Identifying Alzheimer's risks – as early as 17 years before diagnosis

In order to develop approaches for the prevention and treatment of Alzheimer's dementia in clinical trials, it would be helpful to be able to identify people with a particularly high risk of developing the disease. But which biomarkers can indicate an increased likelihood of disease early on in symptom-free people who actually develop Alzheimer's later?

This was investigated by scientists from the German Cancer Research Center (DKFZ), Heidelberg University and Ruhr University Bochum, as well as the Saarland Cancer Registry. The team now identified the protein GFAP, whose blood concentration is already elevated up to 17 years before the clinical diagnosis of dementia, as a potentially promising early biomarker.

Alzheimer's dementia is usually diagnosed only when characteristic symptoms such as memory problems appear. But by this time, the actual biological onset of the disease is already far in the past and the underlying brain damage is already advanced and irreversible.

Experts see this gradual development as one of the main reasons for the difficulty in developing effective methods of prevention and treatment. "Approaches to prevention and treatment would probably be most effective in the asymptomatic early phase of the disease, when the first brain changes occur. To test such interventions in clinical trials, it is crucial to identify people who are at particularly high risk of developing AD," says Hermann Brenner of the German Cancer Research Center. "Detecting biomarkers in the blood that indicate very early changes could be particularly helpful for this.

Several blood biomarkers are already known whose levels characteristically rise in Alzheimer's dementia. These include P-tau 181, which is determined in the course of Alzheimer's differential diagnosis, or NfL (neurofilament light chain), a biomarker for neurodegeneration, as well as GFAP, a characteristic cell building block in certain brain cells. "We now wanted to know whether one or more of these markers is detectable in people who develop Alzheimer's later in life, long before the first symptoms appear," Brenner explains.

For this investigation, Brenner's team used blood samples from participants in the ESTHER[1] trial. This cohort study, led by Brenner and conducted jointly with the Saarland Cancer Registry, has been running since 2000. For the current work, the research team considered the baseline blood samples of 145 ESTHER participants who were diagnosed with Alzheimer's dementia over of up to 17 years of follow-up. As a control, 507 participants without a dementia diagnosis were randomly selected.

Key findings of the evaluation:

- Elevated blood GFAP levels occur up to 17 years before diagnosis in people who later develop Alzheimer's disease.
- Among the three markers studied, elevated GFAP levels had the highest predictive power for later Alzheimer's dementia.
- Blood concentrations of the other two biomarkers studied, NfL and P-tau 181, do not increase until about nine years before disease manifestation.
- The predictive value of elevated NfL and P-tau 181 levels was highest in study participants with low risks for cardiovascular disease. Cardiovascular health plays an important role during all stages of dementia development, and cardiovascular disease can negatively affect disease progression.

"We found evidence for the first time that an increase in the concentration of GFAP in the blood could be a very early Alzheimer's risk marker. Elevated P-tau 181 levels, on the other hand, have long been discussed as an Alzheimer's risk marker. However, further and preferably even larger studies must clarify when exactly the concentration of this marker increases in order to best determine a possible use for early detection and prevention," explains first author Hannah Stocker from the Network Aging Research at Heidelberg University.

Study leader Hermann Brenner adds: "A stepwise approach would be conceivable for predicting Alzheimer's risk: A positive GFAP result could serve as an indication of which individuals should undergo further testing. In this way, it could be possible to narrow down the point in time at which there would be the greatest chance of actually stopping the disease process or at least positively influencing it."

1) ESTHER: Epidemiological Study on Opportunities for Prevention, Early Detection and Optimized Therapy of Chronic Diseases in the Elderly Population

Publication:

Hannah Stocker, Léon Beyer, Laura Perna, Dan Rujescu, Bernd Holleczek, Konrad Beyreuther, Julia Stockmann, Ben Schöttker, Klaus Gerwert, Hermann Brenner: Association of plasma biomarkers, P-tau181, glial fibrillary acidic protein, and neurofilament light, with intermediate and long-term clinical Alzheimer's disease risk: Results from a prospective cohort followed over 17 years
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Further information

- German Cancer Research Center (DKFZ), Heidelberg