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NEW BIOLOGICAL MARKERS IN ALZHEIMER DISEASE

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Alzheimer's disease (AD), a neurodegenerative disease and leading cause of dementia, has emerged as a major public health challenge for ageing populations all over the world. The characteristic pathological changes are of irreversible neuronal loss, and deposition of plaques laden with amyloid-β peptide; and neurofibrillary tangles made up of abnormally hyperphosphorylated tau protein in critical areas of brain have been well established (Hardy J, Selkoe DJ Science. 2002 Jul 19; 297(5580):353-6.). The poor understanding of the pathogenesis of AD and consequent lack of definitive therapy provides opportunity for development of newer diagnostic and treatment strategies. The search for biomarkers to aid accurate diagnosis, predict progression and for use in clinical trials has become a major research goal. (Expert Rev Proteomics. 2007 Apr; 4(2):227-38.) The most widely used strategy for the discovery of biomarkers is predicated on the identification of potential candidate biomarkers using knowledge of disease processes followed by validation, comparing healthy control to affected subjects

SIRITIN

In this scenario recent studies have indicated a possible mechanism involving the sirtuin proteins which may have diagnostic and therapeutic potential in AD. Sirtuins are NAD-dependent deacetylases, which have wide spectrum of metabolic and stress-nce properties. Among them SIRT1 is well characterized and is considered to be responsible for delaying the process of ageing. (*Picard F, Kurtev M, Chung N, Topark-Ngarm A, Senawong T, Machado De Oliveira R, Leid M, McBurney MW, Guarente L Nature. 2004 Jun 17; 429(6993):771-6.).* SIRT1 has also been credited to have neuro-protective action against stress in cell cultures. (*J Biol Chem. 2006 Aug 4; 281(31):21745-54.).* It has been reported that SIRT1 increases the expression of ADAM10 gene encoding α secretase which protects against accumulation of pathogenic Aβ peptide.(*Donmez G, Wang D, Cohen DE, Guarente LCell. 2010 Jul 23; 142(2):320-32.)* . The significant decrease in SIRT1 concentration in parietal cortex in autopsy specimens of AD patients was reported earlier and a strong correlation was established between tissue SIRT1 concentration, duration of symptoms and tau accumulation, but the exact relationship and its role in the sequence of events leading to development of AD remains unclear (*J Neuropathol Exp Neurol. 2009 Jan; 68(1):48-58.).* The role of sirtuins in prevention of brain degeneration especially in AD has been reported. SIRT1 increases the expression of ADAM10 gene encoding α secretase. In case of AD the down regulation of SIRT1 reduces the expression of α-secretase and as a result the accumulation of pathogenic Aβ peptide formed by β and γ secretase (*Haass C, Selkoe DJ Nat Rev Mol Cell Biol. 2007 Feb;*

8(2):101-12.). The serum Aβ1–40 levels are higher in the AD group than both controls and MCI. It can correlate that as SIRT1 down regulate in AD which control the expression of Aβ peptide through ADAM10 hereby upregulated the level of Aβ peptide (*Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2009 Mar; 16(2):203-18.*

AMYLOID PRECURSOR PROTEIN B AS BLOOD-BASED BIOMARKER OF ALZHEIMER'S DISEASE

The soluble amyloid precursor proteins (sAPP) α and β, which are the products of physiological and amyloidogenic cleavage of APP, are related to central upstream pathophysiological events in Alzheimer's disease (AD) (*Zhang H, Ma Q, Zhang YW, Xu H J Neurochem. 2012 Jan; 120 Suppl 1():9-21.)* changes in Concentration of cerebrospinal fluid (CSF) have been repeatedly observed in AD, and the diagnostic utility of the markers is supported by a growing number of publications.(*Neurology. 2011 Jul 5; 77(1):35-8*). Decreased plasma sAPPβ concentrations were found in patients with probable AD compared with age-matched control subjects and patients with a non-Amyloid-β (Aβ) type of dementia, suggesting a potential role as diagnostic marker. Biomarkers such as the CSF proteins Aβ1–42, total-Tau and phosphorylated Tau181 and structural and functional imaging techniques such as [18F]-fluorodeoxy-glucose positron emission tomography show reasonable but not perfect accuracy in distinguishing probable AD from physiological aging and other neurodegenerative disorders. *(Neurology. 2012 Jan 3; 78(1):47-54.).* Study compared with healthy aging and a non-Aβ type of dementia, which is in line with a reduced concentration of sAPPβ in AD brain cortex. Even though increased concentrations of full-length APP protein in blood platelets and APP mRNA levels in blood mononuclear cells have been reported in AD (*Int J Immunopathol Pharmacol. 2011 Apr-Jun; 24(2):529-34.).* That is reduced sAPP levels possibly mirror decreased cortical APP expression in AD, which limits APP clearance across the blood-brain-barrier and/or decreased processing of APP into sAPP in blood.

