Longitudinal Analysis of Olfactory Deficits in HIV Infection

Holly James Westervelt and Robert J. McCaffrey
University at Albany, State University of New York

Joseph P. Cousins and William A. Wagle
Albany Medical College

Richard F. Haase
University at Albany, State University of New York

The presence and degree of odor identification deficits in 55 HIV-infected (30 asymptomatic, 25 symptomatic) and 29 HIV-negative at-risk control volunteers were examined longitudinally using the University of Pennsylvania Smell Identification Test (UPSIT). Factors other than HIV infection that could account for olfactory loss (i.e., sinusitis or upper respiratory infection) were also considered by obtaining MRI scans of the nasal passages and information from an olfaction questionnaire. No differences were found among groups at the first administration of the UPSIT, with significant differences among groups emerging at the 1-year and 2-year follow-ups. The symptomatic group showed a significant decline in odor identification scores across time, while means for the asymptomatic and control groups remained stable. The presence of sinusitis or an upper respiratory infection appeared to have no effect on odor identification. The implications for these findings in relationship to cognitive decline in neurodegenerative diseases are discussed. © 1997 National Academy of Neuropsychology. Published by Elsevier Science Ltd
1991), and other non-Alzheimer’s dementias (Schiffman et al., 1990). In addition, Brody, Serby, Etienne, and Kalkstein (1991) recently reported smell identification deficits in a cross-sectional study of individuals with HIV infection.

Brody et al. (1991), administered the University of Pennsylvania Smell Identification Test (UPSIT) to three HIV+ groups: an asymptomatic, a symptomatic, and a demented group of patients. An age and gender matched HIV− group served as a control. Results showed that all of the HIV+ groups scored significantly lower on the UPSIT than did the control group, with no significant differences between the asymptomatic and symptomatic groups, and with the demented group performing the poorest. The olfactory impairments seen in the HIV+ subjects were attributed to early central nervous system (CNS) involvement of HIV infection, which worsened with disease progression.

Generally, olfactory disorders can be divided into two etiologic subtypes: obstructive/mechanical and neural (Mott & Leopold, 1991). Obstructive/mechanical disorders arise from interference with the access of odorants to the olfactory receptors and include sinusitis, allergic rhinitis, nasal polyposis, intranasal tumors, and adenoid hypertrophy (Mott & Leopold, 1991). Neural disorders result from damage to the receptor cells or olfactory pathways. Examples of neural disorders include neurodegenerative diseases, previous URI, and head injury.

Researchers often assume that the olfactory deficits observed in the various neurological diseases are attributable to CNS involvement (e.g., Brody et al., 1991). In the few studies examining olfactory deficits in neurodegenerative disorders that included rhinologic evaluation, the assumption of neural impairment as the cause of olfactory dysfunction rather than an obstructive disorder seems to have been supported (Feldman et al., 1991; Murofushi et al., 1991).

In a review of patients treated at three major chemosensory dysfunction centers, Mott and Leopold (1991) found sinus disease to be the second leading cause of olfactory deficits, accounting for deficits in 21% of the population. Despite the fact that sinus disease is one of the leading causes of olfactory dysfunction, it has seldom been ruled out as a causal factor in olfaction studies. Given the occurrence of immunocompromise in HIV infection, it is important to rule out obstructive disorders, such as sinus disease, as being responsible for olfactory loss in HIV-infected populations. The incidence of sinus disease in HIV infection has been found to range from 11% to 68% (Rubin & Honingberg, 1990). Chong et al. (1993) reported the incidence of moderate to severe sinus disease to be 15% in the HIV+ subjects and 65% in the HIV− controls. Similar findings were reported by Armstrong, McArthur, and Zinreich (1993) with 13% of the HIV+ subjects showing moderate to severe sinusitis. As in the Chong et al. (1993) study, none of the controls showed a comparable degree of sinus disease.

URIs also frequently cause olfactory dysfunction. Mott and Leopold (1991) reported that 19% of observed chemosensory dysfunctions was attributable to URI. During the course of a URI, swollen mucosa may prevent the odorant molecules from reaching the olfactory receptors (Leopold, Hornung, & Youngentob, 1991). Typically, when the swelling subsides, olfactory function returns to the pre-infection level. In some cases, however, olfactory loss remains. This loss is typically attributed to neural damage (Leopold et al., 1991). Incidence of URIs in HIV+ populations (33%) is typically not reported to be much greater than that of HIV− controls (26%) (Wallace, Rao, & Glassroth, 1993). URIs, however, do occur frequently enough in both HIV+ and HIV− populations to be considered a potential cause of olfactory loss.

