4-year evaluation of the strategic research area Systems Neurobiology

3. Best case descriptions

Biomarkers for Alzheimer disease – Implications for diagnostics and therapy

Summary of the impact

We have discovered six proteins that are upregulated in cerebrospinal fluid from Alzheimer patients. Today no disease modifying treatment exists and accurate diagnosis is possible first by postmortem analysis of the brain. To be able to develop effective treatment strategies biomarkers are needed both for enrollment of pure Alzheimer cases to clinical trials and as read out for clinical trials. Also the ability to stratify patients for different types of treatment will be of great importance. There is a great need to identify biomarkers for Alzheimer disease. We are now characterizing such proteins by investigating the pathological mechanisms they are mirroring in the brain. This has led to the discovery that one of the proteins is involved in the inflammation process in the brain and has a neuro-protective effect. We have submitted a provisional patent application to the USPTO which describes a pattern (an algorithm) of the proteins that can be used for diagnostics, stratification, and readout for clinical trials for Alzheimer disease. We are just writing up a second provisional patent application which describes substances that enhance the secretion of the discovered neuro-protective protein as new therapeutics for Alzheimer disease.

In Sweden there are approximately 120 000 persons that suffer from Alzheimer disease. The cost for the care of these patients is 50 billion SEK per year. A delay of the onset of the disease with five years would reduce the cost with 50%. The discovery of any kind of biomarker that reflects the pathological mechanisms of Alzheimer disease and can be used as a drug target will have a great impact for both the research society and for the diagnostic and pharmacy companies. The discovery of these six proteins can lead to a well needed breakthrough in the Alzheimer disease research area.
Underpinning research

During 2012 and the beginning of 2013 we investigated three cohorts of CSF from Alzheimer patients and control individuals. In total 45 Alzheimer cases and 45 control individuals were analysed and 35 proteins were screened in total. This research was performed by me, the PhD student Andrea Armstrong and the technician PhD Camilla Janefjord. Co-inventors of the patent application are me, Andrea Armstrong and Professor Samuel Svensson (CBD Solutions AB). The patent application was submitted in April 2013 and thereafter we published the article: “Lysosomal Network Proteins as Potential Novel CSF Biomarkers for Alzheimer’s Disease”, Armstrong A, Mattsson N, Appelqvist H, Janefjord C, Sandin L, Agholme L, Olsson B, Svensson S, Blennow K, Zetterberg H, Kågedal K. 2013, Neuromol Med Oct 8.

The neuro-protective protein was identified in the same three cohorts of individuals described above. The protein prevents aggregation propagation of amyloid-β via binding to amyloid-β with a binding constant of 5.85 (µM)-1. This binding constant was calculated via FRET analyses. We have also seen that this protein prevents the toxicity of amyloid-β in both cellular experiments and in amyloid-β transgenic Drosophila melanogaster. We are now screening small molecule drugs on cells that secrete this neuro-protective protein and we are evaluating the drugs that mediate an increased secretion of this protein while pro-inflammatory proteins are not being overexpressed. This research is performed by me, the PhD students Linda Helmfors and Andrea Armstrong, PhD Sangeeta Nath and Associate Professor Ann-Christine Brorsson. The second patent application will be based on the small molecules that stimulate the secretion of this neuro-protective protein. Inventor of the patent will be me.

References to the research

The article of the biomarkers for Alzheimer disease was recently published (October 2013) and the impact and references to this research is still lacking. However, interest in collaborations around the biomarker proteins has been initiated with Professor Jonas Bergquist (Uppsala University), Professor Lars Lannfelt (Uppsala University), Professor Lars-Olof Wahlund (KI) and Professor Richard Mayeux (Columbia University) and the continuation of the collaboration with Professor Kaj Blennow and Professor Henrik Zetterberg both at Sahlgrenska Academy.

The company BioArctic is interested in using the six discovered proteins as readout of a clinical trial and AstraZeneca is interested in the neuroprotective protein as a potential drug target.

I was awarded with one grant of 2 000 000 SEK from Uppsala BIO (2013-2014) and one grant of 200 000 SEK from InnovationskontorEtt (Innovation office) at Linköping University (2013-2015). Both the grants has the title: “Biomarkers for Alzheimer disease”
Synthetic MRI in clinical practice

Summary of the impact

Magnetic Resonance Imaging (MRI) is an imaging method providing high soft tissue contrast, and high sensitivity for detecting pathological changes. However, MRI exams are presently very time-consuming compared to other imaging modalities, e.g. computed tomography (CT). Whereas a CT examination only take a few minutes, an MRI examination requires repeated scans, often resulting in examination times of 30–60 minutes per patient. Given the scarcity of scanner time, this bottle-neck is a severe problem in the handling of patients with diseases of the brain.

Normally, each MRI examination consists of several separate pulse sequences, each with different characteristics depending on the scanner setting, e.g. T1-, T2 or proton density (PD-) weighted images. Since the images retrieved within a conventional MRI examination depend on a multitude of scanner settings, the signal intensity will inevitably vary from one examination to the next. Thus it is not possible to compare different exams in terms of signal intensities.

A novel technique, newly developed at the Center for Medical Image Science and Visualization (CMIV) of Linköping University, using synthetic MRI, allows a complete examination to be performed in considerably shorter time than has hitherto been possible. The technique relies on quantitative MRI, i.e. the acquisition and quantitative calculation of the MR physics parameters: T1, T2 and PD. These data are then used to produce images of very similar appearance to the images to which clinicians are used. In a typical examination of the brain, acquisition time is reduced from 15 minutes to 6 minutes. This opens the possibility of radically increasing through-put in the care process, provided that the procedure results in equivalent diagnostic accuracy.

The method is potentially applicable to diagnosis of a number of diseases of the brain, including multiple sclerosis (MS), brain tumours and atrophy [4].
Underpinning research

The basic principle for acquisition and calculation was developed by Marcel Warntjes, who is a clinical scientist in MR Physics at CMIV, and Peter Lundberg, adjunct professor of MR physics. Quantitative and synthetic MRI had been described earlier, but only with examination times that were prohibitively long for standard clinical use.

The technique is currently being further developed and clinically evaluated by two doctoral students within our group, Janne West (MR physics) and Ida Blystad (radiology), and has also resulted in the formation of a new company, Synthetic MR AB (www.syntheticmr.com). Much of the physics work is included in the doctoral dissertation of Janne West (planned defence 14 Febr, 2014) [1-11]. Clinical evaluation of the technique is the topic of the dissertation of Ida Blystad (half-time seminar planned in the spring of 2014).

References to the research
