Presence of Both Odor Identification and Detection Deficits in Alzheimer’s Disease

RICHARD L. DOTY,*†‡§ PATRICIO F. REYES§ AND TOM GREGOR*†

*Smell and Taste Center, †Department of Otorhinolaryngology and Human Communication and §Department of Physiology, School of Medicine, University of Pennsylvania
Philadelphia, PA 19104

and ¥Department of Neurology and Pathology, Jefferson Medical College, Thomas Jefferson University
Philadelphia, PA 19107

and Department of Neurology and Research, Coatesville Veterans Administration Medical Center
Coatesville, PA 19320

Received 3 March 1987

DOTY, R. L., P. F. REYES AND T. GREGOR. Presence of both odor identification and detection deficits in Alzheimer’s disease. BRAIN RES BULL 18(5) 597-600, 1987.—Recent studies of Alzheimer’s disease patients have demonstrated (a) marked structural and biochemical alterations in brain regions associated with olfactory function (including the olfactory bulb and entorhinal cortex) and (b) decrements in the ability to identify odorants. In light of such findings, we administered the University of Pennsylvania Smell Identification Test (UPSIT) and a forced-choice phenyl ethyl alcohol odor detection threshold test to a relatively large number of patients diagnosed, on the basis of stringent criteria, as having mild to moderately severe Alzheimer’s disease. Compared to age-, gender-, and race-matched normal controls, these individuals evidenced consistent and marked decrements on both types of olfactory tests (p<0.001). Surprisingly few of the patients were aware of their disorder, despite its appearance early in the disease process. These findings indicate that both odor identification and odor detection problems are present in dementia of the Alzheimer’s type, and raise the possibility that the odor identification problem may be secondary to the odor detection problem.

METHOD

Subjects

Thirty-four patients who satisfied stringent criteria for the clinical diagnosis of Alzheimer’s disease [25] and who had no other complicating diseases served as the primary study

ALZHEIMER’S disease is among the most common causes of dementia, accounting for at least half of demented patients over the age of 65 years [22,23]. The cost of caring for patients with this disorder is staggering, exceeding 11 billion dollars annually. Excluding advances in early detection, prevention, and treatment, the annual cost of such care by the year 2030 will likely be eight times the amount now spent on all medical and mental health research [33,37].

Recent studies of brains from Alzheimer’s disease patients reveal marked structural and biochemical alterations in regions associated with olfactory function, including the olfactory bulb and entorhinal cortex. In addition to loss of cholinergic neurons in the nucleus basalis of Meynert and noradrenergic neurons in the locus coeruleus [4,45], such brains clearly evidence large numbers of neuritic plaques and neurofibrillary tangles—classical markers of Alzheimer’s disease—in the olfactory bulb, the anterior olfactory nucleus, and the prepiriform cortex [2,15,35,36,46]. Interestingly, in addition to high levels of plaques and tangles, total loss of layer II stellate cells has been found in the entorhinal cortex of such brains [19,32]. This region receives many afferent fibers from the lateral olfactory tract, and is generally considered a major part of the primary olfactory cortex [5].

In this article we report that Alzheimer’s disease is accompanied by consistent alterations in both the ability to detect and to identify odorants, as measured by well-validated odor perception tests [10,17]. In addition, we demonstrate that the deficit is present early in the disease process. These findings confirm and extend recent observations that Alzheimer’s disease patients perform more poorly than age-matched controls on the University of Pennsylvania Smell Identification Test [24,44] and other odor identification tests [6,31], and indicate that odor detection ability, per se, is involved in the syndrome.

Subjects

Thirty-four patients who satisfied stringent criteria for the clinical diagnosis of Alzheimer’s disease [25] and who had no other complicating diseases served as the primary study

1Supported by National Institute of Neurological and Communicative Disorders and Stroke Grant NS 16365.

2Requests for reprints should be addressed to Richard L. Doty, Ph.D., Director, Smell and Taste Center, 5 Ravdin Building, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104.
population, along with 34 healthy non-institutionalized control subjects matched to this group on the basis of age, gender, and ethnic background. The patients had unexplained progressive dementia for at least six months prior to the study, and had undergone (a) psychiatric, neuropsychological, neurological, and general medical examinations, (b) diagnostic studies, such as computerized axial tomography of the brain (CAT), electroencephalogram (EEG) with compressed spectral array, cerebral spinal fluid examination, electrocardiogram, chest X-ray, and—in a few cases—magnetic resonance imaging of the brain, cisternogram, and cerebral arteriogram, and (c) blood studies, including normal complete blood count with sedimentation rate, VDRL, electrolytes, urinalysis, liver, renal and thyroid function tests, heavy metal screen and fasting blood sugar. Individuals with history of transient ischemic attack or cerebral vascular accident, or with evidence of focal neurologic signs, chronic depression, schizophrenia, significant cranio-cerebral injury, brain or visceral neoplasms, recent or remote central nervous system infection, seizures, moderate to severe hypertension, valvular heart disease, cardiac arrhythmia, or chronic syncope were excluded from consideration. According to the criteria of Cummings [7], which are based upon data from computerized tomography, electroencephalo-