The purpose of this study was to: (a) longitudinally monitor the natural history of HIV+ olfactory deficits; and (b) determine whether deficits were attributable to CNS involvement or an alternate cause.
METHOD

Subjects

The three study groups consisted of a total of 84 volunteers: 30 asymptomatic patients, including 7 females and 23 males (mean age = 37.0, $SD = 9.1$); 25 symptomatic patients, including 4 females and 21 males (mean age = 38.1, $SD = 7.4$); and 29 “at risk” controls. Controls were considered “at risk” based on their lifestyles and included 14 heterosexual females and 15 homosexual males (mean age = 36.7, $SD = 11.2$).

Inclusion Criteria

Asymptomatic volunteers. Patients in the asymptomatic group were HIV+ as determined by ELISA and confirmed by Western blot with T4 lymphocyte counts greater than 200 at the beginning of the study.

Symptomatic volunteers. Symptomatic patients were HIV+ as determined by ELISA and confirmed by Western blot with T4 lymphocyte counts less than 200 at the beginning of the study. In addition, symptomatic patients manifested one or more of the following criteria: (a) ECOG performance status of 0–1; (b) involuntary weight loss of more than 5% of body weight occurring over the 8-week period prior to enrollment; (c) Karnofsky score ≥ 50, but demonstrating a fall ≥ 20 from previous level of functioning on two assessments at least 14 days apart; (d) unexplained fever of ≥ 38.0°C for more than 7 days, despite negative proper clinical evaluation; (e) newly diagnosed oral hairy leukoplasia, oral candidiasis, or recurrence of a previously quiescent multidermatomal varicell-zoster; (f) appearance of dermatologic afflictions (e.g., psoriasis, molluscum contagiosum, or newly diagnosed seborrheic dermatitis) or; (g) appearance of chronic herpetic ulcers not responsive to acyclovir therapy.

Controls. Controls were determined to be “at risk” based on their lifestyles and were confirmed HIV– through Western blot, ELISA, and PCR testings at the beginning of the study and annually thereafter.

Exclusion Criteria

Volunteers were ineligible if they failed to meet the specific inclusion criteria listed above, or if they were prisoners, substance abusers, IV drug users, or had a history of major mental illness. Pregnant women were excluded. Volunteers who developed any acute AIDS-defining opportunistic infections, or who developed focal brain lesions larger than 1 cm³ in the area of the spectroscopic examination performed in the main project were excluded from further participation. Subjects who were involved in, or became involved in, a therapeutic trial were not excluded. Lastly, all subjects were at least 18 years of age of either gender and from any racial or ethnic background.

Subjects remained in their originally assigned groupings throughout, despite any change in HIV status.

Procedure

Smell identification was assessed using the UPSIT, which consists of 40 multiple choice “scratch and sniff” items. Raw scores were analyzed in order to provide continuity within the
literature because Brody et al. (1991) analyzed raw scores. The UPSIT was administered to all subjects at baseline, 1-year, and 2-year follow-ups.

We also devised a questionnaire, administered at each UPSIT administration, to assess common causes of olfactory dysfunction. Items on the questionnaire were obtained from a number of sources (Commetto-Muniz & Cain, 1991; Doty, Bartoshuk, & Snow, 1991; Goodspeed et al., 1986; Mott & Leopold, 1991; Schiffman, 1991; Smith & Seiden, 1991). These items, combined with the MRI data, address at least 63% of the most common causes of chemosensory dysfunction reported in the literature (a copy of the olfactory questionnaire may be obtained from the authors).

The occurrence of sinus disease was determined by MRI rather than self-report because sinus disease may be minimally symptomatic (Godofsky, Zinreich, Armstrong, Leslie, & Weikel, 1992) and is best identified with neuroimaging (Cheng, Yousem, Doty, & Kennedy, 1994). The report of head injury, URI, and other items included in the olfaction questionnaire were obtained from subject self-report.

Questionnaire data were used to: (a) identify initial olfactory deficits attributable to factors other than an HIV+ status, and (b) assess for factors not attributable to HIV infection causing changes in olfactory functioning between evaluations.

