

Stopping Alzheimer's before first symptoms appear

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Old man in island of Santorini by Klearchos Kapoutsis.

New research just out in the journal *Science Translational Medicine* opens the door for the development of treatments capable of stopping

Alzheimer's disease (AD) before its first symptoms, that is to say before any crucial damage occurs. In fact, if AD is a devastating disorder it is also an extremely slow one; it takes more than 10 years for the first symptoms to appear making this preclinical period (pre-symptoms) the ideal time to intervene.

And now a study from the Hertie Institute for Clinical Brain Research in Tübingen and the Hospital de Santo António-CHP, Porto, Portugal could be the first step towards that – Luís Maia and Stephan Kaeser found that changes occurring in the [cerebrospinal fluid](#) (the liquid around the spine and the brain also designed as CSF) of two animal models of AD parallel [disease progression](#), and as such can be used to monitor the disease without resorting to symptoms.

Remarkably these biomarkers ([biological changes](#) that signal disease) have already been seen in AD patients, but a direct link to the disease could not be proved since the brain (and its destruction) can only be observed post-mortem. So the new study introduces two animal models of AD that can be instrumental to understand the disease and the effect of different treatments in patients, in particular during the preclinical period. The work also gives support to a recent suggestion that these biomarkers could be used to predict disease development in preclinical patients what would be great news.

AD is a public health disaster waiting to happen - 36 million people were affected in 2010 with numbers predicted to double by as early as 2020 and still no treatment on the horizon. The disease, which normally comes with old age, irreversibly destroys the patients' brain causing [loss of memory](#), language and even time and space perception. And, often, ends in total dependence with devastating social, emotional and economical consequences for families and society. Just in 2010, the WHO calculated that 640 billions dollars were spent caring for Alzheimer's dementia patients. With the world's population living longer and longer pushing

AD numbers, it is urgent to find some kind of cure or treatment, what has not been easy.

So the recent observation that biomarkers - amyloid-beta (Ab) peptide and Tau protein - in the cerebrospinal fluid (CSF) of AD patients could inform on the disease progression was particularly exciting because it raised the possibility of finally be able to intervene during the disease preclinical period.

In fact, even if we do not know why or how the brain is destroyed during AD, the disease has three clear hallmarks: death of the brain cells and the two insoluble aggregates that form in the brain as the disease develops of amyloid-beta (Ab) peptide (called Ab plates) and Tau protein (called neurofibrillary tangles).

And recently scientists discovered that AD patients had less Ab peptide and more tau in their CSF than normal individuals and the first suspicion was that this had to do with disease progression. Because this liquid is in direct contact with the outside of brain, it should reflect the biochemical changes that occur in this organ. So, as Ab plates grow in size and number, less soluble Ab peptide exists to pass into the CSF. On the other hand, the total levels of tau in CFS are believed to reflect the neurofibrillary tangles and nervous cells destruction (the brain damage), so tau in the CFS increases as tangles increase. But these were indirect assumptions based only on symptoms and not on brain observations

So the next step was to find an [animal model](#) that reproduced these characteristics and test the possibilities.

Transgenic mice with human AD-linked mutations that overproduce Ab peptide, develop Ab plates (but not tau neurofibrillary tangles) and have no symptoms, are routinely used to study AD. Using a new more sensitive detection method Maia and Kaeser decided to investigate the

CSF of two of these animal models trying to find the biomarkers and investigate their relationship with the Ab plates. To their surprise they discovered that not only CSF Ab levels drop as the Ab plates formed, but this reduction was followed by a concomitant increase in CSF tau levels. This is quite remarkable as the mice do not develop neurofibrillary tangles neither present frank neuronal loss.

These results challenge the assumption that tau CSF increase seen in humans was linked to the neurofibrillary tangles and the neural loss of AD and will need further investigation. But, and more importantly, they clearly show that as Ab plates grow, the concentration in the CFS of Ab peptide diminishes and that of tau increases, and that this occurs in a time scale very similar to what is seen in humans.

Although Maia and Kaeser's findings will need more research, they suggest that these transgenic mice can be used to test new drugs for AD using CFS analysis to monitor disease (or potential treatments' effects), what means that the results might be transferable to preclinical patients, where they will be of particular clinical significance particularly for those with the same mutations carried by the mice. This is great news; after all, to be able to arrest the disease before symptoms appear, means to stop it before the devastating mental destruction occur.

More information: Maia, L. et al., Changes in Amyloid-b and Tau in the Cerebrospinal Fluid of Transgenic Mice Overexpressing Amyloid Precursor Protein, *Sci Transl Med* 17 July 2013: Vol. 5, Issue 194, p. 194re2. [DOI: 10.1126/scitranslmed.3006446](https://doi.org/10.1126/scitranslmed.3006446)

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