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Olfactory Impairment in Presymptomatic Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) impairs olfaction, but it is uncertain how early this occurs in the disease process and whether the effect can be accounted for by other behavioral or genetic markers of the disease. We administered the Brief Smell Identification Test (BSIT) to 471 older people without dementia or cognitive impairment who then completed annual clinical evaluations and brain autopsy at death. BSIT score was associated with more rapid decline in episodic memory and with increased risk of developing incident mild cognitive impairment (MCI), even after controlling for baseline level of episodic memory and possession of an apolipoprotein E $\epsilon 4$ allele. In 34 people who died without evidence of cognitive impairment, lower BSIT score was associated with higher level of AD pathology, even after controlling for $\epsilon 4$ and for level of episodic memory function when olfaction was assessed. These analyses suggest that among older people without clinical manifestations of AD or MCI, olfactory dysfunction is related to both the level of AD pathology in the brain and the risk of subsequently developing prodromal symptoms of the disease and that these associations persist after accounting for the effects of other recognized behavioral and genetic markers of the disease.

Alzheimer's disease (AD) is a leading cause of disability in old age, and the public health challenges posed by the disease are likely to increase in the coming decades with the aging of the United States population. Definitive classification of AD currently requires a brain autopsy, underscoring the need for biological or behavioral markers of the disease in the living. In particular, markers are needed to support early diagnosis because disease-modifying therapeutic compounds for AD are under development, and it is generally assumed that such compounds will be most effective early in the disease course before pathology is widespread [1-3]. In addition to certain practical characteristics (i.e., reliable, non-invasive, simple to perform), the ideal biomarker should be related to AD neuropathology [1] in those with little or no clinical evidence of the disease. In view of the substantial clinical and neuropathologic heterogeneity of AD, accurate early diagnosis will most likely require the use of several markers in conjunction. In this context, therefore, markers that have little or no correlation with other markers will be most useful.

In the present study, we focus on olfactory impairment as an early sign of AD. With clinical and neuropathologic data from the Rush Memory and Aging Project, we previously showed that difficulty identifying familiar odors predicted subsequent development of mild cognitive impairment, a precursor to dementia in AD [4], and was robustly correlated with level of AD pathology on postmortem examination [5]. Here, we conduct further analyses of individuals without dementia or MCI at study enrollment to test whether the association of olfactory dysfunction with AD is evident in this well functioning subgroup and whether it persists after accounting for other recognized behavioral and genetic markers of the disease.

METHODS

Participants

All subjects were from the Rush Memory and Aging Project, a longitudinal clinicalpathologic study of common chronic conditions of old age [6]. Eligibility for the present analyses required intact cognitive functioning and a valid score on the Brief Smell Identification Test [7] at the time of study enrollment; 471 individuals met these criteria, and analyses are based on this group; 383 were excluded because MCI or dementia was identified on the baseline clinical evaluation (below). Study subjects had a mean age of 79.3 (SD = 7.0) at baseline and a mean of 14.5 years of education (SD = 2.9); 76.2% were women and 91.3% were white and non-Hispanic (Table 1).

Clinical Evaluation

At baseline and annually thereafter, participants had a uniform clinical evaluation that included a medical history, a complete neurological examination, and administration of a battery of 21 cognitive tests. Seven of these assessed episodic memory: immediate and delayed recall of the East Boston Story and Story A from Logical Memory and Word List Memory, Word List Recall, and Word List Recognition. As previously described, we formed a composite measure of episodic memory by converting raw scores on each test to z scores, using the mean and standard deviation from the full cohort, and then averaging the z scores to yield the composite [8,9]. In addition, ratings of impairment in 5 cognitive domains were made by a neuropsychologist, guided by educationally adjusted cutoff scores on a subset of the tests [10].

On the basis of this evaluation, an experienced clinician diagnosed MCI, dementia, and AD, as previously described [4,11]. Dementia required a history of cognitive decline and impairment in at least two cognitive domains, one of which had to be memory to meet criteria for AD [12]. Persons who did not meet criteria for dementia but who showed evidence of impairment in at least one cognitive domain were classified as MCI. These criteria for dementia, AD, and MCI have been widely used and pathologically validated in this and other [13,14] cohorts.