MRI scans of nasal passages were reviewed by a neuroradiologist. Nasal passages evaluated included: maxillary, ethmoid, sphenoid, and frontal sinuses; nasal cavities; and septum nasi. Scores for each sinus cavity reflected the degree of opacification such that: 0 = normal; 1 = <25%; 2 = 25% to 75%; 3 = >75% (Armstrong et al., 1993). Deviation of the septi nasi was scored such that: 0 = normal; 1 = mild; 2 = moderate; and 3 = severe.

RESULTS

Covariates

The following variables taken from the olfactory questionnaire or demographic information were considered as possible confounding variables based on theoretical reasons or the frequency of endorsement of these items: the presence of sinusitis; recent URI; smoking history; gender; and age. Other items on the olfactory questionnaire, with the exception of the presence of allergies, were endorsed too infrequently at baseline to be useful in these analyses. Furthermore, no subjects endorsed any of these items at subsequent administrations, indicating no change between administrations on these factors. As olfactory disturbances associated with allergic rhinitis are the result of nasal obstruction, not neural damage (Baroody & Naclerio, 1991), current or chronic allergy-related sinus problems could be detected with MRI scans and would, therefore, be included in the sinus score. Thus, the presence of allergies was not included as a covariate, despite reports of increasing allergic symptoms in HIV infection (Semple et al., 1988).

Sinusitis was coded as a dichotomous variable noting the presence of moderate-to-severe sinusitis, which was defined as a score of 2 or greater in at least one sinus (Armstrong et al., 1993). No significant correlations were found between the presence of moderate-to-severe sinusitis and the UPSIT score.

The presence of a URI occurring within the previous year was also coded as a dichotomous variable. A significant negative correlation was found between the occurrence of a recent URI and UPSIT scores at the baseline evaluation \( r = -0.23, p < 0.018 \). In examining the correlations for individual groups, we found a significant correlation in the symptomatic group only \( r = -0.52, p < 0.008 \). No significant correlations were found at subsequent evaluation points in the group as a whole or in any subgroup.
The following smoking variables were considered as covariates based on research by Joyner (1964) and Frye, Schwartz, and Doty (1990): a categorical variable that identified subjects as nonsmokers, ex-smokers, and current smokers, and continuous variables representing number of years of smoking, number of years since the cessation of smoking, and the average number of cigarettes smoked per day. There were no significant correlations between any of the smoking variables and the UPSIT scores.

Age and sex were also considered covariates for theoretical reasons, as previous research has suggested that females and younger adults tend to score better on tests of olfactory functioning than do males or older adults (Engen, 1991). There were no significant correlations between UPSIT scores and age or gender.

**Baseline.** A three-group analysis of variance (ANOVA) of the baseline UPSIT scores revealed no significant differences between groups \[F(2, 81) = 0.83, p = .440\]. No significant findings were revealed with the addition of covariates to the analyses.

**1-Year follow-up.** At the 1-year follow-up, there was a disproportionate loss of subjects in the symptomatic group. In addition, the symptomatic patients who were unavailable at the 1-year follow-up scored significantly worse at baseline than those who were available at follow-up. This pattern of attrition suggests a bias in the data toward the null hypothesis. Nevertheless, at this follow-up, a three group by two evaluation points (baseline—1 year) repeated measures ANOVA revealed a significant interaction between group and time for the UPSIT scores \[F(2, 65) = 5.69, p < .005\]. Comparisons between groups at both evaluation points revealed significant differences at the second administration only \[F(2, 65) = 6.15, p = .0036\]. Post-hoc contrasts at time two revealed no significant difference between the asymptomatic and control groups, with significant differences present between the symptomatic and asymptomatic groups \[t(65) = 2.95, p = .004\] and the symptomatic and control groups \[t(65) = 3.29, p = .002\]. Significant differences between groups remained unaffected when analyses were adjusted for covariates.

