Alzheimer’s disease: biomarker discovery and assay development

Baiba Jansone reports on this year’s EuroSciCon Alzheimer’s Disease Congress, which focused on biomarker discovery and assay development, and how these may lead to treatment for this devastating condition.

The annual EuroSciCon Alzheimer’s Disease Congress was held in London in June. The following is an overview of the topics covered during the event.

The first speaker, and chair of the session, was Professor Amos Korczyn (Tel-Aviv University Medical School, Israel). Professor Korczyn is chairman of the Scientific Advisory Board of the Israeli Alzheimer’s Disease Association (EMDA), and a member of the SAB of Alzheimer’s Disease International. His presentation was entitled ‘Why Have We Failed to Cure AD?’.

One of the most common causes of dementia is Alzheimer’s disease and it is characterised by a clinicopathological entity of progressive dementia with specific neuropathological changes. Alzheimer’s disease is very complex and includes many factors such as cholinergic loss, trophic factor loss, aluminium toxicity, calcium excitotoxicity, oxidative stress, glutamate toxicity, Tau hyperphosphorylation and amyloid toxicity. One simple solution has not solved the problem to ensure effective treatment for Alzheimer’s disease. In 2012, even large pharmaceutical companies were saying that research into Alzheimer’s disease is too difficult and costly. So, why are we still failing to cure the disease?

Professor Korczyn asked which of the well-known hallmarks of Alzheimer’s disease such as amyloid plaques, neurofibrillary tangles, cholinergic depletion and hippocampal degeneration are responsible for the cognitive decline. He also pointed out that the assumption that Alzheimer’s disease is due to enhanced β-amyloid production should not be seen as a generalisation as there are many reports of people with high levels of β-amyloid who are not demented. Deposits of amyloid can be found, for example, after ischaemia, trauma and in epilepsy.

Recent research by Andrade-Moraes et al. shows that cell number changes are more important in Alzheimer’s disease and relate to dementia, not to plaques and tangles. We have to keep in mind that the disease is not an homogeneous disease entity. Professor Korczyn discussed Alzheimer’s disease complexity that cannot be solved by simple solution targets because almost all dementia is presented as a mixed multifactorial condition. His take home message was that preventative therapy should start early and therapy should be directed at many targets simultaneously.

Speakers and delegates at the EuroSciCon 2014 Alzheimer’s Disease Congress.

The role of pathology in Alzheimer’s disease has been indisputable so far and is used as the gold standard. However, pathologists can only identify features such as cortical Lewy bodies, cortical microbleeds and leukoaraiosis, but they cannot establish time of onset of the cognitive decline or of brain damage, and there is missed evidence of vascular damage. Professor Korczyn asked which of the well-known hallmarks of Alzheimer’s disease such as amyloid plaques, neurofibrillary tangles, cholinergic depletion and hippocampal degeneration are responsible for the cognitive decline. He also pointed out that the
**PRESENILIN DETECTION**

Professor Javier Sáez-Valero (Professor and Group Leader, Instituto de Neurociencias de Alicante, Universidad Miguel Hernández-CSIC, and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Spain) talked about ‘Cerebrospinal Fluid Presenilin-1: A Potential New Biomarker for Alzheimer’s Disease.’ He noted that the ideal Alzheimer’s disease biomarker should have a diagnostic sensitivity and specificity exceeding 80% for distinguishing Alzheimer’s disease from other dementias. Existing biomarkers, such as cerebrospinal fluid (CSF) T-tau, is a rather good biomarker; however, we should take into account that the weak point is that it partially overlaps with other neurological disorders. Also, β-amyloid has shown diagnostic accuracy for incipient Alzheimer’s disease; however, there is still a need to identify additional, more specific biochemical markers of the disease.

Professor Sáez-Valero mentioned that one of the approaches for new diagnostic biomarkers could be proteins involved in the pathological processing of β-amyloid, and other amyloid precursor protein (APP) fragments are potential CSF biomarker candidates. He presented data from a study that showed the methodology of presenilin-1 (PS1) detection in CSF as 100–150 kDa heterocomplexes containing both the N- and C-terminal fragments of the protein, as well other γ-secretase components, but differ from active γ-secretase membrane complexes.

Results of the studies revealed that PS1 complexes are present in human and mouse (PS1 cKO) CSF and plasma; however, it was noted that stability of the CSF-PS1 complexes may be affected by the methodological conditions. Data show that stable complexes of presenilin-1 are increased in Alzheimer’s disease post-mortem CSF, suggesting a potential value as a biomarker for the disease.

Estimation of PS1 CSF levels may be useful to determine the disease-modifying effects of newer Alzheimer’s therapy. The future direction will be development of a more sensitive assay for PS1 complexes. Also, it would be useful to be able to check the specificity compared with other neurological disorders, such as frontotemporal dementias, vascular dementia, Lewy bodies dementia and some focal atrophies.

**MEMORY MAN**

The presentation entitled ‘Biomarker Assessment in a Memory Clinic: Is There Any Added Value?’ was given by Professor Adrian Ivanoiu (Saint Luc University Hospital and Institute of Neuroscience, Catholic University of Louvain, Brussels, Belgium). In his presentation, the speaker looked at how a doctor could establish a diagnosis of preclinical Alzheimer’s disease in patients attending a memory clinic.