CSF AS MARKERS OF THE ALZHEIMER'S DISEASE

Cerebral spinal fluid (CSF) is suggested as biomarkers amended to existing diagnostic criteria of mild cognitive impairment (MCI) and Alzheimer's disease (AD). CSF markers, including Aβ42, t-tau, and p-tau, distinguished MCI or AD from NC, while the Aβ42 CSF marker contributed to the differentiation between MCI and AD.(*Alzheimers Dement. 2011 May; 7(3):263-9.).* CSF markers, Aβ42, t-tau, and p-tau, showed statistically significant differences between NC and AD and between NC and MCI. CSF and structural markers were complementary; their combination showed great improvement in the classification accuracies at all the stages of AD. CSF Aβ42 and neurodegenerative biomarkers, including CSF tau protein show significant differences between NC and MCI groups. CSF Aβ42 reaches a plateau before the appearance of MRI atrophy and cognitive symptoms, and remains static thereafter continued to show appreciable power discriminant between MCI and AD. (Lancet *Neurol. 2010 Jan; 9(1):119-28.)* CSF tau lost its

discriminating power in distinguishing MCI and AD patients, suggesting that CSF Aβ42 reaches its plateau after CSF tau in the Alzheimer's pathological cascade. Study show that the CSF markers are complementary to each other in the AD pathological cascade & suggests that the CSF markers, (Aβ42, t-tau, and p-tau) with the volumes of the hippocampus and lateral ventricles, is a good combination for distinguishing NC and MCI, while CSF Aβ42 marker with the shape of the hippocampus and lateral ventricles is a good combination for identifying MCI and AD.

NEUROINFLAMMATION

Mechanistically implicated as both neuro-toxins and neuroprotectants in AD pathophysiology, molecules of 'neuroinflammation' are also widely reported as candidate biomarkers. This Included are cytokines, chemokines, complement proteins, proteases, protease substrates and their cleavage products, protease inhibitors, and other glia-derived proteins with well-known, little-known or unknown functions in the brain. These molecules have received preferential attention as potential biomarkers because they are abundant in CSF – thus, easily 'discovered' in proteomic screens.(*Acta Neuropathol. 2010 Jun; 119(6):669-78.).*

COMPLEMENT PROTEINS/PROTEASES/PROTEASE INHIBITORS

These include complement proteins C3 , C3a des-arg, C4a des-arg , C3/C4 homologous protein α-2-macroglobulin and factor H (*Am J Pathol. 2011 Apr; 178(4):1509-16.).* Protease-inhibiting serpins, α-1 antitrypsin (*Neurology. 2007 Oct 16; 69(16):1569-79)*, α-1 antichymotrypsin and neuroserpin have received particular attention. α-1 antichymotrypsin additionally shows potential for disease staging *(Ann Neurol. 2003 Jan; 53(1):81-90.).* Complementing the serpins are matrix metallo proteinases MMP-2 and MMP-3, which appear to correlate with Aβ42 in CSF *(Neurosci Lett. 2009 Dec 11; 466(3):135-8.)*, and MMP-10, which appears to be increased in AD.*(PLoS One. 2011 Apr 19; 6(4):e18850.)*

