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Olfactory dysfunction is an early and common symptom of many neurodegenerative diseases, particularly of Parkinson's disease, Alzheimer's disease, and mild cognitive impairment that heralds progression to dementia. Olfactory impairment is known to be related to several pathologic changes including the deposition of α -synuclein, hyperphosphorylated tau protein, neurofilament protein, Lewy bodies and neuritis inducing a complex cascade of molecular processes such as oxidative stress, neuroinflammation, and cytosolic disruption of cellular processes leading to cell death. The areas mainly showing these pathologic changes are the olfactory epithelium, olfactory bulb and tract, primary olfactory cortices, and their secondary target areas. Since early loss of olfactory function is common among several common neurodegenerative disorders, recent investigations have focused on its utility as a biomarker for early diagnosis and progression. Olfactory impairment appears to be an important sign for early detection, a useful biomarker for disease progression and a useful differentiator between neurological disorders.

Key Words: Olfaction; Neurodegenerative Diseases; Biological Markers

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Received 29 May 2014
Revised 27 June 2014
Accepted 7 July 2014

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INTRODUCTION

The olfactory sensory network is a unique brain system. Among human sensory systems, only olfaction has a direct connection to the brain and no thalamic relay. In terms of tissue and cellular repair, the olfactory system is unusual, along with the hippocampal dentate gyrus, as an example of central nervous tissue in which neurogenesis persists. Additionally, olfaction has been shown to have an essential role in behavior and memory.

Extensive investigations have confirmed an association between neurodegenerative disease and olfactory impairment. Olfactory dysfunction is a common and early feature of neurodegenerative diseases including Alzheimer's disease (AD) and Lewy body diseases (LBD), including Dementia with Lewy bodies (DLB), Parkinson's disease (PD), and Parkinson's disease dementia (PDD) [1-3]. Additionally, other neurodegenerative diseases such as frontotemporal dementias (FTD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) also show varying degrees of olfactory dysfunction [1,4-6].

NEURODEGENERATIVE DISEASES AND OLFACTORY DYSFUNCTION

Olfactory senescence begins at the 4th decade and accelerates with aging. It is reported that over 75% of the population over 80 years old has a tendency towards major olfactory dysfunction and more than 60% of people between the ages of 80 and 97 are subject to olfactory dysfunction [7]. Thus, even normal aging is related with the loss of identification and discrimination of smells.

Olfactory impairment in neurodegenerative diseases can be quantified using the ability to detect odours at threshold and to recognize and identify odours from memory. A meta-analysis on the effect of AD and PD on olfaction showed that AD and PD patients are more impaired on odour identification and recognition than on odour detection threshold tasks [8]. PD patients are more impaired on detection thresholds than AD patients, suggesting that PD patients are more impaired on low-level perceptual olfaction tasks, whereas AD patients are more impaired in higher-order olfactory tasks involving specific cognitive processes [8]. The olfactory deficits observed in patients with AD are similar in se-

verity to those in PD. Olfactory testing cannot distinguish between early AD and early PD [9].

ALZHEIMER'S DISEASE

AD is the most common neurodegenerative disease whose pathologic finding is the deposition of amyloid plaque in certain areas of the brain in early stage. Progressive neurofibrillary degeneration of the neurons and vascular amyloid depositions contribute to the extensive loss of cerebral mass in the end stage [7].

Olfaction is invariably impaired in AD. Olfactory involvement is present in up to 90 % of patients with AD [10]. Occurring in early AD, olfactory dysfunction can predict the conversion of mild cognitive impairment (MCI) to AD [11]. MCI is a diagnostic label for a defined cognitive syndrome that denotes a transitional stage between normal aging and dementia. Populations affected by MCI have been shown to be at higher risk than the general population for developing dementia [12]. Recent research on MCI patients [11], has demonstrated that 47% of MCI olfactory impaired subjects progressed to dementia while only 11% of MCI olfactory-normal subjects progressed to dementia at 2 year follow up. In a multivariable analysis, a lower score on a Mini-Mental Status Examination and a pathological smell identification test at baseline were independently associated with the progression to dementia within 2 years. This study confirms that smell identification testing may be useful in identifying the high-risk patients for developing dementia.

The olfactory bulb area often shows the typical pathology in Alzheimer's disease (neurofibrillary tangle and amyloid deposit) [13]. These pathologic changes have also been shown in the peripheral and central olfactory cortices, and in layer II and III of the entorhinal cortex in AD. According to Braak's stage, neurofibrillary tangle that begins in the olfactory bulb (OB) has also been correlated with olfactory dysfunction in AD [14].

