Alzheimer's disease is composed of four distinct subtypes

29 April 2021

Credit: Unsplash/CC0 Public Domain

Alzheimer's disease is characterized by the abnormal accumulation and spread of the tau protein in the brain. An international study can now show how tau spreads according to four distinct patterns that lead to different symptoms with different prognoses of the affected individuals. The study was published in *Nature Medicine*.

"In contrast to how we have so far interpreted the spread of tau in the brain, these findings indicate that tau pathology in the brain varies according to at least four distinct patterns. This would suggest that Alzheimer's is an even more heterogeneous disease than previously thought. We now have reason to reevaluate the concept of typical Alzheimer's, and in the long run also the methods we use to assess the progression of the disease," says Jacob Vo-gel from McGill University, and the lead author of the study.

The spread of tau in the cerebral cortex is a key marker for Alzheimer's. In recent years, it has become possible to monitor the accumulation of the toxic protein in the brain of Alz-heimer's patients with the help of PET technology, an advanced medical imaging technique.

For the past thirty years, many researchers have described the development of tau patholo-gy in Alzheimer's using a single model, despite recurring cases that do not fit that model. However, the current findings explain why different patients may develop different symp-toms.

"Because different regions of the brain are affected differently in the four subtypes of Alz-heimer's, patients develop different symptoms and also prognoses. This knowledge is im-portant for doctors who assess patients with Alzheimer's, and it also makes us wonder whether the four subtypes might respond differently to different treatments. Right now, research on various drugs that reduce the amount of tau in the brain is very active, and it will be exciting to see if they vary in efficacy depending on the subtype of Alzheimer," says Oskar Hansson, professor of neurology at Lund University, who supervised the study.

The current study is a collaboration between sites in Sweden, Canada, USA and Korea. To-gether, the researchers have examined the largest and most diverse population in the world to date with tau-PET, which spans the entire clinical picture of Alzheimer's disease. The study included participants who had not yet developed any symptoms, so-called pre-symptomatic Alzheimer's, participants with mild memory difficulties and those with fully developed Alzheimer's dementia.

In a first sample, long-term data was compiled from 1,612 individuals within five independ-ent multicenter studies. Among these, the researchers identified a total of 1,143 individuals who were either cognitively normal or individuals who had developed Alzheimer's in various stages.

An algorithm was applied to the data from the tau PET images from the 1,143 individuals, the so-called SuStaIn (Subtype and Staging Inference)

algorithm. The material was pro-cessed with machine learning in an automated process, in order to be able to distinguish subtypes and patterns as impartially as possible.

As expected, many individuals did not show any abnormal tau PET signal, and these were therefore automatically assigned to a tau-negative group. By then cross-validating the tau PET images with a sixth independent cohort, and following up the individuals for about two years, the researchers were able to develop four patterns that best represented the data from the remaining individuals. Although the number of subgroups varied in relation to the individuals, all were represented in all cohorts.

"We identified four clear patterns of tau pathology that became distinct over time. The prevalence of the subgroups varied between 18 and 30 percent, which means that all these variants of Alzheimer's are actually quite common and no single one dominates as we pre-viously thought," says Oskar Hansson.

- Variant one: Tau spreads mainly within the temporal lobe and primarily affects memory. Variant one occurred in 33 percent of all cases.
- Variant two: In contrast to variant one, this variant spreads in the rest of the cerebral cor-tex. The individual has less memory problems than in the first variant, but on the other hand has greater difficulties with executive functions, that is, the ability to plan and per-form an action. Variant two occurred in 18 percent of all cases.
- Variant three: The accumulation of tau takes place in the visual cortex, i.e. in the part of the cerebrum where information from the optic nerve is processed and classified. The visuospatial processing of sensory impressions in the brain is affected in individuals with this pattern. They have difficulty orienting themselves, distinguishing shapes and contours, distance, movement and the location of objects in relation to other objects. Variant three occurred in 30 percent of all cases.
- Variant four: Tau spreads asymmetrically in the left hemisphere and primarily affects the individual's language ability. Variant four occurred in 19 percent of all cases.

"The varied and large databases of tau-PET that exist today, along with newly developed methods for machine learning that can be applied to large amounts of data made it possi-ble for us to discover and characterize these four subtypes of Alzheimer's. However, we need a longer follow-up study over five to ten years to be able to confirm the four patterns with even greater accuracy," says Oskar Hansson.

The researchers believe that this new knowledge can give patients more individualized treatment methods in the future.

More information: Vogel, J.W., Young, A.L., Oxtoby, N.P. et al. Four distinct trajectories of tau deposition identified in Alzheimer's disease. *Nat Med* (2021). doi.org/10.1038/s41591-021-01309-6

Provided by Lund University