

FROM SPECIMEN TO BIOMARKER? HARMONISATION OF BIOBANK SOP'S IN THE DISCOVERY OF NOVEL CANDIDATE BIOMARKERS FOR ALZHEIMER'S DISEASE (AD)

Rivka Ravid

Royal Netherlands Academy of Sciences, Brain Bank Consultants. Amsterdam, The Netherlands

The fierce search for valid Biomarkers for AD in body fluids such as blood, cerebro-spinal fluid (CSF) and urine is still ongoing. Biomarkers will facilitate early detection and differential diagnosis and may act as predictor in the transition from MCI to AD. Due to the large diversity and variation between individuals, centers and the applied procedures, there is currently no single international acceptable Biomarker which can be clinically / successfully applied..

Aims

Future plans are to create a collaborative global network of Biobanks, high quality specimens using harmonized protocols and make them widely available for clinical and basic research. These specimens will be used to identify novel candidate Biomarkers, which will be reliable, non-invasive, simple to detect, inexpensive and potentially have a predictive value of disease progression.

Methods

The current search we perform for valid AD Biomarkers includes; clinical interview, clinical dementia rating scale (CDR), neuropsychological testing, neuroimaging (functional MRI and PET), genetic markers and the analysis of blood, CSF and urine obtained from living donor and validation in brain tissue correlates by postmortem autopsy. Biomarker detection in postmortem autopsy material is still problematic because of data fluctuation due to rapid post-mortem changes. The combined use of Amyloid and Tau as early diagnostic markers in the pathology of dementia has been reported in differential involvement in Alzheimer's disease (AD), Lewy Body dementia (DLBD), Vascular dementia, fronto-temporal lobar degeneration (FTLD) and non-neurological controls, but the variation is still too high. We are in the stage of introducing a consensus protocol for the collection, handling, storage and documentation of the donated specimens.

Results

Procurement of high quality specimens from the relevant clinical groups and controls, in combination with globally accepted standardized collection/handling/storage/analytical protocols, is currently ongoing in a large number of Biobanks, in Europe, The US, Asia and Australia; these Biobanks are collaborating and exchanging specimens and data in the framework of ISBER, ESBB, BBMRI and P3G. There is still a large inter laboratory variation in the pre analytical procedures, assay performance and outcome.

Large scale specimen cohorts and clinical data-sets enabled the testing of the diagnostic accuracy and combined retrospective analysis of large number of specimens resulted in a more reliable quantification of Abeta (1-42), Tau and phosphorylated Tau in blood and CSF of AD patients. Genetic factors like the APOE $\epsilon 4$ genotype, seem to predispose patients to vulnerability in the medial temporal areas, which leads to memory loss. Non carriers of the APOE $\epsilon 4$ allele and with early-onset AD are more prone to be predisposed to vulnerability of cerebral networks. Currently we search for Ante mortem CSF Bio markers to differentiate between the 2 main causes of frontotemporal lobar degeneration (FTLD), i.e., FTLD with TDP-43 pathology (FTLD-TDP) and FTLD with tau pathology (FTLD-tau). Cerebrospinal fluid (CSF) levels of the biomarker α -synuclein are investigated as diagnostic tool in differential diagnosis of dementia with Lewy bodies (DLB) and Alzheimer's disease (AD).

Conclusions

Large scale of specimens from patients and controls will be collected, assessed and stored by multicenter Biobanks, worldwide, using the same protocols before statistically significant longitudinal followup studies can be performed and lead to routine clinical application. Biobanks and Research Tissue banks, who apply highly robust assays, are vital to assess the validity of ante-mortem and post-mortem bio markers in reflecting the hallmarks of AD to support the development of valid novel Biomarkers.

When moving from specimens to Bio markers there are still many question marks for the future; should CSF analysis be considered in patients with cognitive problems and will CSF-analysis become a routine procedure in people with memory complaints?

References

Ravid R - Biobanks for biomarkers in neurological disorders: The Da Vinci bridge for optimal clinico-pathological connection. J Neurol Sci 283, 119-26, 2009.

Ravid R- Standard Operating Procedures, ethical and legal regulations in BTB (Brain/Tissue/Bio) banking: what is still missing? Cell Tissue Bank 9, 151-67, 2008.

Ravid, R., W. Kamphorst, J.C. Van Swieten and P. Heutink - New Distinctive pathology in Fronto-temporal dementia (FTD) cases in the Netherlands. In: *Contemporary Neuropsychiatry* K. Myoshi, C. Shapiro, M. Gaviria, Y. Morita (Eds.), Springer-Verlag Tokyo, 171-174, 2001.

Ravid, R., D.F. Swaab, W. Kamphorst and A. Salehi - Brain banking in aging and dementia research - The Amsterdam experience. In: *Progress in Alzheimer's and Parkinson's Disease*, A. Fisher, M. Yorshida and I. Hanin (eds.), Plenum Press, New York, pp. 277-286, 1998.

Cruz-Sánchez, F.F., R. Ravid and M.L. Cuzner - The European Brain Bank Network (EBBN) and the need of standardized neuropathological criteria for brain tissue cataloguing. In: *Neuropathological Diagnostic Criteria for Brain Banking, European Union Biomedical and Health Research, Vol. 10*, F.F. Cruz-Sánchez, M.L. Cuzner and R. Ravid (Eds), IOS Press, Amsterdam, The Netherlands, pp. 1-3, 1995.