RECENT UPDATES IN THE FIELD OF ALZHEIMER'S DISEASE

Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disease affecting memory, other cognitive functions, and behaviour.[1] Knowledge of the pathophysiology of AD is rapidly evolving, reflected by the increased focus on using biomarkers for disease diagnosis and staging. In this short article, we report on recent updates in this area.

Recent updates in the pathophysiology of AD

Contribution of LATE-NC co-morbidity to AD

When abnormal accumulation of the TDP-43 protein is associated with an amnestic dementia syndrome, it is defined as limbic-predominant age-related TDP-43 encephalopathy neuropathological changes (LATE-NC).[2,3] LATE-NC is a comorbidity of AD neuropathological changes in more than 50% of cases,[4,5] and when associated with AD pathology, lowers the threshold for developing dementia, worsens cognitive decline and is associated with other neuropathological changes in the brain, such as hippocampal sclerosis.[6,7] In a recent study, Tomé et al, found that treating mice with brain homogenates from patients with AD plus LATE-NC have increased phosphorylated-tau (P-tau) seeding severity.[5] Additionally, patients with AD plus LATE-NC had higher P-tau deposition versus those without LATE-NC, and that TDP-43 pathology was negatively correlated with neuronal density and Braak stages.[5] Although this suggests a more severe pathology in patients with AD and LATE-NC, comorbid co-pathology should be considered in the context of clinical diagnosis and stratification of patients with cognitive decline.

Tracking disease progression via the retina and the role of microglia in AD

The only part of the nervous system that can be accessed using non-invasive techniques is the retina.[8] Hart de Ruyter et al, demonstrated increased levels of P-tau in the retinas of patients with AD and primary tauopathies versus controls, and that retinal P-tau levels and microglia correlated with Braak stages for neurofibrillary tangles.[8,9] Additionally, P-tau levels were positively correlated with microglia counts in the retina, suggesting a pro-inflammatory environment in the presence of P-tau accumulation.[9] Although microglia are anti-inflammatory early in AD, having a role in network remodelling, phagocytosis and trophic support,[10] their sustained activation leads to a shift towards pro-inflammatory effects including excitotoxicity, synaptic pruning and demyelination.[10] Therefore, retina microglia may represent a potential biomarker of neurodegeneration.

Changes in wake-promoting neurons in AD

Disrupted sleep is a very common early feature of AD, but also in primary tauopathies with no amyloid accumulation.[11] Previous evidence indicates that the subcortical nuclei involved in the arousal network, including orexinergic neurons are extremely vulnerable to tau toxicity but are relatively spared in the pure tauopathy, progressive supranuclear palsy (PSP).[11] Son et al, demonstrated that there is a 75% decrease in the volume of the suprachiasmatic nucleus (SCN), the master regulator of sleep-wake at Braak stage VI versus 0.[12] Furthermore, SCN neurons have twice the burden of P-tau levels as the adjacent hypothalamic region, the supraoptic nucleus, and shows an increase in proteins associated with glia and immune responses.[12]

Role of gonadotropin-releasing hormone (GnRH) in AD

Down's syndrome is characterized by amyloid deposits and neurofibrillary tangles, as well as clinical dementia in most patients by approximately 60 years of age.[13,14] A reduction in GnRH levels may contribute to the cognitive deficits of Down's syndrome. Indeed, although best known for its role in reproduction, the expression GnRH and its receptor in brain areas not involved in reproduction suggests a role in higher brain

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functions.[15] In new research, Prévot et al found that in a mouse model of trisomy 21, cognitive and olfactory symptoms are related to a post-pubertal decrease in GnRH expression in the hypothalamus and extra hypothalamic areas.[16] In these mice, restoring normal GnRH secretion was able to rescue olfactory and memory function.[16] In people with Down's syndrome, a pilot study of pulsatile GnRH therapy for six months improved cognition and stimulate brain functional connectivity between cortical areas that are classically hypo-connected.[16]

