Olfactory dysfunction in multiple sclerosis: Relation to longitudinal changes in plaque numbers in central olfactory structures

We recently reported, in 26 well-validated MS patients, that one-third had some degree of olfactory dysfunction, as measured by the University of Pennsylvania Smell Identification Test (UPSIT), a well-validated test of olfactory function.\textsuperscript{1,2} Importantly, we observed a strong inverse correlation ($r = -0.94$) between UPSIT scores and the number of plaques within central brain structures associated with olfactory processing (inferior frontal and temporal lobes [IFTLs]), a correlation not present when plaque numbers in other brain regions were similarly examined. This suggests that discrepant findings among studies evaluating olfactory function in MS patients\textsuperscript{3-5} may reflect the waxing and waning over time of plaques in central olfactory structures.

The current study supports this view. We evaluated plaque numbers and olfactory function repeatedly in five MS patients over an 18- to 20-month period, demonstrating that as plaque numbers decline in the IFTLs, olfactory function increases, whereas as plaque numbers increase in these brain regions, olfactory function decreases.

Methods. The UPSIT was administered bilaterally to each subject\textsuperscript{6,7} in light of our earlier observations that olfactory loss in MS generally is bilateral and symmetric.\textsuperscript{3} Thin-section magnetic gadolinium-enhanced resonance images (MRI) of the brain were obtained on the same day as UPSIT scores using a General Electric 1.5-T signal scanner and 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.\textsuperscript{8} Two experienced neuroradiologists counted the plaques without knowledge of the olfactory test scores; the scans were reviewed independently and, in all cases, counts were agreed on in a consensus reading.

Plaque numbers were determined within the IFTLs and in the remainder of the brain. The left (L) and right (R) inferior frontal lobes were designated as being inferior and anterior to the body and genu of the corpus callosum, respectively. The L and R inferior temporal lobes were considered bounded by the plane of the Sylvian fissure superiorly. These two regions contain the major zones of known olfactory connections and include, respectively, 1) the olfactory striae, subcallosal medial frontal lobe, paramedian gyrus, orbitofrontal zone, and gyrus rectus; and 2) the prepiriform, entorhinal, amygdaloid, hippocampal, and parahippocampal regions of the brain.

Results. The data from the five subjects are presented in figure 1. In figure 1A, the data are from a 49-year-old man with a 6-year history of MS before our testing who exhibited no plaques, on any test occasion, within the IFTLs. This individual’s UPSIT scores remained within the normal range across all test occasions. Figure 1B shows data from a 49-year-old woman with a 5-year history of relapsing-remitting MS at the time of our first test. In this individual, olfactory function was borderline normal for the first two tests but decreased to moderate microsmia (27/40) 11 months later, when her plaque numbers more than doubled from 4 to 9. In figure 1C, data are presented from a 32-year-old man who had chronic progressive MS of 4 years’ duration. His major symptoms were difficulties in ocular movement and coordination of upper and lower extremities. Relatively few plaques were present within the target regions on the first two tests, when the UPSIT scores were well within the normal range. However, on the subsequent two tests, plaque numbers increased to seven and eight, respectively, and UPSIT scores declined to 32 on each occasion, indicative of mild microsmia. The data from a 44-year-old woman who had relapsing and remitting MS for 8 years are shown in figure 1D. Her major symptoms were numbness and walking difficulties. The UPSIT score on the first test occasion was 30 (moderate microsmia), and the number of plaques, 12. On the second test, the UPSIT score was 29 and the number of plaques, 12. On the third test, there was little change in either the UPSIT score (30) or the number of plaques (11). However, on the fourth test, the number of plaques decreased to 7, whereas the UPSIT score increased to 35, a score that falls within the normal range. Examples of plaques from this patient are seen in figure 2, A and B. The last patient of this series (figure 1E), a 41-year-old woman with a 6-year history of
Figure 1. Longitudinal changes in University of Pennsylvania Smell Identification Test (UPSIT) scores and plaque numbers within the inferior frontal and inferior temporal lobe regions of five MS patients (A through E). Notice that plaque number is inversely plotted. Also notice the close association between the measures across time in all cases.

Figure 2. Examples of plaques observed in a 44-year-old patient with MS whose longitudinal data are presented in figure 1D. (A) Axial T2 (2500/90) MRI scan through inferior temporal brain region shows several high signal intensity plaques bilaterally (arrows). The UPSIT score on this day was indicative of mild microsmia (30/40). (B) Axial T2 (2500/90) MRI scan of same patient taken 18 months later through the same general sector of the brain exhibits reduction in number of high signal-intensity plaques. At this time, the UPSIT score was within the normal range (35/40).

MS exhibited UPSIT scores ranging from 27 to 30 (all indicative of moderate microsmia) and plaque numbers ranging from 13 to 14.

To assess whether the previously observed association between UPSIT scores and plaque numbers within the IFTLs also was seen in the current study, we averaged the UPSIT scores and the plaque numbers for each subject across the longitudinal test days. We then computed Pearson correlations among the following measures: UPSIT scores, IFTL plaque numbers, plaque numbers outside of the IFTLs, and total plaque numbers. Only the correlation coefficient between the UPSIT scores and the plaque numbers within the IFTLs was statistically significant ($r = -0.979$, $p < 0.01$), which is in accord with our earlier findings.

Discussion. These data support our earlier observation of a nearly perfect association between UPSIT scores and the number of plaques within the IFTLs. They imply that olfactory function waxes and...
wanes in response to plaque exacerbation and remission, which partly explains discrepancies in the literature on the presence and degree of olfactory dysfunction in MS.3,4 In addition to further demonstrating the cause of olfactory dysfunction in MS patients, the current work supports the idea that MS, with its relatively discrete focal regions of inflammation, demyelination, and gliosis, may be a useful model for studying the influences of CNS lesions on sensory perception. Despite the widespread use of sensory measures, particularly auditory, visual, and somatosensory evoked potentials in the diagnosis of MS, the degree to which associations analogous to those noted here is unknown, since earlier studies mostly have focused solely on total brain plaque content. Most of these studies are further limited by small sample size and a sole focus on the diagnostic value of these tests for generally assessing MS. In a rare instance where statistical correlations were computed in a large study group (n = 63), the total area of abnormal MRI signal intensity within the entire cerebrum was used to quantify plaque activity.9 The resulting correlations between plaque load and unspecified elements of visual and auditory evoked potentials were comparatively small (0.56 and 0.38, respectively), likely reflecting dilution of the MRI measure from brain regions unrelated to the sensory pathways involved. The current work reiterates our earlier suggestion that refined assessment of plaque numbers within specific brain regions may be of considerable value in understanding the function of the structures in which the plaques are found.

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 with MS, can be dangerous. A reduced sense of smell also diminishes the flavor of flavor of foods and beverages, adversely altering the quality of life. The current study, along with our earlier work, provides for the first time a plausible explanation for the olfactory dysfunction of a common neurologic disease. Furthermore, this research suggests that physicians and others involved with the care of MS patients should be aware of the potential for olfactory loss with this debilitating neurologic disease and should counsel their patients accordingly.

References