For this purpose, a clinical and neuropsychological examination are traditionally performed, but the sensitivity and specificity of the clinical method is unsatisfactory Therefore, biomarkers have been assessed in support of the clinical diagnosis, targeting either β-amyloid accumulation through levels in the CSF or by positron-emission tomography (PET) scan with amyloid tracers, or neuronal degeneration and injury (ie tau and ptau in CSF; fluorodeoxyglucose [FDG] PET; atrophy detected in specific brain areas by magnetic resonance imaging [MRI]).

Professor Ivanoiu pointed out that available biomarkers can improve the clinical classification of non-demented patients. However, he cautioned that biomarkers are sensitive but unfortunately, not specific as they can be positive also in asymptomatic elderly individuals. There is a clear need for standardisation and setting of specific cut-off values for the Alzheimer’s disease biomarkers.

**MOLECULAR DYNAMICS**

The presentation entitled ‘Amyloid Hypothesis for AD: Insight from Single Molecule Experiments and Computational Analyses’ was given by Professor Yuri Lyubchenko (University of Nebraska Medical Center, USA), who presented an experimental approach of atomic force microscopy (AFM) spectroscopy developed in his department. This approach allows detailed characterisation of misfolded amyloids and provides missing specific knowledge regarding the aggregation process.

The study data provide evidence that the dimers, compared to monomers, are highly stable, suggesting that dimerisation is the mechanism by which the misfolded states of proteins are stabilised, and thus is suggested as the key step for amyloid aggregation and triggering of the disease.

Professor Lyubchenko pointed out the importance of environmental conditions that can also modulate the misfolding and aggregation of proteins, and therefore disease development, as well as the imbalance of nutrients that can contribute to the disease onset and progression.

In his talk, Professor Lyubchenko also demonstrated the advantages of using all-atom molecular dynamics (MD) computer analysis and demonstrated AFM as a nanotool for drug design in the treatment, diagnosis and prevention of Alzheimer’s disease.

**A MODEL SYNDROME**

In the presentation ‘Alzheimer’s Disease in Down’s Syndrome – An Ideal Model for Biomarker Discovery’, Dr Shahid Zaman (Cambridge Intellectual and Developmental Disability Research Group, Department of Psychiatry, University of Cambridge, UK) discussed the close relationship between Down’s syndrome and Alzheimer’s disease, this being most likely due to amyloid precursor protein. The gene coding for APP is present in triplicate on chromosome 21. Epidemiology and neuropathology of Alzheimer’s disease in Down’s syndrome reveals that by the age of 40 years the pathological hallmarks of Alzheimer’s disease (ie amyloid plaques, neurofibrillary tangles and neuronal death) are observed almost universally in the brains of patients with Down’s syndrome, but that not all Down’s syndrome patients over the age of 40 years fulfill the clinical criteria for a diagnosis of dementia. Therefore, by the time a clinical diagnosis is made, it may be too late to treat effectively, as the clinical phenotype ‘lags behind’ the neuropathology by 10–15 years.

This clearly shows a need to define a prediagnostic or mild cognitive impairment (MCI) state where the discovery of biomarkers would be beneficial. Cerebrospinal fluid Aβ42, amyloid PET, CSF tau, structural MRI, [18F] FDG PET (to measure glucose uptake and metabolism) and cognitive impairment are some of the biomarkers currently used in Alzheimer’s disease.

Dr Zaman discussed some of potential biomarkers being explored in Down’s syndrome and presented preliminary data on β-amyloid neuroimaging using [11C] PiB-PET and mitochondrial function assay in vivo. He presented a study in which 30 patients with Down’s syndrome were included, all of whom had [11C] PiB-PET, sMRI, [18F] FDG PET (to measure glucose uptake and metabolism) and cognitive impairment. The results presented showed a significant positive correlation between age and BPND (a measure of the...
degree of [14C] PiB binding and therefore fibrillar amyloid in frontal, parietal and temporal cortices.

The data also showed that the prevalence of binding starts to rise dramatically from about the age of 45. Several subjects displayed a subcortical pattern of binding similar to that previously seen in cohorts with mutations in the presenilin 1 gene, and a study of non-demented people with Down’s syndrome suggested striatal binding may be common in this population. Participants with binding in more than one area of cortex or thalamus always had binding in the striatum.

The next issue raised by Dr Zaman was the importance of mitochondria, which are known to be involved in Alzheimer’s disease pathology by their bi-directional interaction with amyloid and mitochondrial dysfunction, and mutations in mitochondrial DNA were mentioned as key hallmarks of biological ageing. Recent work by Phillips et al., involving a [31P] MRS study, showed defective mitochondrial function in vivo in skeletal muscle in non-demented adults with Down syndrome.

Dr Zaman concluded that Down’s syndrome is an ideal model to study the pathogenesis of Alzheimer’s disease, test the amyloid cascade hypothesis and develop biomarkers. He suggested that striatal binding may be an early preclinical marker of Alzheimer’s disease in Down’s syndrome and that mitochondrial dysfunction occurs pre-symptomatically, which is likely to be contributing to Alzheimer’s disease pathology.

FURTHER READING

Dr Baiba Jansone (baijansone@inbox.lv), Associate Professor, Department of Pharmacology, Faculty of Medicine, University of Latvia. EuroSciCon’s 2015 Alzheimer’s Disease Congress is scheduled to take place on 23–25 June 2015 (www.regonline.co.uk/Alz2015).