Olfactory Dysfunction in Multiple Sclerosis
Relation to Plaque Load in Inferior Frontal and Temporal Lobes

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ABSTRACT: The question of whether and to what degree multiple sclerosis (MS) influences the ability to smell is controversial. We administered the University of Pennsylvania Smell Identification Test (UPSIT) to 26 MS patients and concurrently employed high-resolution magnetic resonance imaging (MRI) to quantify the number of demyelinating plaques within central brain structures. 38.5% of the patients demonstrated olfactory loss, with 7.7% exhibiting severe microsmia, 19.2% moderate microsmia, and 11.5% mild microsmia. None was anosmic, and no consistent left:right asymmetry in olfactory function or in hemispheric plaque numbers was observed. A strong negative correlation was found (Spearman $r = -0.94$) between UPSIT scores and the number of plaques within the inferior frontal and temporal lobes, but not within the rest of the brain. This study unequivocally demonstrates that a sizable proportion of MS patients suffer from olfactory loss commensurate with plaque activity within olfactory-related central brain regions, and is the first to explicate a physical basis for the olfactory dysfunction of any common neurologic disease.

Although decreased ability to smell is among the first signs, if not the first sign, of Alzheimer’s disease and idiopathic Parkinson’s disease, olfactory dysfunction is absent or occurs at a much lower frequency in most other neurodegenerative disorders, including progressive supranuclear palsy, multiple system atrophy, amyotrophic lateral sclerosis, and parkinsonism induced by the prionneurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). In the case of multiple sclerosis (MS), the most common cause of neurologic disturbance in the young adult, considerable controversy exists concerning the presence or absence of olfactory dysfunction. Some investigators report that decreased odor perception can be the presenting sign of MS and that up to two-thirds of MS patients exhibit demonstrable smell loss, whereas others deny finding any olfactory alterations in MS at all. Other authorities erroneously note that the human olfactory system is unmyelinated and conclude, therefore, that olfactory function is spared in MS. While it is true that the primary olfactory neurons (which serve as both the olfactory receptor cell and the first order projection neuron) are unmyelinated

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nated, myelinated dendrites and partly myelinated perikarya of mitral, tufted, and periglomerular cells are present in the olfactory bulbs of both humans and monkeys, and myelin is found in higher-order olfactory processing regions (e.g., in long projection axons).12

The purpose of this study was to evaluate, using a sensitive and well-validated test of the ability to smell, olfactory function in a relatively large group of patients with MS and to determine if a correlation exists between the olfactory test scores and the number of plaques within the inferior frontal and temporal lobes. These two brain regions contain the major zones of known central olfactory connections and include, respectively, (i) the olfactory striae, subcallosal medial frontal lobe, paraterminal gyrus, orbitofrontal zone, and gyrus rectus and (ii) the prepiriform, entorhinal, amygdaloid, hippocampal, and parahippocampal regions of the brain.

METHODS

Twenty-six well-characterized MS patients [9 men, mean (SD) age: 42.11 yr (9.42); 17 women, mean (SD) age: 42.12 (6.84)] were evaluated. All were administered the University of Pennsylvania Smell Identification Test (UPSIT), a standardized 40-item forced-choice test that correlates strongly with other types of olfactory tests, including detection threshold tests.13-15 Testing was performed separately for the left and right sides of the nose in 14 of these patients (20 UPSIT items on each side) to determine if asymmetry in such function was present. In these cases, the nasal contralateral to testing was occluded using a piece of Microfoam™ tape (3M Corp., Minneapolis, MN) to prevent retronasal movement of air from the opposite nasal chamber. Thin section magnetic resonance imaging (MRI) of the brain with gadolinium enhancement was performed on the same day as administration of the UPSIT using a General Electric (Milwaukee, WI) 1.5-T signal scanner employing a standard head coil. All MRI evaluations included T1-weighted sagittal sections and double-echo long-TR axial scans with 3-mm thick slices through the entire brain, allowing for detailed assessment of MS plaques in all brain areas.13 The matrix was 256 × 192 pixels; the field of view was 240 mm². The counting of plaques was done by two experienced neuroradiologists without knowledge of the olfactory test scores. The inferior frontal lobes were designated as being inferior and anterior to the body and genu of the corpus callosum, respectively. The inferior temporal lobes were considered bounded by the plane of the Sylvian fissure superiorly.

RESULTS

Relative to normative data based on nearly 4,000 subjects,16 38.5% of the study group had demonstrable olfactory loss, with 7.7% exhibiting severe bilateral microsmia, 19.2% moderate bilateral microsmia, and 11.5% mild bilateral microsmia. None was anosmic. No L:R asymmetries in either the UPSIT scores or the number of plaques within the target brain regions were observed [respective L and R mean (SD) 20-item UPSIT scores: 15.93 (2.90) & 15.38 (2.85); respective L and R mean (SD) inferior frontal + temporal lobe plaque numbers: 3.86 (2.74) & 3.79 (2.67)]. Spearman r left:right values for UPSIT and plaque numbers were 0.88 and 0.86, respectively (p <0.001).