**2-Year follow-up.** A three group by three evaluation points (baseline—1 year—2 year) repeated measures ANOVA revealed a significant interaction between group and time \[F(2, 26) = 11.13, p < .0001\]. Comparisons between groups at each evaluation point showed significant differences at the third administration point only \[F(2, 26) = 8.10, p < .002\]. Post-hoc contrasts at time three revealed no significant differences between the asymptomatic and control groups, with a significant difference between the symptomatic and asymptomatic groups \[t(26) = 2.85, p < .009\] and between the symptomatic and control groups \[t(26) = 3.99, p < .001\]. Unlike the data at the 1-year follow-up, there were no significant differences among groups at the second administration point for this analysis. This most likely reflects the fact that attrition in the symptomatic group was again greater among those who scored poorly at the second administration. The differences in scores at the 1-year follow-up between those evaluated at the 2-year follow-up and those lost at 2 years, however, were not statistically significant. Results were unaffected by the addition of covariates.

**Descriptive and idiographic review.** The means and standard deviations of UPSIT scores and the frequencies of URIs, sinusitis, and abnormal UPSIT scores are presented in Table 1. Abnormal UPSIT scores were defined as scores falling at least two standard deviations below the mean score of the control group (raw score ≤ 34 at each administration point).

One-way ANOVAs revealed no significant differences between groups in the frequency of URIs or sinusitis at any administration point. Significant correlations between URIs and UPSIT scores only occurred in the symptomatic group at baseline (\(r = -.52, p < .008\)). The
TABLE 1
Descriptive Information

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>UPSIT M (SD)</th>
<th>N_{UPSIT&lt;34}</th>
<th>N_{URI}</th>
<th>N_{SINUS}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>30</td>
<td>36.60 (2.34)</td>
<td>8 (27%)</td>
<td>4 (13%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>1 year</td>
<td>25</td>
<td>36.96 (1.93)</td>
<td>4 (16%)</td>
<td>1 (4%)</td>
<td>6 (24%)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>36.58 (2.39)</td>
<td>2 (16%)</td>
<td>3 (25%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>25</td>
<td>36.28 (2.81)</td>
<td>4 (16%)</td>
<td>4 (16%)</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>1 year</td>
<td>17</td>
<td>34.76 (3.73)</td>
<td>6 (35%)</td>
<td>2 (12%)</td>
<td>4 (23%)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>33.43 (2.94)</td>
<td>5 (71%)</td>
<td>2 (29%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29</td>
<td>37.07 (1.58)</td>
<td>2 (7%)</td>
<td>3 (10%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>1 year</td>
<td>26</td>
<td>37.19 (1.44)</td>
<td>1 (4%)</td>
<td>5 (19%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>38.0 (1.70)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

presence of URI in the symptomatic group was also correlated with abnormal UPSIT scores \( (r = .70, p < .0005) \) at baseline, with three of the four patients reporting URIs obtaining an abnormal score. The presence of moderate-to-severe sinusitis appeared to have a negligible effect on olfactory identification, as there were no significant correlations between the presence of sinusitis and UPSIT scores within any group at any evaluation point.

One-way ANOVAs revealed significant differences among groups in the frequency of abnormal UPSIT scores at 1-year \([F(2, 65) = 3.87, p < .03]\) and 2-year follow-ups \([F(2, 26) = 9.30, p < .002]\), with more abnormal scores within the symptomatic group than in the other two groups. It is interesting to note that in the symptomatic group, 12 of the 25 patients obtained abnormal scores at least once throughout the study, compared with 9 of the 30 asymptomatic patients and 2 of the 29 controls. Furthermore, in the symptomatic group, once an abnormal score was obtained, there were no improvements above the cutoff score of 34. This was also true for only three of the nine asymptomatic patients and one of the two control subjects who obtained at least one abnormal UPSIT score.

DISCUSSION

Although no differences in olfactory identification ability were present among the three groups at the initial assessment, at the 1-year and 2-year follow-ups, deficits were observed in the HIV+ symptomatic volunteers, while the performance of HIV+ asymptomatic patients and “at-risk” controls was comparable. During the 2 years, 50% of the symptomatic group obtained an abnormal UPSIT score at least once, with none of the subjects who obtained abnormal scores showing improvement at subsequent administrations. It is also notable that at the 2-year follow-up, 71% of the symptomatic group obtained abnormal UPSIT scores. Although the 2-year follow-up data may need to be considered with some caution, given the small sample size at this evaluation point, it should be noted that those symptomatic volunteers who were available at the final assessment period most likely represent the healthiest members of the group.

