Should olfactory dysfunction be used as a biomarker of Alzheimer's disease?

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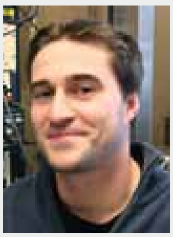

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"When combined with other markers, however, olfactory perceptual screens for Alzheimer's disease disposition could prove to be useful to enhance diagnostic sensitivity and specificity for Alzheimer's disease..."

A major effort in Alzheimer's disease (AD) research is driven by the need to identify biomarkers of the disease. Such biomarkers would ideally predict a prognosis of AD prior to the development of significant neuropathology and subsequent loss of cognitive function. Early indicators of disease are especially important for implementing interventions while brain systems are still functioning relatively normally. Thus, determination of an accurate and robust biomarker model may be pivotal in reducing the global impact of AD.

Currently, several biomarkers of AD are being explored. Concentrations of amyloid-β and tau in the cerebrospinal fluid, ^{18}F-fluorodeoxyglucose, amyloid-β and hippocampal volume imaging, and neuropsychological testing are all being explored for their utility in predicting the onset and stage of AD [1]. A recent overview of the typical progression of these biomarkers has resulted in a timeline model of AD progression wherein abnormalities are first detected in amyloid-β biomarkers, followed by neurodegenerative and cognitive biomarkers [2].

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While presently not in routine use, perceptual disorders may also serve as biomarkers for AD. Perceptual disorders are common in AD, including losses in olfactory [3,4], visual [5] and auditory perceptual abilities [6]. Perhaps owing to the olfactory system's close associations with emotion and memory [7] – two cognitive features often impacted in AD – deficits in olfaction are commonly reported in the disease. A 1996 meta-analysis of 43 studies on olfactory perception and AD found significant deficits in odor detection thresholds, odor identification and odor recognition in presumed and confirmed AD cases in comparison to age-matched controls [8]. Such deficits have even been related to genetic factors associated with increased risk for AD. For instance, Gilbert and Murphy demonstrated that people carrying one or two copies of the ε4 allele of apolipoprotein E had significant odor recognition deficits in comparison to those not carrying this allele [9]. Importantly, the authors also showed that this effect was specific to olfactory, but not visual stimuli [9], highlighting the power and sensitivity of using olfaction as a diagnostic tool in this context. Finally, adding to the strength of olfactory screens as potential early diagnostic tests for AD prior to other substantial cognitive loss, Devanand and colleagues found that addition of olfactory function assays to neuropsychological tests and MRI of brain volume (hippocampus and entorhinal cortex) enhanced the sensitivity of predicting the conversion of mild cognitive impairment to AD [10]. These studies have suggested that olfactory dysfunction may have potential utility as a biomarker in assessing the onset and progression of AD.

Neurological investigations have uncovered that multiple brain regions crucial for normal olfactory function are severely impacted by AD pathology [11]. These include the initial site of olfactory neural conduction (the olfactory epithelium in the nasal cavity), the olfactory bulbs, the primary olfactory cortices and higher order regions involved in odor recognition and

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memory (entorhinal cortex and hippocampus). Amyloid-β plaques and neurofibrillary tangles, the two core pathological hallmarks of AD, are found differentially across these structures [12]. To date, relatively few studies have attempted to link the prevalence of these pathologies with olfactory function. One such study suggested that in aged persons (87 ± 6 years of age), olfactory loss may be due to neurofibrillary burden in central olfactory processing regions [13] and another showed that the severity of tau pathology in the olfactory system correlates with neuropathological staging of AD progression beginning at a stage associated with mild cognitive impairment [14]. Work in rodent models of AD has provided evidence for both neurofibrillary and amyloid-β-related mechanisms of olfactory loss [15,16]. For instance, recent studies from our group in transgenic mice overexpressing mutant human amyloid precursor protein, show that these mice display age-dependent olfactory dysfunction in comparison to age-matched control mice. These deficits in olfaction include abnormal odor investigation, odor habituation (short-term memory) and odor discrimination [16]. Furthermore, these abnormal behaviors correlate with the spatiotemporal deposition of fibrillar and/or nonfibrillar amyloid-β. Interestingly, we found that amyloid-β burden occurs first in the olfactory bulbs followed by deposition in the olfactory cortex and hippocampus. These data suggest that amyloid-β deposition in the olfactory bulb and olfactory cortical areas may contribute to olfactory sensory loss in early- and late-life, respectively.