Assessment of Odor Identification

Odor identification was assessed with the Brief Smell Identification Test [7]. For each item, a microcapsule containing a familiar odor was scratched with a pencil and placed under the nose of the participant who matched the smell with one of four choices. There are 12 items and the score is the number of correct recognitions. In previous research, this score has been shown to correlate with the 40-item University of Pennsylvania Smell Identification Test from which it was derived [15].

Apolipoprotein E Genotyping

Apolipoprotein E genotyping was done blinded to all other study data using methods adapted from Hixson and Vernier [16], as previously described [17,18]. In all analyses,

individuals were dichotomized into those with at least one copy of the $\epsilon 4$ allele (i.e., $\epsilon 2/4$, $\epsilon 3/4$, or $\epsilon 4/4$) versus those without a copy (i.e., $\epsilon 2/2$, $\epsilon 2/3$, or $\epsilon 3/3$).

Neuropathological Evaluation

A standard protocol was followed for brain removal, sectioning and preserving the tissue, and quantifying pathologic findings, as reported in more detail elsewhere [13,14]. Tissue from five brain regions (midfrontal gyrus, inferior parietal gyrus, middle temporal gyrus, entorhinal cortex and hippocampus (CA1/subiculum)) was cut into 0.5-cm-thick blocks, embedded in paraffin wax, and sectioned at 6 mm and stained with modified Bielschowsky silver. For each of the five brain regions of interest, a neuropathologist or trained technician, blinded to all clinical data, separately counted neuritic plaques, diffuse plaques and neurofibrillar tangles in a 1-mm² area using a 610 objective (with 610 eyepiece) in the site judged to have the most of a given type of pathology. For each type of pathology in each region, the raw count was divided by the SD of all counts of that pathology in that region to yield a standard score. These standard scores were averaged to produce a composite measure of cortical plaques and tangles and summary measures of each type of pathology, as reported previously.

Data Analysis

We used a proportional hazards model [19], to test the relation of odor identification score to risk of incident MCI. The analysis controlled for age, sex, education, presence of the $\epsilon 4$ allele, and level of episodic memory function. We used a mixed-effects model [20] to characterize change in a composite measure of episodic memory and to test the relation of odor identification score to rate of memory decline, while accounting for initial level of memory function and controlling for age, sex, and education, and $\epsilon 4$. In a final analysis, we regressed a composite measure of AD pathology on odor identification score in a linear regression model adjusted for age at death, sex, education, time from olfactory testing to death, $\epsilon 4$, and episodic memory.

RESULTS

At the time of study enrollment, scores on the Brief Smell Identification Test ranged from 1 to 12 (mean = 9.2, SD = 1.9), with higher values indicating better ability to identify familiar odors.

Odor Identification and Incidence of MCI

During up to 5.5 years of follow-up (mean = 2.7, SD = 1.4), 155 individuals (32.9%) developed MCI. To determine the relation of odor identification to risk of developing MCI, we constructed a proportional hazards model. In addition to controlling for age, sex, and education, the model included terms for two established disease markers: possession of at least one copy of the apolipoprotein E $\epsilon 4$ allele (present in 19.8%) and level of episodic memory function (mean = 0.39, SD = 0.47) as indicated by a previously established composite measure [8,9]. In this analysis, risk of MCI was associated with odor identification test score (hazard ratio = 0.874; 95% confidence interval: 0.812, 0.941). Thus, a person who made 4 errors (score = 8) was about 50% more likely to develop MCI than a person who made one error (score = 11).

Odor Identification and Episodic Memory Decline

Decline in episodic memory is one of the earliest clinical manifestations of AD, often beginning several years before a clinical diagnosis can be made [21]. Table 1 shows the distribution of the composite measure of episodic memory at baseline. To test the relation of

odor identification to change in episodic memory, we constructed a mixed-effects model with the composite measure of episodic memory as the outcome. The model also included terms to control for the effects of age, sex, education, $\epsilon 4$, and level of episodic memory at level. In this analysis, lower odor identification score was robustly associated with more rapid decline in episodic memory (parameter estimate = 0.014, SE = 0.004, $p < 0.001$). Odor Identification and Alzheimer's Disease Pathology