As shown in Figure 1A, a strong negative relationship (Spearman r = -0.94, p <0.0001) was found between the UPSIT scores and the number of demyelinating plaques within the inferior frontal and temporal lobe regions of the brain. Both the correlation between UPSIT scores and inferior frontal lobe plaque numbers and the cor-
FIGURE 1. Relationships between number of plaques in olfactory (A) and non-olfactory (B) brain regions and scores on the University of Pennsylvania Smell Identification Test (UPSIT). (From Doty et al. Reprinted by permission from the New England Journal of Medicine.)
relation between UPSIT scores and inferior temporal lobe plaque numbers were statistically significant; however, the temporal lobe correlation was largest, accounting for the most variance [Spearman \( r_{\text{USIT(frontal)}} = -0.46, p < 0.05 \); \( r_{\text{USIT(temporal)}} = -0.92, p < 0.0001 \)], reflecting, in part, the wider distribution of individual plaque numbers in the temporal than in the frontal lobes. The mean (SD) number of plaques in the temporal lobe regions was 3.69 (3.68) and in the frontal lobe regions 1.69 (1.64). The respective medians (ranges) were 1.00 (0–7) and 3.00 (0–14).

No meaningful relationship was present between UPSIT scores and plaque numbers in the non-olfactory related brain regions (\( r = -0.08, \text{ns} \)) (Fig. 1B), implying that the association shown in Figure 1A was specific to brain structures directly involved in higher-order olfactory processing and not due to generalized MS-related dysfunction. An example of the plaques found in the subtemporal and subfrontal regions of a patient with severe microsmia is shown in Figure 2.

**DISCUSSION**

The findings of this study imply that for olfactory dysfunction to exist in an MS patient, plaques of sufficient number must be present within olfactory eloquent regions of the brain. This presumably explains the diversity of findings of olfactory function in MS in the literature. In some neurologic disorders, including Alzheimer’s disease and idiopathic Parkinson’s disease, there is circumstantial support for the theory that the associated olfactory loss could be due to the passage of viruses or environmental agents into the central nervous system (CNS) via the olfactory fila.\(^{17,18}\) Cranial nerve I serves as as a major, often primary, route of invasion of numerous viruses and toxins into the CNS.\(^{19,20}\) and damage to the olfactory pathways can occur from such factors en passant.\(^{21}\) Our finding of a nearly invariant association between olfactory test scores and the number of localized central brain lesions makes it unlikely that the olfactory dysfunction of MS is caused by damage to the olfactory pathways at the time of invasion by a virus or other agent. This does not negate the possibility, however, that MS is caused by an environmental factor or factors that enter the brain through the olfactory fila.

The present data are in accord with the observations of others that plaque involvement in MS is multifocal, diffuse, and usually present in both hemispheres.\(^{22}\) As will be reported elsewhere, our longitudinal data indicate that the olfactory function of patients with MS waxes and wanes in response to plaque exacerbation and remission in a near perfect association. Whether this association breaks down in patients with long-standing or unremitting MS is unknown, but is certainly possible. It is well documented in other neural systems that compensation for progressive axon loss becomes less effective as more neurons subserving the specific function under consideration disappear.\(^{23}\)

Our research, including our recently completed longitudinal study, is the first to provide a physical basis for an olfactory disorder in a common neurologic disease, and unequivocally demonstrates that a sizable proportion of MS patients suffer from olfactory loss commensurate with plaque activity within higher-order olfaction-related brain regions. Given that the sense of smell provides a basic means for detecting smoke, leaking natural gas, and environmental pollutants, its compromise in mobility-restricted individuals, such as persons suffering from MS, can be dangerous. A reduced sense of smell also diminishes the flavor of foods and beverages, adversely altering the quality of life. Clearly, physicians and others involved with the care of MS patients should be aware of the potential for olfactory loss in this debilitating neurologic disease and should counsel their patients accordingly.
FIGURE 2. Axial T2-weighted MRI scans (TR: 2500/TE: 90) from a severely microsmic (UPSIT score = 20) 50-year-old man with an eight-year history of MS. The plane of section in (A) is 6 mm below that of (B). Note the prominent plaques (≈10 × 5 mm each) within the posterior part of the white matter of the gyrus rectus of the L and R subfrontal lobes (arrows 1 & 2, respectively), and the bilateral high signal-intensity plaques in the subtemporal lobes (arrows 3 & 4).
REFERENCES