> “...multiple brain regions crucial for normal olfactory function are severely impacted by Alzheimer’s disease pathology.”

Research over the past 30 years has conclusively established that olfaction is impaired in AD, but not invariably [17]. Recent research has also begun to elucidate the possible mechanisms of olfactory loss in AD. However, is olfactory dysfunction a suitable biomarker for AD? The answer to this question may not be simple. Olfactory function can be quite variable within a population. Furthermore, over half of adults 60 years of age and older have problems smelling [18], which is far greater than the proportion of adults over 60 years of age with AD [19]. Common causes of olfactory loss include head-trauma, nasal disorders (including those induced by environmental exposure to smoke and allergens), endocrine dysfunction, congenital syndromes and some neuropsychiatric disorders [18]. The high prevalence of anosmia in several other dementias, including Parkinson’s disease [20], Lewy body disorder [21] and frontotemporal dementia [22], indicates that olfactory deficits alone, at least as currently assessed, are not sufficiently specific as a biomarker for AD by themselves [10]. When combined with other markers, however, olfactory perceptual screens for AD disposition could prove to be useful to enhance diagnostic sensitivity and specificity for AD, especially given that they are noninvasive, reflect the functioning of brain circuits affected at early stages of AD, and are free of expensive and technical equipment that may preclude the use of other biomarkers in regions of the world where such technology is not available.

Beyond their possible use in a diagnostic ‘profile’, olfactory assays may find greater utility as a noninvasive index of altered function in the brain regions underlying olfactory deficits, which is currently detected mainly by neuroimaging [22] or neuropathological examination [14]. Olfactory measures might, therefore, be used in conjunction with existing measures to track the progression of disease in a patient or to evaluate the efficacy of therapy. These uses would not depend on olfactory loss being specific for AD. In this regard, changes in smell identification in a recent small study were shown to be useful in predicting treatment response to donepezil in AD [1]. Given that olfactory deficits develop at high frequency in cognitively intact ε4 allele of apolipoprotein E carriers, olfaction may be a particularly useful noninvasive outcome measure in intervention or prevention trials in this higher risk population in AD [1].

Several further developments will be necessary in order to test the direct utility of olfactory screens as indices of incipient AD and to make such tests suitable for widespread use. First, a standardized odor testing battery that reduces user error and is adapted for different ethnic groups needs to be established as a ‘standard’ measurement. Possible tests that may be used (if formally adapted to different ethnic groups) are the University of Pennsylvania Smell Identification Test and the ‘Sniffin’ Sticks’ test [23]. Second, using such a ‘standard’ test, a large-scale, multicultural testing battery needs to be performed alongside other biometric assays (i.e., cerebrospinal fluid, amyloid-β and tau, cognitive testing) to robustly assess the relationship between olfactory loss and other factors implicated in AD. Importantly, this should be done throughout disease progression in order to explore the possible addition of olfactory dysfunction into established timelines of AD biomarker progression [2]. Third, establishing a method that robustly differentiates the origin of olfactory loss as being either AD or non-AD-related will be instrumental in allowing definitive diagnoses. Finally, longitudinal studies of individuals during the progression of disease, coupled with independent measures of structural or functional deficits in relevant brain regions, will be critical to establishing utility of olfactory tests as a disease progression or treatment outcome measure.

> “...establishing a method that robustly differentiates the origin of olfactory loss ... will be instrumental in allowing definitive diagnoses.”

In summary, olfactory dysfunction is well established in AD. Further elucidating the mechanism of olfactory loss in AD (pathological changes in cellular- and circuit-level information processing) will be especially important in understanding why the disease particularly affects smell function. If the previously listed steps are taken, and the results are still positively in favor of a strong relationship between early olfactory loss and the development of AD, then olfactory dysfunction can become a useful biomarker to include in the identification and prognosis of the disease.

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