An ideal early marker of AD would be related to the underlying pathology in people with little or no clinical evidence of the disease. At the time of these analyses, we identified 34 individuals who met 2 criteria: (i) no evidence of cognitive impairment on baseline or follow-up evaluations; (ii) died and underwent brain autopsy. These individuals died at a mean age of 85.2 (SD = 6.4), they had a mean of 14.0 years of education (SD = 2.2), 67.7% were women, and 94.1% were white and non-Hispanic (Table 2). In a uniform neuropathologic examination done blinded to all clinical data, crude counts of neuritic plaques, diffuse plaques, and neurofibrillary tangles in 5 brain regions were converted to a standard scale and averaged. Because the resulting distribution was skewed, a square root transformation was used (see Table 2). In a linear regression model adjusted for age, sex, education, time from olfactory testing to death, $\epsilon 4$, and episodic memory function when olfaction was tested, lower odor identification score was associated with higher level of AD pathology (parameter estimate = -0.063, SE = 0.027, $p = 0.028$).

DISCUSSION

We studied the relation of the ability to identify familiar odors to the development of AD in nearly 500 older persons without evidence of cognitive impairment at enrollment. The analyses suggest that among older persons without the clinical manifestations of AD or its precursor, MCI, olfactory dysfunction is related to both the level of AD pathology in the brain and the risk of subsequently developing prodromal symptoms of AD in the form of MCI and declining episodic memory.

It has long been recognized that olfaction is impaired in persons with clinically diagnosed AD [22-27]. Olfactory function is also impaired in MCI [26-31], a precursor of AD, and in those with at least one copy of the apolipoprotein E $\epsilon 4$ allele [28,32-34], a well established risk factor for AD. In previous research in this cohort, we showed that odor recognition performance predicted incidence of MCI and AD, rate of cognitive decline, and level of AD pathology on postmortem examination [4,5]. The present analyses extend these findings by showing that the association of olfactory function with the clinical and pathologic manifestations of AD can be seen in otherwise asymptomatic individuals and that it persists even after accounting for the effects of other recognized behavioral and genetic markers of the disease. These data suggest that olfactory testing, when combined with other behavioral and biologic markers, may contribute to early detection of AD.

Prior research in this cohort suggests that the association between olfactory dysfunction and clinical AD is largely due to the accumulation of AD pathology, particularly neurofibrillary tangles, in central olfactory regions, especially entorhinal cortex and hippocampus [5]. The involvement of these sites is important because they are thought to be among the first areas affected by the pathologic changes of AD [36-38]. Thus, olfactory symptoms might conceivably precede cognitive impairment in AD by a substantial period of time. In addition, decline occurs in other sensory systems with advancing age in association with cognitive decline [39]. Because the entorhinal cortex processes input from multiple sensory modalities, it is possible that subtle changes in other sensory functions might be early signs of AD.

Confidence in these findings is strengthened by several factors. The diagnoses of MCI and AD were based on uniform structured clinical evaluations and widely accepted criteria. Rates of participation in follow-up clinical evaluations and brain autopsy were high. Odor identification was assessed with a standard scale. Episodic memory and AD pathology were assessed with previously established composite measures. An important limitation is that the cohort is selected so that the generalizability of the findings remains to be determined. In addition, securely establishing the value of olfactory testing in early diagnosis will likely require more extensive assessment of olfactory processing conducted proximate to death in a larger group of people.

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Table 1

Descriptive information on the 471 study participants at baseline*

Characteristic	Value
Age	79.3 (7.0;55-100)
Education	14.6 (2.9;5-28)
Women, %	76
White non-Hispanic, %	92
Brief Smell Identification Test	9.2 (1.9;1-12)
Episodic memory	0.39 (0.47;−0.87-1.85)
Apolipoprotein E ε4	20

* Data are presented as mean (standard deviation; range) unless otherwise indicated.

Table 2

Descriptive information on the 34 study participants who died without cognitive impairment and underwent brain autopsy*

Characteristic	Value
Age at death	85.2 (6.4; 67-98)
Education	13.9 (2.2;11-19)
Women, %	68
White non-Hispanic, %	94
Brief Smell Identification Test	8.6 (1.8;6-12)
Episodic memory	0.35 (0.46;−0.63-1.23)
Apolipoprotein E ε4	21
Months from olfactory test to death	26.0 (12.9;3.5-47.1)
Composite AD pathology	0.58 (0.33;0.05-1.18)

* Data are presented as mean (standard deviation; range) unless otherwise indicated.