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Editorial

Biomarkers of Alzheimer's Disease

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Editorial

Alzheimer's disease (AD) is clinically characterised by progressive impairment in memory and cognitive decline. AD is pathologically characterized by extracellular deposition of β-amyloid (Aβ) in senile plaques and formation of intracellular neurofibrillar tangles, mainly composed of the hyper phosphorylated microtubule associated protein *tau* [1-2]. The senile plaques and the neurofibrillary tangles, allowing a definite diagnosis and excluding the other types of dementia. Identification of proteins affecting the degree of neurodegeneration could contribute to the development of biomarkers or new drug targets in the management of AD. The use of magnetic resonance imaging (MRI), 18F- 2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET), amyloid (Aβ) PET, and Cerebro spinal fluid (CSF) biomarkers for AD has been investigated extensively for a number of years.

CSF Biomarkers

CSF tau (T-tau), CSF (P-tau) and CSF Aβ42 represent the pathological features of AD, which are neuronal loss, the intracellular neurofibrillary tangles and extracellular senile plaques. A decreased level of CSF Aβ42 reflects deposition of the peptide in plaques in the cortex. An increasedlevels of CSF P-tau reflects the phosphorylation state of tau and the formation of tangles in the brain. In contrast, high concentrations of CSF T-tau reflect the intensity of neuronal damage and neuronal degeneration in the brain. Several studies have revealed the use of CSF biomarkers as a predictor of disease progression. Moon is et al., found decreased levels of CSF Aβ42 in presymptomatic subjects with pathogenic mutations in the PS1 gene as compared to control group, which open an opportunity to evaluate the ability to decrease, arrest, or reverse abnormalities in Aβ42 metabolism before the clinical symptoms of AD occur [3]. Ringman et al., measured CSF markers in 13 carriers of familial AD (FAD) mutations that are fully penetrate for causing AD (*PSEN1 and APP*) and in 5 non-mutation-carrying family members. The carriers of FAD mutations showed decreased levels of CSF- Aβ42 and increased levels of CSF T-tau and P-tau [4]. Hansson et al., assessed the association between CSF biomarkers and incipient Alzheimer's in patients with mild cognitive impairment (MCI) followed for 4-6 years. Concentrations of T-tau, P-tau181, and Aβ42 in CSF are strongly associated with future development of Alzheimer's disease in patients with MCI with a sensitivity of 95% and a specificity of 87% [5]. Bateman et al., analyzed data from 128 participants who underwent baseline clinical and cognitive assessments, brain imaging and CSF and blood tests. Concentrations of amyloid-beta Aβ42in the CSF appeared to decline 25 years before expected symptomonset. Aβ deposition, as measured by PET with the use of Pittsburgh compound B (PIB), was detected 15 years before expected symptomonset. Increased concentrations of tau protein in the CSF and an increase in brain atrophy were detected 15 years before expected symptomonset. They found that autosomal dominant Alzheimer's disease was associated with a several pathophysiological changes over decades in CSF biomarkers of AD [6]. CSF or blood plasma remain the most promising sources for AD biomarkers as compared to brain tissue.

Blood Biomarkers

CSF limits the ability to access DNA and RNA, In contrast blood's biomarkers provide a rich source of genetic materials and proteomic species for investigations. Several data indicate that miRNAs are deregulated in brain, CSF, and in blood, therefore they might be used as biomarkers in the diagnosis of AD. Kiddle et al., used Soma Logic's SOMA scan proteomics technology, they were able to conduct a large-scale replication study for 94 of the 163 candidate biomarkers from 21 published studies in plasma samples. Nine of the 94 previously reported candidates were associated to AD phenotype. These proteins may be considered as a biomarker set for further investigations [7]. Lin Tan et al., investigated the potential role of serum miRNAs as diagnostic biomarkers for AD. They indicated that serum miR-125b may serve as a useful noninvasive biomarker for AD [8]. Leidinger et al., revealed the involvement of 12 miRNAs in AD. They differentiated between AD and controls with an accuracy of 93%, a specificity of 95% and a sensitivity of 92% [9]. Galimberti et al., demonstrated that cell-free miR-125b serum levels are decreased in serum from patients with AD as compared with non-inflammatory neurological controls with an accuracy of 82% [10].

Blood is an attractive source for biomarkers due to minimal discomfort to the patient. Unfortunately the sensitivity and specificity of blood biomarkers remain lower than those from CSF. Ray et al., found 18 signaling proteins in blood plasma that can beused to classify Alzheimer patients from control subjects with 90% accuracy and to identify patients who had mild cognitive impairment that progressed to AD 2–6 years later [11]. Lundstrom et al., revealed the alteration of blood plasma IgG Fc glycans in AD which can discriminate cognitively normal (CN) subjects from those with MCI and AD, with a sensitivity of 89.3% and a specificity of 79.1% [12].

