Use and Limitations of Olfactory Tests in Diagnosis of Alzheimer's Disease

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Abstract

Olfaction may be one of the most powerful aids in diagnosis of Alzheimer's Disease (AD) that has been introduced in quite a while, as it locates the earliest neuropathological changes in the disease. Although clinical diagnosis of AD requires several steps, including a medical history, mental status evaluation, clinical examination, and laboratory tests, these are not always seen as part of the same continuum. One of the objectives of this article is to demonstrate the intrinsic link between these steps in order to provide accurate progress in the research and practice of AD diagnosis using olfaction. Issues of medical and environmental history, diet, and genetics must be considered in order for these procedures to accurately impact the diagnostic regimen.

Keywords: Alzheimer's disease; early diagnosis; olfaction; environment; medication use; etiology

Introduction

Several reports[1-4] have demonstrated that investigation of olfaction may be one of the most powerful aids in diagnosis of Alzheimer's Disease (AD) that has been introduced in quite a while. For example, Bacon, Bondi, Salmon, and Murphy[5] found preclinical changes in olfaction for those individuals who later developed the disease. What makes this truly important is that the findings occurred up to one year before onset of classic AD symptoms. With such a potentially powerful tool in diagnosis potential comes for great things, but the limitations of such tests must also be acknowledged. As researchers develop tests and diagnostic tools, these limitations must be especially considered to ensure accuracy and environmental validity for the populations being tested.

Although clinical diagnosis of AD requires several steps, including a medical history, mental status evaluation, clinical examination, and laboratory tests, these are not always seen as part of the same continuum. One of the objectives of this article is to demonstrate the intrinsic link between these steps in order to provide accurate progress in the research and practice of AD diagnosis.

Olfaction and AD

For quite some time[6], it has been known that the earliest neuropathological changes in Alzheimer's Disease (AD) are found in the entorhinal cortex[7-8], thus compromising the sense of smell early in the etiology of the disease. The physiological processes of the pathology begin in the olfactory bulb and can severely limit the abilities of that sense*.

Before consideration of diagnostic tools is discussed, it must be mentioned that research summarized by Cain and Stevens[10] showed that chronological age is strongly associated with impairment of the sense of smell. Doty, Shaman, Applebaum, Giberson, Sikorsky, and Rosenberg[11] reported that by age of eighty, scores for three-quarters of individuals tested were nearly chance performance. Olfaction in older adults is influenced by disease, dementia, nutritional deficiencies, environment, medication use, and insults and injuries. Among the most powerful of these may be the effects of environmental conditions that would provide heightened risk of insult and injury to the olfactory system[12,13], which without a full medical history exploring, the diagnostic procedures will not function effectively.

Limitations and considerations

It is vitally important at this point to point out that specific controls must be put in place for the appropriate diagnosis of AD aided by olfactory tests. Moberg and colleagues[14] compared AD and schizophrenic patients to healthy controls, and found huge differences between the pathological groups and the controls. What is essential to recognize here is that, using the Mini Mental State Exam (MMSE)[15] to screen, the control participants were all assessed as being cognitively intact ($\underline{M}$ = 29.8 ±0.5) and having an UPSIT score of 36.5 (±2.5), far better than typically reported for people in that age group in other reports[11]. Cognitively intact, community-dwelling

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centenarians have also demonstrated superlative performance on olfaction tests[16], supporting the conclusion that decreased olfaction is a potential indicator of pathology, but also is subject to risks that must be controlled for. In order to control the largest number of risks, we must consider where changes in olfactory abilities occur.

Lehrner, Brucke, Dal-Bianco, Gatterer, and Kryspin-Exner[17] helped to forward answers to where losses in olfactorial ability occur, in either central or peripheral systems, and why. They posited that the decrements are primarily in central processing deficits of the central nervous system. They examined olfactorial abilities of 22 AD patients (2 males, 20 females; mean age =77.4 years ±8.8), 21 PD patients (13 males, 8 females; mean age = 67.9 ± 10.2), and 19 healthy, non-demented adults (4 males, 15 females, mean age = 67.8 ±15.1). They found that odor memory and identification was very poor for AD patients. Curiously, odor memory was intact for non-demented PD patients, although they had poor identification abilities, thus strengthening the case for olfactory tests in early AD diagnosis due to the differentiation between these syndromes at early stages. They concluded that these findings supported the notion that the olfactory system is capable of odor memory processes without adequate verbal labeling[18], and also that olfactorial memory testing was an effective aid to AD diagnosis when used with other tests.

