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Hereditary Alzheimer's: Blood Marker for Defective Neuronal Connections Rises Early

Ulm, Halle (Saale)/Germany, April 16, 2025. Individuals with a genetic predisposition to Alzheimer's disease show altered blood levels indicating damaged neuronal contacts as early as 11 years before the expected onset of dementia symptoms. This is evident in the levels of the protein "beta-synuclein". An international team, including researchers from DZNE, Ulm University Hospital and University Medicine Halle report these findings in the journal "Alzheimer's & Dementia". The biomarker studied here could potentially help to detect neurodegeneration at an early stage and thus indicate an adequate time for starting treatment.

Presently, new medicines for the treatment of Alzheimer's disease, the most common form of dementia, are becoming available. These "amyloid antibodies" trigger the removal of tiny deposits from the brain and can delay disease progression. However, treatment in the initial stages of the disease is a prerequisite. "Early diagnosis is therefore becoming increasingly important. But at the moment, Alzheimer's is usually diagnosed quite late. Thus, we need advances in diagnostics. Otherwise, we won't be able to tap the full potential of these new drugs," says Dr. Patrick Öckl, a research group leader at DZNE's Ulm site and at the Department of Neurology at Ulm University Hospital.

That's why we have been studying beta-synuclein for quite some time. Blood levels of this protein reflect neuronal damage and can be determined relatively easily. In this, we see a potential biomarker for the early detection of neurodegeneration. This assessment is supported by our current study results." The potential for application probably extends beyond Alzheimer's, according to the scientist: "This marker indicates neuronal damage that can also result from a stroke, for example. Nevertheless, our research shows that it is particularly relevant in the context of Alzheimer's disease."

Fragments from the synapses

Beta-synuclein is a protein found primarily at the junctions between neurons. These so-called synapses, through which neurons exchange signals with each other, gradually break down in the course of Alzheimer's disease: As a result, beta-synuclein is released, enters the bloodstream from the brain and can then be detected by blood test. "Our research shows that synaptic degradation starts very early. It begins before cognitive impairment manifests," says Öckl. "This makes beta-synuclein a marker that responds at a pre-symptomatic stage. Specifically, this means that blood levels of the protein go up."

Familial Alzheimer's disease

The findings are based on data from DIAN, an international research network dedicated to the hereditary form of Alzheimer's disease, which is caused by mutations in the genome. Since these genetic anomalies can be passed on to offspring, cases of dementia run in the families of the affected individuals. "The hereditary variant of Alzheimer's is very rare and can manifest in early or middle adulthood. However, from a pathological point of view, it is very similar to the sporadic variant of Alzheimer's, which is much more common and usually doesn't occur before senior age", says Prof. Markus Otto, head of the Department of Neurology at University Medicine Halle, who also played a major role in the current research. Based on present knowledge, these genomic errors almost inevitably lead to dementia. It is possible to estimate when symptoms are likely to begin. "For a person with a mutation, it is possible to predict the years until the onset of dementia symptoms. Experience tells us that this can be calculated on the basis of the age at which cognitive impairments first occurred in older relatives," explains Otto. "This estimate is available for all participants in DIAN and allows disease progression to be put into a time frame."

Blood marker correlates with symptomatology

In the current study, blood of more than 100 adults with such gene mutations was examined for beta-synuclein. These individuals were between about their mid-30s and mid-40s. All study participants were assessed for cognitive performance: about one-third showed signs of dementia, while the remaining subjects had no symptoms. In some cases, the researchers

were also able to characterize the health status using samples of cerebrospinal fluid and brain scans. Some participants were even examined multiple times, allowing their condition to be monitored over several years. Ultimately, the various data provided a picture of how blood levels of beta-synuclein changed in the course of Alzheimer's disease. "The concentration of beta-synuclein in the blood begins to rise about 11 years before the first symptoms of dementia are expected. In other words, there are early signs of synaptic degeneration," says Otto. "Loss of brain mass and other pathological changes that also occur in Alzheimer's disease do not happen until later. And, after the onset of symptoms, the more severe the cognitive impairment, the higher the beta-synuclein level in the blood. Thus, this biomarker reflects pathological changes in both the pre-symptomatic and symptomatic stages."

Perspectives

DZNE researcher Öckl expects similar effects also to occur in the sporadic form of Alzheimer's disease: "In view of the similarities with the hereditary variant, I consider this to be very likely. But obviously, this still needs to be verified in studies. If confirmed, this biomarker could perhaps be applied in the context of extended diagnostics to confirm or rule out a suspected case of Alzheimer's disease." And he sees further potential: "Besides early detection, this marker could possibly also be useful for assessing whether a therapy is taking effect, slowing synaptic loss and thus disease progression." Such a monitoring tool would be equally important for the development of therapies in clinical trials and for treatment in routine care. "In the future, we will likely have a whole range of biomarkers available to assess the status of Alzheimer's disease. I can well imagine that beta-synuclein will play a role in this repertoire," says Öckl.

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