Alzheimer's disease: detecting pathophysiological and neuropathological changes with biomarkers

Elisei Cosovan

Neurodegenerative diseases such as Alzheimer's Disease (AD) affect more than 3 million people in the U.S annually. AD is a progressive illness that impairs normal brain function. Therefore, obstructing the formation of new memories and disrupting behavioral and social skills. Symptoms are typically not present at the time of onset, making the disease difficult to diagnose – let alone treat. The only way to currently detect this illness as of now is through histopathological techniques in post-mortem brains. With this limitation in mind, this paper reviews current research on biomarkers and how they can be applied to detecting the onset of AD *in vivo.*

Biomarkers are used to indicate physiological changes. As an example, a blood pressure cuff can be considered a biomarker because it is able to detect changes in blood pressure. So far, the focus in research has been on cerebral imaging biomarkers. More specifically, on amyloid-beta proteins – which form the plaques that are principal to the development of AD – and on phosphorylated tau – a principal component of neurofibrillary tangles.[1,2,3] The reason why these two cerebral spinal fluid (CSF) biomarkers have drawn the most attention is due to their role in predicting cognitive decline in healthy people.

Yet even with the ability for these biomarkers to identify neuropathological changes in AD, there are some downsides to using them in clinical trials, and eventually, in patient care. CSF biomarkers may provide scientists with inaccurate results. In recent studies, CSF biomarkers were able to detect plaque buildup and neurofibrillary tangles, but were not accurate enough to provide the researchers with enough information to indicate whether the disease present was AD or another form of dementia.[4,5] CSF biomarkers are also too invasive to be added to routine clinical use, as they require lumbar puncture. In addition to its invasiveness, CSF biomarkers are just too expensive to be used in the general population screening.[6]

Blood-based biomarkers on the other hand, hold a more promising future for identifying AD as they may be able to detect pathophysiological and neuropathological changes more efficiently than CSF biomarkers. Such biomarkers can be used through epigenetic mechanisms since they modify gene expression, but do not affect the DNA code.[7,8] These biomarkers work similarly to the CSF biomarkers but are less invasive because they are contained in the plasma of the blood. This means that the blood-based biomarkers can be used in screening patients when blood is collected. In a similar manner to how the blood is tested for syphilis upon extraction, the patient would also be tested for AD. Current studies also show that blood-based biomarkers can be used to predict progression in both, disease and prodromal states – making them good candidates for early diagnosis of AD.

One blood-based biomarker that can be used in detecting AD is miRNA. miRNA regulates mRNA translation through complimentary binding, therefore blocking the protein expression.

miRNAs work by dysregulating beta-site amyloid precursor protein-cleaving enzyme 1 and by regulating Hirano bodies. Hirano bodies consist of actin, cofilin, and granulin – proteins which are uniquely seen in the progression of AD. miRNAs are also tissue and cell specific, which means they are disease-specific as well. They are not only found intracellularly, but extracellularly as well. Hence, being located in the blood, these miRNAs can be drawn out of the live body when the blood is screened.

So far, twenty-six studies on mice mimicking AD symptoms have identified at least one miRNA which is expressed significantly differently in AD cases compared to the control cases. Of the 8,098 miRNAs measured, 395 were found to be considerably associated with AD. The most consistent and extensively studied miRNA is miR-107.[8] This miRNA is the strongest candidate as it has been shown to decrease in AD throughout all trials. As miR-107 decreases, the number of proteins associated with AD increase. In a study by Wang and a team of researchers, published in *The Journal of Neuroscience* showed through a one-way ANOVA test that miR-107 significantly decreased in all groups tested, with a p-value of 0.014 (indicating that it significantly decreases in the AD groups compared to the control groups). Particularly, mi-R107 levels decreased significantly in non-demented patients lacking pathology, in comparison to those with mild cognitive impairment. This correlation was represented by a p-value of 0.008. This data suggests that miR-107 is expressed in the earliest stages of AD.[9] From the data in this experiment, and from other such studies, miR-107 can be considered a strong candidate for further testing.

Although blood-based biomarkers hold a promising future for detection of early stages of AD, there are a few limitations to these studies.[10] So far, there are no standardizations between studies. This means that the way each biomarker is tested for effectiveness and efficiency can vary from study to study. Furthermore, Receiver Operating Characteristic curves (ROC curves), which are used by researchers to evaluate how useful certain measures are in predicting binary outcomes (AD cases, control cases) can be biased. ROC curves can be cut and specified to a certain selection of data. The ROC curves must be homogenized across all studies to improve accuracy and reliability of results. For future studies, the multiple testing used by some studies needs to be adjusted. Failure to adjust for multiple testing leads to an increased risk of a type I error. A type I error is considered a report in which an association has not occurred. Additionally, future studies will depend on how accessible large samples will be. Larger samples will allow future studies to obtain more specific and accurate results – increasing the likelihood of discovering a blood-based biomarker that can enter clinical trials.

References

1. Hampel, H., O'Bryant, S.E., Molinuevo, J.L. *et al.* Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. *Nat Rev Neurol* 14**,** 639–652 (2018).
2. Blennow, K., Hampel, H., Weiner, M. *et al.* Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. *Nat Rev Neurol* 6**,** 131–144 (2010).
3. Gong, C., Liu, F., Grundke-Iqbal, I. *et al.* Post-translational modifications of tau protein in Alzheimer's disease. *J Neural Transm* 112**,** 813–838 (2005).
4. Blennow, K., Zetterberg, H. (The Sahlgrenska Academy at University of Gothenburg, Mölndal, Sweden). Biomarkers for Alzheimer's disease: current status and prospects for the future (Review). *J Intern Med* 2018; 284: 643– 663.
5. Hansson, O., Lehmann, S., Otto, M. *et al.* Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. *Alz Res Therapy* 11**,** 34 (2019). https://doi.org/10.1186/s13195-019-0485-0
6. Hampel, H., Blennow, K., Shaw, L. M., Hoessler, Y. C., Zetterberg, H., & Trojanowski, J. Q. (2010). Total and phosphorylated tau protein as biological markers of Alzheimer's disease. *Experimental gerontology*, *45*(1), 30-40.

7. Denk, J., Boelmans, K., Siegismund, C., Lassner, D., Arlt, S., & Jahn, H. (2015). MicroRNA Profiling of CSF Reveals Potential Biomarkers to Detect Alzheimer`s Disease. *PloS one*, *10*(5), e0126423. https://doi.org/10.1371/journal.pone.0126423
8. Fransquet, P. D., & Ryan, J. (2018). Micro RNA as a potential blood-based epigenetic biomarker for Alzheimer's disease. *Clinical biochemistry*, *58*, 5-14.
9. Wang, W. X., Rajeev, B. W., Stromberg, A. J., Ren, N., Tang, G., Huang, Q., Rigoutsos, I., & Nelson, P. T. (2008). The expression of microRNA miR-107 decreases early in Alzheimer's disease and may accelerate disease progression through regulation of beta-site amyloid precursor protein-cleaving enzyme 1. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, *28*(5), 1213–1223.
10. Pedlar, C. R., Newell, J., & Lewis, N. A. (2019). Blood Biomarker Profiling and Monitoring for High-Performance Physiology and Nutrition: Current Perspectives, Limitations and Recommendations. *Sports medicine (Auckland, N.Z.)*, *49*(Suppl 2), 185–198. https://doi.org/10.1007/s40279-019-01158-x