When we have any stimuli presented, overt or covert labeling occurs, invoking lexical abilities within an individual. The impact of lexical functioning and detection sensitivity on the deficit of odor identification in AD was studied in persons diagnosed with probable and questionable AD by Morgan, Nordin, and Murphy[1]. Tests consisted of lexical-based odor identification (UPSIT), lexical-based picture identification (PIT)[19], picture-based odor identification (Child-odor-identification test[20]), and odor-detection thresholds of 18 probable AD and six questionable AD adults and matched groups of normal adults. Their results suggest four specific conclusions. First, odor identification is poorer than picture identification in probable and questionable AD. Second, odor identification continues to be poor even when lexical demands are eliminated. Third, odor detection does contribute to the odor-identification deficit, but does not account for it completely. Finally, they concluded that odor identification tests have a correct AD classification rate of 83-100%. This was superior to the 25% and 58% rates provided by color naming and color association tasks. This multimodal approach to AD testing is a compelling reason to examine further the integration of sensory modalities both in health and disease states.

Even validated measures for intensely researched topics in aging are not always completely accepted, as is the case of the multitude of assessment instruments for Alzheimer's disease[21,22]. Alzheimer's has a relatively consistent onset, clinical presentation, and course of illness and relatively definable manifestations that can be defined using neuroimaging and examination of neurologic and motor changes. It also has a relatively consistent pathologic picture. Although Alzheimer's is among the most stereotypic of disease processes, it is still considered to be a diagnosis of exclusion[23] due to differences of opinion on issues of diagnostic tools and concerns over quality of life after such a diagnosis. Diagnosis is especially difficult as there is minimal understanding of the etiology of the disease.

Special considerations of genetics

The etiology of AD and many other neuropathologies are understood to be multifactorial, and one of the most researched physiologic areas in recent years has been in oxidative stress. This pursuit of antioxidants has stemmed from the brain's high oxygen consumption, abundant lipid content, and relative paucity of antioxidant compounds as compared to other tissues[24,25]. As one of the major characteristics of AD is the presence of amyliod plaques in the brain, it is important to explore alpha-tocopherol and other substances effective in combating lipid peroxidation and reducing the neurotoxicity of Amyliod η (A η), a major component of these plaques. Diet may play an important role in AD onset, but whether direct, through expression of genotypes, or both is yet to be seen.

As there is evidence for genetic contributions to propensity towards developing AD[26], genetics should play a role in the interpretation of olfactory tests in this capacity. One of the more powerful genetic markers for a heightened propensity to develop AD and other dementing illnesses is the Apolipoprotein E κ4 (APO-E4) allele. There are three common alleles at the locus of APO-E accounting for most of the APO-E alleles globally: κ2 (7%), κ3 (78%), and κ4 (15%)[27]. These variations account for 50% of the genetic load of AD, especially in the age onset groups of 50-80 years of age[28,29]. Examining individuals with and without the APO-E4 allele, Bacon, Bondi, Salmon, and Murphy[5] found that the presence of the allele decreased odor sensitivity regardless of cognitive status.

Homozygous APO-E4 carriers are eight times as likely as a non-APO-E4 person, while heterozygous carriers are 2.2 to 4.4 times as likely to develop AD[30,31]. In the Royal Perth Hospital trials[32], the presence of APO-E κ4 identified only 48% of autopsy-confirmed cases of AD instead of the 75% anticipated from previous literature. The Royal Perth Hospital study did, however, find that patients, who were found to have other neuropathological diagnosis, none carried the κ4 allele, so the specificity and positive predictive value of κ4 in AD diagnosis was 100%. According to a report of the National Institute on Aging/Alzheimer's Association Working Group (1996), some individuals with Apolipoprotein E κ4 (APO-E4) alleles survive to old age and remain cognitively intact. This seemingly paradoxical situation leads to the question of what other influence lead to the onset of AD and other pathological situations.

Over the past few decades it has become clear that olfactory functions are compromised in a number of dementing illnesses[33]. It is thought that the olfactory system is capable of odor memory processes without adequate verbal labeling[18], thus olfactorial memory testing would be an effective aid to AD diagnosis when used with other tests.