Neuroimaging

Hoffman et al., confirmed that bilateral temporo-parietal hypo metabolism is indeed the classic metabolic abnormality associated with AD. The sensitivity, specificity, and diagnostic accuracy of bilateral temporo-pari et al hypo metabolism being associated with AD were 93%, 63%, and 82%, respectively. The sensitivity, specificity,

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and diagnostic accuracy of FDG PET may be used in the evaluation of dementia and particularly to confirm the clinical suspicion of AD [13]. Mosconi et al., revealed that progressive cerebral metabolic rate for glucose reductions on FDG-PET occur years in advance of clinical Alzheimer's-type dementia in patients with pathologically verified disease, also the FDG-PET profiles in life were consistent with the post-mortem diagnosis [14]. According to a study by Minoshima et al., PET could distinguish autopsy-confirmed pure AD patients versus dementia with Lewy bodies patients who had ante mortem PET imaging and autopsy confirmation with a sensitivity of 90% and a specificity of 80% [15]. In A study by Foster et al., involving patients with AD and from to temporal dementia (FTD), adding FDG-PET to clinical summaries, increase diagnostic accuracy and confidence for both AD and FTD [16]. In contraste, A study by Karow et al., showed that FDG PET is more sensitive than MRI to the degeneration occurring in preclinical and mild AD, suggesting that an MRI finding may be a more practical clinical biomarker for early detection of AD [17].

Dukart et al., provided and validated at a group level a generative an automical model of glucose hypo-metabolism and atrophy progression in AD based on FDG-PET and structural MRI data of 80 patients and 79 healthy controls. The model suggests greater and more consistent changes in FDG-PET compared to sMRI at earlier and the inversion of this pattern at more advanced AD stages [18]. Small et al., performed PET after injection of 2-(1-{6-[(2[F18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene) malononitrile (FDDNP), a molecule that binds to plaques and tangles *in vitro*. They concluded that FDDNP-PET scanning can differentiate persons with MCI from those with AD and those with no cognitive impairment. This technique is potentially useful as a noninvasive method to determine regional cerebral patterns of amyloid plaques and tau neurofibrillary tangles [19]. Recently, the Food and Drug Administration (FDA) approved a new radio pharmaceutical agent to assist clinicians in detecting causes of cognitive impairment other than Alzheimer's disease. Florbetapir F18 injection (Amyvid, Eli Lilly) is indicated for PET imaging of the brain in cognitively impaired adults undergoing evaluation for AD and other causes of cognitive decline [20]. Doraiswamy et al, designed a study to evaluate whether subjects with Aβ pathology, detected using florbetapir PET. Their results suggested that in CN, MCI and AD subjects, florbetapir PET Aβ+ subjects show greater cognitive and global deterioration over a 3-year follow-up than Aβ- subjects do. [21]. Klunk et al., described the first human study of a novel amyloid-imaging PET tracer, termed Pittsburgh Compound-B (PIB), in 16 patients with diagnosed mild AD and 9 controls. Their results suggest that PET imaging with the novel tracer, PIB, can provide quantitative information on amyloid deposits in living subjects [22]. Rowe et al., compared brain beta-amyloid (Aβ) burden measured with [(11) C] PIB)-PET in normal aging, Alzheimer disease (AD), and other dementias. Pittsburgh Compound B PET findings match histopathologic reports of Aβ distribution in aging and dementia. Therefore they suggested that Aβ may influence the development of dementia with Lewy bodies, and therefore strategies to reduce Aβ may benefit this condition [23]. Devanand et al., evaluated the Amyloid load in the brain using (11) C-PIB- PET and cerebral glucose metabolism using fluorodeoxy glucose ((18)F-FDG) PET in patients with mild AD, n = 18), MCI, n = 24), and controls CTR, n = 18).(11)C-PIB PET BP(ND) clearly distinguished diagnostic groups and combined with (18)F-FDG PET regional cerebral metabolic rate for glucose (rCMRGlu) [24].

The combination of biomarkers in CSF and imaging can provide an increased diagnostic accuracy with respect to the use of a single technique.Studies have shown that the combination of CSF-Aβ42, -tau T, P tau and imaging may provide a better classification of MCI, AD and controls.

