Short Communication

Insights in diagnostic biomarkers for alzheimer's disease

Abstract

Alzheimer's disease is a chronic brain degenerative condition arising from increasing human aging population stemming high costs in the health system. Since post-mortem brain biopsy is regarded as the definitive diagnosis of AD, developing a non-invasive approach is highly valued. Current cutting-edge medical devices, liposomal and nanoparticle-drug delivery systems as well cerebrospinal fluid biomarkers and structural magnetic resonance imaging biomarkers have limited diagnostic benefits. Emerging genomics and proteomics biomarkers show encouraging results at distinguishing mild cognitive impairment converters to non-converters progressing to AD dementia. Multi-biomarkers offer a better alternative by predicting on a short period those asymptomatic subjects who are more susceptible to progress into the prodromal stage. Other applications are currently investigating which medical conditions foster aging dementia. Since cardiovascular diseases have shown to advance the temporal stage of neurodegeneration and the extent of neuroanatomical damage, combining proteins associated with vascular diseases with current cerebrospinal fluid biomarkers enhances the diagnostic accuracy while others proteins can serve as staging biomarkers.

Keywords: alzheimer's disease, biomarkers, diagnostic, amyloid-beta

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Abbreviations: AD, alzheimer's disease; CSF, cerebrospinal fluid; Aβ42, amyloid beta1-42; MCI, mild cognitive impairment; miRNA, micro RNA

Introduction

Alzheimer's disease (AD) is a highly prevalent chronic neurodegenerative condition caused by heterogeneous uncharacterized pathologic processes that occur at different time and duration in aging brain. A big scientific deal focuses on the development of normal brain aging to decipher the possible causes underlying the progressive neuropathological hallmarks of AD. Prior developing effective therapeutic agents, scientists must set a multidisciplinary approach consisting of 1) elaborating better high throughput devices, more sensitive and accurate in data assessment, 2) conceiving the exposure, diagnostic and prognostic biomarkers specifically targeting the pathological process during the asymptomatic, prodromal and mild cognitive impairment stages in genetically predisposed people, called mutated carriers, and 3) developing efficient drug delivery systems to preserve synaptic plasticity at the early disease stage.

Designing an effective biomarker is the first step towards diagnosing a specific pathological stage characterized by the extent of biological fluids perturbation, microglia inflammation leading to oxidative stress response, increase neuronal damage-to-repair mechanism ratio or sequential time-course neuroanatomical regions atrophy. The abnormal cerebrospinal fluid (CSF) amyloid beta 42 (Aβ42), 18F-fluorodeoxyglucose-positron emission tomography, magnetic resonance imaging hippocampal atrophy and abnormal CSF T-tau are the most frequent biomarkers used in predicting Alzheimer's disease outcome in subjects with mild cognitive impairment (MCI). Yet when these imaging biomarkers are combined together, not all MCI converters and MCI non-converters are distinguished between AD and healthy patients as well correctly classified. These observations suggest that other putative biomarkers are relevant in the AD pathogenesis. Emerging findings describe numerous microRNAs (miRNAs) that may act as putative biomarkers differentially regulated in AD inflammation via acetylcholinesterase, AD apoptosis and AD protein aggregates involving Aβ, neurofilament heavy chain and tau accumulation.[1] For example, miRNA-29a was shown to have a 2-fold increase in CSF of AD patients[2,3] while other miRNAs have been shown to be deregulated in brain and plasma of AD patients.[4] A large set of miRNAs can be discovered by applying deep sequencing technology in order to profile miRNA signatures in serum, plasma, CSF, urine, saliva, sweat, and eye secretions in progressive development of AD pathogenesis. Exosomes can also contain miRNA species involved in the processing of amyloid precursor protein and could be excreted in the urine where they can serve as a future diagnosis value in AD patients.[5] Furthermore, diagnostic biomarkers could be assessed in AD-causative genes subjects (e.g. presenilin-1, presenilin-2 and amyloid precursor protein), AD-susceptible genes subjects (e.g. apolipoprotein E epsilon 4) as well in new AD susceptible loci subjects.[6] Other disease-related biomarkers should be explored such as those involving cell cycle regulating proteins p53 and p21 dysregulated in peripheral blood cells of AD patients Tan et al.,[7] as well as Bax, superoxide dismutase-1 and caspase-6.[8,9] Since it has been reported that AD and ischemic stroke share a common mechanism Lucke-Wold et al.,[10] an approach can look at the receptor level in the blood-brain barrier. Recently, a distinct p75 neurotrophic receptor profile shows a decrease CSF level and an increase serum level in AD subjects. When combining with CSF or serum Aβ42 and p-tau181, the diagnostic accuracy is improved Jiao et al.[11] Therefore, p75 neurotrophic receptor can be likely a diagnostic marker in monitoring AD progression. Another application describes the use of visinin-like protein-1, a calcium sensor protein, as a potential biomarker of AD in early diagnosis, prognosticator from MCI to full stage of dementia subjects and distinguishing AD patients from those affected by Lewis body disease Babic Leko et al.[12]

It becomes obvious that searching for multi-biomarker profile signatures using high-throughput genomics system combined with proteomics system will definitively provide an accurate prognostic profile in asymptomatic patients. The accuracy of prognostic can access the probability of developing dementia from earlier stages, and yet the challenge resides at determining the utility of biomarkers for predicting time progression to dementia over three years period Dickerson & Wolk.[13] together pathognostic proteins (POLG: a DNA polymerase gamma and granzyme B) involved in opposing neuronal death mechanism by ELISA microarray provide evidence their reduction levels are noticed in AD CSF compared to healthy control subjects Olah et al.[14]

Conclusion

Numerous biomarkers are currently investigated worldwide to decipher the role each can play in specific staging of AD pathogenesis events. Current and new predicted biomarkers are evaluated in combination by ELISA multiplex assays and multimodal imaging techniques to set higher diagnostic accuracies while establishing earlier detection, better specificity and reproducible in AD population before therapeutic interventions will be conducted in clinical trials. Aforementioned, diagnosing genetically susceptible patients is taking a look at post-transcriptional regulated gene expression that profoundly impact the progressive pathophysiological aspect of dementia. Having the right biomarker tool in hand for diagnosing the right sick patient is what comes down to developing further scientific and translational biomedical research. Since numerous miRNAs are affecting different pathophysiological pathways, the implication that each has in neuronal inflammation, amyloidosis, tau pathology, neuronal cell death, and brain degeneration are cardinal features of AD for successful treatments.

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Conflict of interest

The author declares no conflict of interest.

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