The role of biomarkers in diagnosis, staging, and characterisation of AD

Optimal patient pathway when suspecting early symptomatic AD

The optimal patient pathway would start with the first potential symptoms of cognitive decline being assessed by the primary care practitioner, with a short cognitive test, performed to determine whether there is impairment.[17] Following the exclusion of other potential causes of impairment e.g. thyroid dysfunction or medication side effects,[17] patients with impairment are referred to a specialist for extended neuropsychological assessment to determine the level of cognitive impairment and function in daily living.[17] If the presence of mild cognitive impairment/mild dementia is confirmed, brain imaging is used, for example, to determine the pattern of atrophy or the presence of vascular lesions and AD biomarkers assessment is performed to establish etiology of impairment. This allows for the disclosure of an accurate diagnosis and the definition of an appropriate care plan in a meeting with the patient and family.[18]

Biomarkers for the diagnosis and staging of AD

There are several cerebrospinal fluid (CSF) and imaging biomarkers available for AD. In the CSF, both Aβ42 and Aβ42/Aβ40 ratio are biomarkers, with the latter shown to correlate with cerebral amyloid as determined by amyloid positron emission tomography (PET) and post-mortem samples.[19,20] Also many different P-tau isoforms can be measured in the CSF.[19] P-tau 181, is one of the most frequently measured isoforms and correlates with aggregated P-tau and the neurofibrillary tangles in the brain.[19,20] Total tau in CSF can indicate general neuronal damage.[20] For imaging biomarkers, PET can be used to measure the density of amyloid plaques, and the density and distribution of tau tangles.[20] Amyloid and tau tracers have been validated with post mortem examination.[20] Beyond CSF and imaging, blood-based biomarkers (BBM) are currently in development and will be used clinically in the future once robustly validated. Another area of research is the use of biomarkers for disease staging including CSF neurofilament light chain.[20] However, currently the National Institute on Aging and Alzheimer's Association propose only using both amyloid- and tau-based biomarkers for diagnosis and staging.[21]

Utility of biomarkers of AD pathology for clinical diagnosis

Biomarkers of AD pathology have utility in several ways. These include a mismatch between symptoms and pathology, particularly at the very early symptomatic or mild cognitive impairment stage of AD when other conditions such as dementia with Lewy bodies can lead to misdiagnosis.[19,22] Patients may also have an atypical presentation e.g., posterior cortical presentation and only biomarkers can determine whether AD is the cause.[23] Additionally, the underlying pathology is important for patient prognosis and eligibility for potential future treatments.[24] Finally, timely communication of the accurate diagnosis and the involvement of patients in shared decision-making with physicians may empower both patients and their families, and support them in future life planning.[25,26]

Advantages and limitations of AD biomarkers

PET can provide *in vivo* localization of amyloid or tau, allowing the pattern of brain pathology to be assessed.[19] However, its use can be restricted by the cost of the technology, the need to use radioactive tracers and access limitations beyond specialized memory clinics.[19,20] The main advantages of using CSF are that it allows for the assessment of several types of biomarkers simultaneously, provides more diagnostic precision than other assessments not able to detect the core AD biomarkers like magnetic resonance imaging, and is accessible from a cost and training perspective in most countries.[19,20] However, the disadvantages of CSF biomarkers are that they require a lumbar puncture and do not indicate the location of the pathology. BBM share similar advantages and limitations as CSF but may be easily repeated over time, potentially allowing for disease progression to be monitored regularly. However, additional validation is required for accuracy and thresholds need to be standardized globally.[20]

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Steps to implementing BBM into clinical practice

Several steps are required to implement the use of BBMs in clinical practice. The first is to establish appropriate use and threshold criteria.[27] Secondly, the infrastructure for analysing and reporting BBM values needs improvement to ensure it is sufficient to prevent long-waiting lists.[27] Finally, physicians will need to be educated on the selection of appropriate biomarkers for testing, and how to interpret test results in symptomatic patients.

Summary

In summary, our knowledge of the pathophysiology of AD is progressing rapidly, with a better understanding of the contribution of LATE-NC co-pathology, the role of microglia, the change in wake promoting neurons and the role of GnRH. Alongside learnings in pathophysiology, the increased focus on using biomarkers for disease diagnosis and staging may facilitate a timely and accurate AD diagnosis, allowing for the potential to intervene in the disease before symptoms have progressed to dementia.

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