In an attempt to account for the cause of the observed olfactory deficits, several potential variables were considered in addition to HIV status and the presence or absence of HIV-related symptomatology. These variables included the presence of MRI-verified sinusitis and recent URI. This study found no relationship between sinusitis and odor identification scores. The occurrence of a recent URI, however, appeared to have a substantial correlation with odor identification in the symptomatic group only, despite the fact that the incidence of URI was no greater in this group than in the asymptomatic and control groups. Even if these data represented a causal relationship between URI and olfactory deficits in those HIV+ symp-
Olfactory Deficits in HIV 563

Asymptomatic subjects with URIs, the URI data cannot account for the olfactory dysfunction found in most patients displaying identification deficits. Hence, as assumed in the Brody et al. (1991) study, the olfactory deficits found in the HIV+ symptomatic group appear to be attributable to the progression of HIV infection and not to comorbid illnesses.

Our findings differ from those obtained by Brody et al. (1991) in several important respects. Asymptomatic volunteers in our study did not differ statistically from the “at risk” control group, even at 2-year follow-up. Furthermore, at initial administration of the UPSIT, there were no differences between any of the groups. Our use of an “at-risk” control group (a recommendation made by Brody et al. (1991)) may account for these differences. The follow-up data, however, do support Brody et al.’s (1991) finding of small, but statistically significant, differences in odor identification among subjects’ UPSIT scores at different stages of HIV infection.

In sum, our data support Brody et al.’s (1991) assumption that impaired olfaction appears to be a consequence of CNS involvement of HIV infection, although peripheral nerve damage (i.e., cranial nerve I) could not be ruled out. Sinusitis and URIs contributed to olfactory identification loss to a minimal degree. Unlike the Brody et al. (1991) study, however, impaired olfaction did not appear to serve as a marker of “early” (i.e., asymptomatic HIV status) CNS involvement, but, rather, appeared only as the disease progressed.

Odor identification deficits have been described in several other neurodegenerative disease processes, which eventually display cognitive decline. These processes include Alzheimer’s disease (Doty et al., 1991; Koss, Weiffenbach, Haxby, & Friedland, 1988; Morgan, Nordin, & Murphy, 1995; Moberg, Pearlson, Speedie, Lipsey, Strauss, & Folstein, 1987; Serby, Larson, & Kalkstein, 1991), Parkinson’s disease (Doty et al., 1991; Doty et al., 1989; Murofushi et al., 1991), progressive supranuclear palsy (Doty, 1991), Huntington’s disease (Doty, 1991; Moberg et al., 1987), and other non-Alzheimer’s dementias (Schiffman et al., 1990). Odor identification deficits are often present at the early stages of the disease process (Koss et al., 1988; Moberg et al., 1987; Serby et al., 1991) and progress as the disease progresses (Moberg et al., 1987; Serby, Larson, & Kalkstein, 1991). Several of these studies have also found that odor identification deficits can occur in the absence of any significant odor detection deficits (Koss et al., 1988; Morgan et al., 1995; Serby, Larson, & Kalkstein, 1991), suggesting that odor identification deficits may be related to disruption in higher cortical functions rather than simply to odor detection deficits. This dissociation between odor identification and odor detection, however, has not yet been determined in HIV infection.

Studies that control for the lexical component of odor identification tasks have demonstrated that the cognitive demands associated with many of the odor identification tests (including the UPSIT) cannot account for the deficits found in odor identification (Moberg et al., 1987; Morgan, Nordin, & Murphy, 1995). This may not be surprising given that olfactory identification deficits appear early in these disease processes, prior to significant cognitive dysfunction. These findings suggest that dysfunction in odor identification may be a precursor to cognitive decline, and, hence, may serve as a useful tool in early detection of pathological changes in otherwise cognitively healthy patients at risk for neurodegenerative diseases, or as an indicator of the progression of the actual degenerative process. Such determinations would be valuable in allowing the patient to seek early intervention methods to slow the process of cognitive decline, prepare him/herself psychologically for the changes that may begin to occur, and to prepare his/her estate in the event that he/she should become incompetent to later do so.

The measurement of odor identification ability has the benefits of ease of administration, noninvasiveness, relatively low cost, and brief administration time. Future studies will need
to examine the sensitivity and specificity of odor identification in predicting cognitive decline in HIV infection, as well as in other neurodegenerative diseases.

REFERENCES