This premise was supported by the work of Razani, Chan, Robideau, and Murphy[34], who were able to maintain 95% and 87.5% AD classification rates through use of odor naming and odor association rates, respectively. This was superior to the 25% and 58% rates provided by color naming and color association tasks, perhaps due to the minimal deterioration of the striate cortex in AD[**]. Bacon, Bondi, Salmon, and Murphy (1998) reported finding changes in olfactory function with Alzheimer's disease and with APO-E status. However, Murphy, Bacon, Bondi, & Salmon[5] (1997) found that the APO-E type is associated with deficits in odor identification ability in nondemented older adults as well as in those with dementia. Thus, neither APO-E status nor olfactory testing alone should be considered as too strong an indicator of propensity toward Alzheimer's susceptibility.

Although there have been many excellent studies dealing with the topic of aging and olfaction, there are methodological issues that prevent most studies from answering important questions concerning the reasons for the diminishment of abilities that most extent research has found. For example, it is surprising that the screening procedures of few studies have included questions about pharmaceutical use of participants. Ship and Weiffenbach[37] reported that general medication use did not statistically influence olfactory abilities, but they did not examine differences in specific drugs. Not all pharmaceutical products influence olfaction, but many broad categories do[38]. For instance, one classification that typically influences olfactory abilities is anticholinergics. This classification of drugs affects olfaction directly by drying and decreasing mucosa[39] as well as by causing or exacerbating cognitive impairment[40]. For the purposes of this study, we will consider pharmacological interactions as a potential confound, but not as an exclusion criterion.

In the general population, Larsson and Bäckman[41] and Murphy[2] et al. suggest that deficits in odor recognition and identification by older adults may be largely attributable to cognitive limitations, especially vocabulary ability. Although they did not control for environmental or pharmacological histories, both research groups posited that vocabulary would be an optimal choice for examination of concurrent decline. This assertion is based on the understanding that odor identification is a semantic memory task in that it refers to an individual's general knowledge or experience with a specific odorant[42,43]. If further evidence is obtained that this is not necessarily the case, it may lead to conclusions that there is some separation of the various memory systems in the individual lexicons for stimuli maintained by each participant. Further, this evidence might mean that these individual lexicons may be able to access each other only to a limited degree.

Considerations of multimodality

According to Herz (1998), "*odors are the best cues to memory*"[***]. Her emphatic statement is based on a multimodal study of memory cues from odors, words, music, visual, and tactile stimuli rated by accuracy and emotional response to the target stimuli. Until studies such as hers, it had been assumed that when paired with other modalities, odors had only modest associative abilities.

A multimodal study of sensory thresholds by Stevens, Cruz, Marks, and Lakatos[44] demonstrated that aging has a detrimental effect on sensation, however substantially different levels of decline for each sensory modality. Their study is one of the few in the literature that explores olfaction as related to other sensory systems and serves as a reminder of how little is known about olfaction compared with other modalities of sensation.

Schab[42] states that one way to conceptualize a hypothesized deficit of odor memory as compared to visual memory is to consider it from two different sources. The first source is poor or nonexistent odor imagery abilities. The second is a relatively low ability of odors to cue the retrieval of odor names. According to Engen[45], odors tend to be named with reference to certain contexts in which they occur or are used and with associations at the same level of abstraction. Odor studies are rarely contextual, so inherently have bias under Schab's paradigm. Disparate contextual cues are analogous to the "cross talk" between concurrent streams of information that can complicate encoding in the working memory paradigm expressed by Stoltzfus, Hasher, and Zacks[46]. If information is out of context, attention is divided at encoding, resulting in less successful comprehension and retrieval.

Conclusions and recommendations

The intent of this article has been to expound on the growing interest in the use of olfaction as a diagnostic aid in Alzheimer's Disease. Specific points outlined in this article have demonstrate that olfaction is one of the most important new avenues of research in the topic, but that issues of medical and environmental history, diet, and genetics must be considered in order for these procedures to accurately impact the diagnostic regimen. Baltes and Lindenberger[47] posited that as we age intelligence does not really decline significantly, but rather that the expression of intelligence becomes limited through decreased sensory functioning. Thus, novel approaches can overcome the limitations of previous investigations. It is logical for us to pursue the same potential in our understanding of Alzheimer's disease and its diagnosis.

* For a review of olfaction in other neurodegenerative pathologies, see Mesholam, Moberg, Mahr, and Doty, 1998[9]

** For relationships between color and odor, see: Kemp, & Gilbert, 1997[35]; Zellner, & Krautz, 1990[36]

*** p. 673, italics in original

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