CYTOKINES

Cytokines markers have received more attention in blood-derived fluids (serum, plasma) than in CSF, scores of AD-related CSF studies have been reported . CSF biomarkers for AD in this category that show greatest consensus include: reduced levels of IL-7 and IL-17E (*J Psychiatr Res. 2009 May; 43(8):749-53.)* and increased macrophage MIF, which induces TNF-α, IL-6 and IFN-γ (*PLoS One. 2012; 7(1):e30525.).c*ytokine response has been described in peripheral monocytes derived from individuals with AD compared with monocytes from healthy controls (IL-1β, IL-2, IL-10, IL-12p70, GM-CSF, IFN-γ and TNF-α), but not IL-6 or IL-8, were noted to increase dramatically in AD patients in response to intrathecal catheterization and repeated CSF draws over a 24-h period.(*Alzheimer Dis Assoc Disord. 2012 Oct-Dec; 26(4):322-8.).* CSF levels of many cytokines (IL-1β, IL-2, IL-10, IL-12p70, GM-CSF, IFN-γ and TNF-α), but not IL-6 or IL-8, were

noted to increase dramatically in AD patients in response to intrathecal catheterization and repeated CSF draws over a 24-h period (*Alzheimer Dis Assoc Disord. 2012 Oct-Dec; 26(4):322-8.).* There is need of new study how cytokine changes might impact concentrations of noncytokine molecules in CSF, the apparent volatility of cytokine levels in response to this relatively innocuous stimulus (or technique of sampling) may account, at least in part, for the variable results reported in different studies.

ASTROCYTIC PROTEINS

Astrocytic proteins are peptides and receptors of neuroinflammation are the structural elements of astrocytes it selves. GFAP and S100β, two molecules that are well-established as immunohistochemical and biochemical markers of astrocytosis, have also been reported as potential candidate CSF biomarkers for AD diagnosis(*J Alzheimers Dis. 2010; 21(2):569-76.*). CSF GFAP additionally appears to correlate with dementia severity (*Eur Neurol. 2001; 46(1):35-8.).* because astrocytosis represents a fundamental reaction of the CNS to injury, these molecules are also increased in the setting of other neurological disorders and brain injuries (e.g., Creutzfeldt–Jakob disease (*J Alzheimers Dis. 2010; 21(2):569-76.*), multiple sclerosis, stroke and acute [1and repetitive. Traumatic brain injury (*PLoS One. 2012; 7(4):e33606.*). GFAP and S100β may show some utility as part of a biomarker panel, particularly for staging, prognosis or theragnosis. Indeed, even for differential diagnosis, these two markers together show some capacity to distinguish Creutzfeldt–Jakob disease from AD *(J Alzheimers Dis. 2009; 17(3):541-51.)*

CRITICAL REVIEW

The AD biomarker field is faced with several challenges it must overcome in order to move promising analytes into clinical practice. From a methodological perspective, biomarker candidates must be validated in large, well-characterized research cohorts, with care taken to evaluate the potential impact of AD-related covariates such as age, gender and *APOE* genotype. Importantly, protocol and assay standardization must be achieved in order to maximize biomarker reliability and permit comparisons between studies. Very few studies have been able to correlate biomarkers in ante-mortem samples with results of post-mortem examination, and the time interval between the two evaluations can be large. It is highly likely that combinations of biomarkers will prove most useful for disease diagnosis (presence vs absence of AD pathology) and prognosis (predicting cognitive decline) *(Lancet Neurol. 2006 Mar; 5(3):228-34.)* within modalities or between modalities (e.g., fluids and imaging)

FUTURE PERSPECTIVE

For diagnosis and differential diagnosis of AD, it is unlikely that CSF Aβ42, tau and p-tau will be supplanted because they represent core features of AD pathology. More than likely, they will be

complemented by markers that reflect the presence of more general neurodegenerative pathologies (e.g., neuro inflammation and synaptic loss/dysfunction. Novel biomarkers are needed to identify additional pathogenic processes that will increase diagnostic/prognostic accuracy, aid in differential diagnosis, identify cases with mixed pathologies and define the trajectory of biomarker changes over time. Once effective disease-modifying therapies have been developed, validated CSF biomarkers with high sensitivity and specificity for AD will likely be utilized in the clinical setting to aid disease diagnosis and prognosis, as has recently been proposed.