graphy, and both neurological and neuropsychological testing, 10 of the patients were at stage 1, 21 at stage 2, and 2 at stage 3 of the disease. The average age of the 15 male and 19 female Caucasian patients was 70.89 years (SD=6.60) and 70.72 years (SD=6.75), respectively.

The control subjects were obtained from a computer-based registry of over 4,000 healthy individuals for whom olfactory identification data were available, and within the constraints of the matching variables, were randomly assigned to each Alzheimer's patient. These individuals consisted of persons with no major diseases or illnesses known to be associated with olfactory dysfunction [11].

Olfactory Measurement

To measure their ability to identify odors, all 68 subjects were administered the University of Pennsylvania Smell Identification Test (UPSIT), a standardized and highly reliable microencapsulated odor test sensitive to such factors as age, gender and smoking behavior [10,12]. In addition, all of the Alzheimer's patients were administered the Picture Identification Test (PIT) [42], a test identical in content and format to the UPSIT except that pictures, rather than odors, serve as stimulus items. The PIT identifies individuals who are too demented to comprehend the non-olfactory components of the UPSIT, thus permitting the elimination of their data from statistical consideration.

To measure the ability to detect odorants, 15 of the Alzheimer's patients (mainly patients who were tested later in the test program) and an equivalent number of age-, race- and gender-matched controls were administered a single staircase, forced-choice odor detection threshold test. This test, which uses the geometric mean of the last four of seven staircase reversal points as the threshold estimate, is described in detail elsewhere [10,17] and provides a measure of the subject's ability to detect low concentrations of phenyl ethyl alcohol, an odorant selected to have minimal ability to stimulate trigeminal free nerve endings within the nasal mucosa [8]. Since phenyl ethyl alcohol detection thresholds correlate relatively well with those of many other odorants (including acetic acid, diallyl sulfide, camphor, phenol, cyclopentadecanolide, scatol, and iso-valeric acid) [47], lack of sensitivity to this compound likely reflects general olfactory sensitivity.

RESULTS

Odor Identification Ability

Eight of the 34 Alzheimer's patients evidenced PIT scores less than 35 (individual test scores=13, 13, 16, 18, 21, 23, 26, and 27 out of 40), and one was unable to complete the test. Thus, the data of these nine subjects and those of their matched controls were excluded from further consideration. The average UPSIT test scores of the remaining 25 Alzheimer's disease patients (14 women and 11 men; respective mean ages=71.97 and 66.36 and SD=7.40 and 9.45) differed markedly and consistently from their 25 matched normal controls (Fig. 1A; Wilcoxon matched-pairs signed-ranks test, T=3, p<0.001) [25]. Indeed, only two of the Alzheimer's patients evidenced UPSIT scores above those of their respective matched controls. Despite the well-known decline in olfactory identification ability in normal older individuals [11], only three of the subjects had scores falling above the 25th percentile of published UPSIT norms [9] for individuals of their own sex and age (27th, 33rd, and 53rd), with 9 of the

FIG. 1. (A) University of Pennsylvania Smell Identification Test scores for patients with Alzheimer's disease and for age-, gender-, and race-matched controls. (B) Detection threshold values for phenyl ethyl alcohol for patients with Alzheimer's disease and for matched controls. Each dot signifies an individual subject's data point. Although some overlap appears between the Alzheimer's disease and control subject data when plotted in this manner, very few of the Alzheimer subjects performed better than their matched controls. See text for details.
remained falling below the 10th percentile.

To ascertain whether a relation was present between the stage of the disease and the degree of olfactory impairment, a Mann-Whitney U-test [38] was performed between the test scores of the subjects in Stage 1 (n=9) and Stage 2 (n=16) of the disease. No statistically significant difference was apparent (U=58.5, p>0.20).