References

1. Ling Y, Morgan K, Kalsheker N. Amyloid precursor protein (APP) and the biology of proteolytic processing: relevance to Alzheimer's disease.Int J Biochem Cell Biol. 2003; 35: 1505-1535.
2. Gómez-Ramos A, Smith MA, Perry G, Avila J. Tau phosphorylation and assembly. Acta Neurobiol Exp (Wars). 2004; 64: 33-39.
3. Moonis M, Swearer JM, Dayaw MP, St George-Hyslop P, Rogaeva E, Kawarai T, et al. Familial Alzheimer disease: decreases in CSF Abeta42 levels precede cognitive decline.Neurology. 2005; 65: 323-325.
4. Ringman JM, Coppola G, Elashoff D, Rodriguez-Agudelo Y, Medina LD, Gylys K, et al. Cerebrospinal fluid biomarkers and proximity to diagnosis in preclinical familial Alzheimer's disease.Dement Geriatr Cogn Disord. 2012; 33: 1-5.
5. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study.Lancet Neurol. 2006; 5: 228-234.
6. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease.N Engl J Med. 2012; 367: 795-804.
7. Kiddle SJ, Sattlecker M, Proitsi P, Simmons A, Westman E, Bazenet C, et al. Candidate blood proteome markers of Alzheimer's disease onset and progression: a systematic review and replication study.J Alzheimers Dis. 2014; 38: 515-531.
8. Tan L, Yu JT, Liu QY, Tan MS, Zhang W, Hu N, et al. Circulating miR-125b as a biomarker of Alzheimer's disease.J Neurol Sci. 2014; 336: 52-56.
9. Leidinger P, Backes C, Deutscher S, Schmitt K, Mueller SC, Frese K, et al. A blood based 12-miRNA signature of Alzheimer disease patients.GenomeBiol. 2013; 14: R78.
10. Galimberti D, Villa C, Fenoglio C, Serpente M, Ghezzi L, Cioffi SM, et al. Circulating miRNAs as potential biomarkers in Alzheimer's disease.J Alzheimers Dis. 2014; 42: 1261-1267.
11. Ray S, Britschgi M, Herbert C, Takeda-Uchimura Y, Boxer A, Blennow K, et al. Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins.Nat Med. 2007; 13: 1359-1362.
12. Lundström SL, Yang H, Lyutvinskiy Y, Rutishauser D, Herukka SK, Soininen H, et al. Blood plasma IgG Fc glycans are significantly altered in Alzheimer's disease and progressive mild cognitive impairment.J Alzheimers Dis. 2014; 38: 567-579.
13. Hoffman JM, Welsh-Bohmer KA, Hanson M, Crain B, Hulette C, Earl N, et al. FDG PET imaging in patients with pathologically verified dementia.J Nucl Med. 2000; 41: 1920-1928.
14. Mosconi L, Mistur R, Switalski R, Tsui WH, Glodzik L, Li Y, et al. FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease.Eur J Nucl Med Mol Imaging. 2009; 36: 811-822.
15. Minoshima S, Foster NL, Sima AA, Frey KA, Albin RL, KuhlDE. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. Ann Neurol. 2001; 50: 358-65.
16. Foster NL, Heidebrink JL, Clark CM, Jagust WJ, Arnold SE, Barbas NR, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease.Brain. 2007; 130: 2616-2635.
17. Karow DS, McEvoy LK, Fennema-Notestine C, Hagler DJ Jr, Jennings RG,

Brewer JB, et al. Relative capability of MR imaging and FDG PET to depict changes associated with prodromal and early Alzheimer disease.Radiology. 2010; 256: 932-942.

18. Dukart J, Kherif F, Mueller K, Adaszewski S, Schroeter ML, Frackowiak RS, et al. Alzheimer's Disease Neuroimaging Initiative. Generative FDG-PET and MRI model of aging and disease progression in Alzheimer's disease. PLoS Comput Biol. 2013; 9: e1002987.

19. Small GW, Kepe V, Ercoli LM, Siddarth P, Bookheimer SY, Miller KJ, et al. PET of brain amyloid and tau in mild cognitive impairment.N Engl J Med. 2006; 355: 2652-2663.

20. Yang L, Rieves D, Ganley C. Brain amyloid imaging--FDA approval of florbetapir F18 injection. N Engl J Med. 2012; 367: 885-887.

21. Doraiswamy PM, Sperling RA, Johnson K, Reiman EM, Wong TZ, Sabbagh MN, et al. Florbetapir F 18 amyloid PET and 36-month cognitive decline: a prospective multicenter study.Mol Psychiatry. 2014; 19: 1044-1051.

22. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 2004; 55: 306-319.

23. Rowe CC, Ng S, Ackermann U, Gong SJ, Pike K, Savage G, et al. Imaging beta-amyloid burden in aging and dementia.Neurology. 2007; 68: 1718-1725.

24. Devanand DP, Mikhno A, Pelton GH, Cuasay K, Pradhaban G, Dileep Kumar JS, et al. Pittsburgh compound B (11C-PIB) and fluorodeoxyglucose (18 F-FDG) PET in patients with Alzheimer disease, mild cognitive impairment, and healthy controls.J Geriatr Psychiatry Neurol. 2010; 23: 185-198.

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