinal implications of MS on olfaction. A previous meta-analysis described the association between MS and OD with a pooled prevalence of 27.2%.[16] Although beneficial, cross-sectional studies are limited to illustrating a snapshot of olfaction in an unstable disease course. A need for larger, longitudinal studies to delineate this relationship led to a recent increase in prospective studies. This review included 9 studies, with 8 occurring in the past 5 years, that measured olfaction in people with MS at multiple points in time.

Two main patterns were identified from the literature: (1) Clinical markers of short-term inflammation, as measured by the presence of relapse and thickened retinal nerve fiber layer, correlated most with an increased odor threshold in people with MS and, in contrast, (2) clinical markers of neurodegeneration, or axonal injury as measured by the sNfL level, correlated most with a decreased ability to discriminate and identify odors. Table 1 summarizes these findings.

Odor threshold has been used in multiple validated olfactory tests, such as Sniffin' Sticks.[17] To test threshold, butanol is presented to subjects at varying dilutions, with higher scores indicating identification at lower concentrations. The relationship between decreased odor threshold scores and increased inflammatory processes in people with acute, early-stage MS has been demonstrated in cross-sectional research.[18] A similar correlation was supported in the selected longitudinal studies[9,11]; however, the longitudinal findings suggest that

PRACTICE POINTS

Multiple sclerosis is associated with an overall decrease in olfaction.

Odor threshold, or ability to detect an odor, declines and improves with disease activity as measured by clinical markers of acute inflammation.

Odor discrimination and identification are decreased in patients with more progressive disease as measured by plaque burden, disability, and neurodegeneration. ■

threshold may play a more fluid role in early disease. The decline and subsequent improvement of threshold scores mirrored that of acute relapse with gradual incomplete recovery. Other clinical markers of relapse and inflammation, such as development of plaques on MRI and inner nuclear layer thickness, also correlated with the threshold's fluctuation.[9,13] Because odor threshold seems to follow the relapsing and remitting nature of disease symptoms, it could potentially be used to monitor occurrence of relapse.

Akin to odor threshold, discrimination and identification are commonly used in olfactory testing, with identification, such as the UPSIT,[19] being included by most testing arrays used in the selected studies. Cross-sectionally, lower discrimination and identification scores have been correlated with lower Expanded Disability Status Scale and quality of life scores, as well as higher plaque burden.[7] By viewing these qualities of olfaction longitudinally, the reviewed studies demonstrated a correlation between disease progression and decreased discrimination and identification scores. Disease progression was denoted in the reviewed studies through gray matter atrophy and a sustained increase in sNfL level, indicating axonal injury.

Discrimination and identification are important components in what has previously been described as an odor object. Odor objects are created in the piriform cortex through its direct communication with the olfactory bulb. These objects are unique and allow the brain to both identify and discriminate between specific odors.[20] Coincidentally, the piriform cortex lies between the insula and the amygdala, areas where increased demyelination in people with MS is often noted.[21]

This finding suggests that, unlike threshold, decreased discrimination and identification are more permanent changes and may relate to lasting neuronal damage. In addition, the presence of lowered discrimination and identification scores at baseline was associated with worse outcomes at study conclusion, including increased frequency of relapse, greater disability, and a higher risk ratio of death in those with more progressive disease. Discrimination and identification scores may correlate with these biomarkers due to the possible association between odor discrimination and identification and the presence of demyelination in the piriform cortex's adjacent structures. Future research should investigate this relationship further.

With the predictive value of these scores, there is potential clinical benefit to the early measurement of discrimination, identification, and absence of OERP. In the study by Comi et al,[22] patients with a neurologic event and clinical and MRI evidence suggesting the presence of MS were administered interferon beta within 3 months. Early administration of interferon beta correlated with lower rates of acute relapse, decreased plaque burden, and longer time before clinically definite disease.[22] The olfaction tests used to measure discrimination, identification, and OERP could serve as an additional test alongside clinical symptoms and MRI to identify those at risk for future disease who could benefit from early treatment. In addition, they could be used to help signal evidence of new breakthrough disease that might require treatment change. These tests have the advantage of being simple, inexpensive, and able to be performed in the course of a normal clinic visit, and their results could help inform the need for more complex or expensive testing.

Note there was not an association between MS course and decline in threshold, discrimination, or identification scores in the 2017 study by Uecker et al.[11] These results may have differed from the other studies secondary to a smaller sample size with a lower mean ± SD relapse rate of 0.3 ± 0.5 across 3 years. By mainly observing those with stable disease, they may have been less likely to observe the olfactory changes that we hypothesize to correlate with inflammatory activity and neurodegeneration.

CONCLUSIONS

The findings from the studies included in this review reinforce previous findings demonstrated in cross-sectional studies; however, these findings also build on the existing literature and demonstrate longitudinal olfactory patterns in the MS disease process. Although each study bore different results, 2 main patterns were apparent when comparing the data of all studies: (1) Clinical markers of acute inflammation correlated most

with an increased odor threshold in people with MS and (2) clinical markers of neurodegeneration, or axonal loss, correlated most with a decreased ability to discriminate and identify odors. These findings suggest that there is a potential clinical benefit to using olfaction in the diagnostic and prognostic journey of this fluctuating, expensive, and challenging disease. Future research of olfaction alongside well-known clinical markers is needed to further understand the patterns discussed in this review and to identify and use olfactory testing as an important clinical marker in people with MS. ■

FINANCIAL DISCLOSURES: Dr Villwock has a patent pending for olfactory testing and training methods (AROMA, Affordable Rapid Olfaction Measurement Array). The other authors declare no conflicts of interest.

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