**Odor Detection Ability**

In addition to the deficit in odor identification, the Alzheimer's patients evidenced, relative to their controls, significant elevations in detection threshold values (Fig. 1B; Wilcoxon matched-pairs signed-ranks test, T=1, p<0.001). Indeed, two of the 15 subjects appeared totally anosmic, being unable to detect the highest concentration of the series. The UPSIT scores of these two patients (values=9 and 13) were also indicative of total anosmia. As in the case of odor identification, the decreased sensitivity was consistent across patients, with only one patient evidencing a threshold value below that of its matched control (and in this case the difference was less than 1/20ths of a log concentration unit).

In a manner analogous to odor identification, no significant differences were present between the stage of the disease and the odor detection threshold values (median log threshold score of the five Stage 1 subjects=-2.63 with range=-4.38 to -1.00; median log threshold score of the 10 Stage 2 subjects=-2.69 with range=-4.13, to -1.63; U=20, p>0.20).

**Patient's Awareness of Olfactory Dysfunction**

Given the consistency of the dysfunction, it is surprising that the olfactory disorder observed in this study has not been previously generally realized. Although this may be due, in part, to the lack of routine testing of the olfactory sense, it is also possible that the patients themselves are usually unaware of the problem. The latter appears to be the case, since only two of the 34 Alzheimer's disease patients responded affirmatively to the question, posed before olfactory testing, "Do you suffer from smell and/or taste problems?"

**DISCUSSION**

The present study, by using well-defined subjects and olfactory tests of known reliability and validity, unequivocally demonstrates that olfactory dysfunction is consistently present in patients diagnosed as having Alzheimer's disease. Furthermore, this work indicates that the dysfunction is apparent in the earliest definable stages of the disease process (suggesting that considerable damage has occurred to the olfactory system by that time) and likely represents a problem in both odor identification and detection, rather than solely anosmia. These observations confirm and extend recent observations that Alzheimer's disease is associated with a decrement in the ability to identify odors [6, 24, 31, 44].

The present study is the first, to our knowledge, to examine olfactory detection thresholds in patients with Alzheimer's disease. Our finding of a threshold deficit in Alzheimer's disease suggests the possibility that the odor identification problem may be secondary to the odor detection problem, since odor detection ability is a prerequisite for odor identification ability. Although a correlation between UPSIT scores and detection threshold scores is not necessary for such a hypothesis to be true, it is of interest that a weak correlation was present between the odor identification test scores and the detection threshold values in this study (Spearman r=-0.45, 0.05<p<0.10).

The physiologic basis of the olfactory dysfunction of Alzheimer's disease is unknown. Although neuritic plaques and neurofibrillary tangles are present throughout olfactory-related structures in patients with Alzheimer's disease [15, 32, 35, 36, 46], it should be noted that other dementia-related diseases, including Huntington's chorea, Parkinson's disease, and Korsakoff's psychosis, are also commonly accompanied by olfactory deficits [1, 13, 20, 21, 27, 29, 43]. It is of interest to note that several of these diseases evidence lesions in neural pathways which are similarly damaged in Alzheimer's disease, including connections between the olfactory cortex (periamygdaloid, prepyriform, entorhinal) and brain structures involved in memory and cognition (e.g., amygdala, dorsal medial nucleus of the thalamus, hippocampus) [3, 14, 16, 28].

Since the primary neurons of the olfactory system are directly exposed to the outside environment, they are particularly susceptible to adverse consequences of viruses and environmental toxins [14]. For this reason, and the fact that olfactory primary neurons evidence atypically active transport mechanisms [38], the olfactory pathway is a principal means of viral entry into the central nervous system, even for viruses experimentally introduced into a body organ or cavity [30, 40, 41]. For example, intraperitoneal inoculation of mice and hamsters with St. Louis encephalitis virus results in a marked rise in virus titer in the olfactory neuroepithelium within a few days, followed by subsequent respective rises in the olfactory bulb and the remainder of the brain [30]. Thus, it is perhaps not surprising that inoculation of rodents with some viruses can result in necrosis of the olfactory neuroepithelium, the olfactory bulbs and tracts, and the prepyriform cortex [18, 34]. These observations, along with recent findings that a number of dementia-related diseases are associated with olfactory dysfunction, leads to the intriguing hypothesis that agents responsible for some of these diseases may enter the central nervous system via olfactory pathways. Research on this point is obviously urgently needed.

Regardless of the neuropathological basis of the olfactory disorder associated with Alzheimer's dementia, the present data suggest that olfactory dysfunction is a common and early correlate of the disease. Whether such dysfunction also signals the early onset of other major dementia-related central nervous system disorders merits investigation.

**REFERENCES**