Olfactory deficits in early AD can be detected by functional MRI [15] and Fludeoxyglucose-PET (FDG-PET) analysis which shows significantly reduced function in olfactory performance in AD compared with controls [16]. MRI studies demonstrating atrophy of the olfactory bulb and olfactory tract in MCI and AD suggest that OB atrophy might be a surrogate marker in AD [17]. Olfactory impairment with ApoE ϵ 4 genotype might be a marker for cognitive decline [18], but it has been suggested that the ApoE gene plays a role in olfactory functioning that is independent of demen-

tia conversion within 5 years [19].

Olfactory dysfunction may occur in healthy, non-demented elderly subjects [20], suggesting an association with dopaminergic denervation and reduced dopamine transporter binding in the aged population [21,22]. PiB-PET studies indicated that AD-related olfactory deficits are not directly related to A β burden in early AD, MCI, and healthy aging [20], while it did correlate with A β burden in an AD mouse model [23].

PARKINSON'S DISEASE

Olfactory dysfunction is one of the main symptoms of PD and is present in up to 96% of patients with PD [3,24], where it occurs as a prodromal symptom typically preceding motor symptoms [25-27]. Even using age-related normal values, almost 75% of PD patients have hyposmia or functional anosmia [28]. The prevalence of olfactory dysfunction in PD is much higher than that of PD's cardinal sign of resting tremor and may also exceed the prevalence of other cardinal motor signs [29]. The sensitivity and specificity of olfactory testing in differentiating PD from non-PD ranges from 79% to almost 100% [30].

Electrophysiologic test using olfactory event-related potentials do not seem to predict the course of the disease [31]. However, measurement of evoked potentials (EPs) after passive olfactory stimulation demonstrated a correlation between EP latency times and the severity of PD [32]. Since olfactory dysfunction is not static in PD patients and progresses over time, hyposmia might be a useful biomarker for evaluating disease progression and valuable in assessing the effects of disease-modifying drugs [33].

PD is a typical alpha synuclein-related pathologic disease. It was proposed that peripheral to central spread of alpha synuclein pathology through the major components of the olfactory system is possible [34]. PD also shows the altered synaptic transmission within the olfactory pathways. Damage to dopaminergic and non-dopaminergic neurotransmitter systems may contribute to olfactory dysfunction in PD [3].

Olfactory dysfunction was shown to be associated with parasympathetic dysautonomia independent of parkinsonism and striatal dopaminergic denervation [35,36], while selective olfactory deficits in PD are associated with nigrostriatal dopaminergic denervation [37], cholinergic denervation of the limbic archicortex, and cardiac sympathetic denervation [38]. Neuropsychiatric manifestations and cognitive impairment in PD were also associ-

ated with olfactory dysfunction [39], which predicted dementia and neuropsychiatric complications in PD patients [40]. On the basis of the above results, progressive olfactory impairment may be used as a biomarker of cholinergic denervation and cognitive decline in PD patients [41].

Olfactory impairment might result from a complex network dysfunction that exceeds structural pathology observed in the OB and mesolimbic cortices [42]. In a study of 361 relatives of PD patients who showed no motor symptoms, 10% of the subjects found to have hyposmia were diagnosed as having PD 2 years later [43]. These findings receive support from the model described by Braak et al. [44], according to which the earliest pathological changes in stage I occur in the OB and the anterior olfactory nucleus, while the substantia nigra is not involved until stage III. In patients found to have normal olfactory function, the diagnosis of PD should be reconfirmed or other diagnoses considered. Hyposmia is rare in atypical Parkinson syndromes, like PSP, CBD, or vascular parkinsonism [45,46]. Additionally, hyposmia has not been proven in essential tremor [47] and parkinsonism induced by the proneurotoxin, MPTP, [48], although decreased cholinergic input to the OB in MPTP-monkeys suggests that dopamine depletion might reduce the cholinergic centrifugal inputs [49].

OTHER NEURODEGENERATIVE DISEASES

Other neurodegenerative diseases can be accompanied by olfactory impairment. Hereditary ataxia such as Friedreich ataxia and spinocerebellar ataxia type 2 and 3 could have olfactory dysfunction. In addition, amyotrophic lateral sclerosis (ALS) shows slight olfactory impairment in some cases. However, olfactory dysfunction in the above diseases is usually not reported as an early symptom [50].

CONCLUSION

Olfactory dysfunction is closely related with many neurodegenerative diseases. Its early occurrence in PD and AD suggest it can play a special role in the early detection and differential diagnosis of these diseases so important to a timely initiation of treatment. Moreover, patients with olfactory dysfunction of unknown cause seem to have a two to threefold risk of developing PD or AD at a later point in time. Therefore, the identification and recognition of olfactory dysfunction appear as the most interesting candidates to

be included in a battery to detect subclinical cases in AD and PD.

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