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Levels of cerebrospinal fluid biomarkers total tau and phosphorylated tau do not predict survival time after diagnosis of Alzheimer’s disease – An 18-year follow-up

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Conclusions

Mortality in Alzheimer’s disease (AD) is complex and depends on many factors e.g., demographic and clinical. In this clinical-practice-based long-term study, almost half of the participants with AD had normal levels of cerebrospinal fluid (CSF) tau. We found no clear results that the levels of total tau (T-tau) and/or phosphorylated tau (P-tau) affect survival after diagnosis in AD. This observation does not support the theory that these patients have a more advanced disease. However, the individuals with pathological levels of tau had fewer years of education and worse cognitive status indicating a lower cognitive reserve capacity, which might influence life expectancy. These findings might be useful when considering new diagnostic criteria and when interpreting outcomes from future clinical trials of potentially disease-modifying AD therapies.

Results

Background

The pathological process in AD probably starts decades before the onset of symptoms and the clinical AD diagnosis. In patients with AD, the level of CSF amyloid-β (Aβ42) is usually lower, and the levels of T-tau and P-tau higher than in healthy elderly people. However, the cutoffs differ between studies and the predictive values are too low to diagnose AD using only CSF biomarkers. Several previous reports have shown that the levels of T-tau and P-tau become pathological later in the course of AD compared with Aβ42. It is unclear if higher levels of tau shorten the individuals’ life expectancy after diagnosis. The current study aims to investigate whether pathological levels of T-tau and/or P-tau can predict survival in AD.

Methods

The Swedish Alzheimer Treatment Study (SATs) is a prospective, observational, multicenter study for the longitudinal assessment of cholinesterase inhibitor treatment in a routine clinical setting. This presentation includes all 151 participants clinically diagnosed with AD, who underwent a lumbar puncture. Patients were evaluated regarding cognitive and functional abilities at baseline (time of diagnosis) and semi-annually over 3 years. Sociodemographic characteristics, concomitant medicaments and the date of death were recorded.

CSF was collected in polypropylene tubes, stored at ~80 °C and analyzed after the clinical follow-up of the study was completed. The levels of T-tau, P-tau phosphorylated at Thr181 (T-tau), and Aβ42 were determined using xMAP technology. Pathological levels of CSF biomarkers were defined as: T-tau > 100 ng/ml, P-tau > 51 ng/ml and Aβ42 < 209 ng/ml [1].

Independent-sample t-tests were used to compare the differences between the means obtained for the four patient characteristics that affected mortality. Potential predictors determined using xMAP technology. Pathological levels of CSF biomarkers were: T-tau, > 100 ng/ml; P-tau, > 51 ng/ml; and Aβ42 < 209 ng/ml [1].

The number and frequency of SATs participants with pathological CSF biomarkers: T-tau, n = 18 (12%); P-tau, n = 14 (9%); and both T-tau and P-tau, n = 46 (31%). All 151 patients had pathological Aβ42.

After 18 years of follow-up, 139 of the 151 participants (92%) had died; their mean (95% confidence interval (CI)) life-span after AD diagnosis was 6.7 (6.2–7.3) years. The numbers (%) of deceased individuals with pathological CSF biomarkers were: T-tau, n = 17 (12%); P-tau, n = 14 (10%); and both T-tau and P-tau, n = 43 (31%).

No linear associations were found between life expectancy after AD diagnosis and Aβ42 (r = -0.005, p = 0.957), T-tau (r = -0.117, p = 0.135), or P-tau (r = -0.020, p = 0.816). Moreover, no significant linear relationships were observed between survival time and any of the CSF biomarkers in the APOE ε4 carrier or in the ε4 carrier groups.

Kaplan-Meier graph of the distribution of time from the time of AD diagnosis to death for the four groups according to normal/pathological levels of CSF T-tau and P-tau. Using pairwise log-rank tests, the SATs patients with normal tau levels showed a longer life expectancy than those with pathological T-tau, >100 ng/ml (p = 0.044) and P-tau, >51 ng/ml (p = 0.026), but neither of both biomarkers were pathological (p = 0.449). No difference in proportion of deaths was observed between the groups (p = 0.497).

For the 139 deceased individuals, the mean (95%) CI life-span after diagnosis was similar in the four AD groups when using an ANOVA, normal T-tau and P-tau, 7.0 (6.1–7.9) years; pathological T-tau, 5.6 (4.5–6.7) years; pathological P-tau, 5.9 (4.4–7.4) years; and both pathological T-tau and P-tau, 7.1 (6.1–8.7) years, p = 0.276.

Participants with the highest quintile and quintile of T-tau (n = 126 and 129 ng/ml) and P-tau (n = 42 and 49 ng/ml), respectively, were also examined, their survival time did not differ from the other individuals.

Figure 1. Normal/pathological CSF tau biomarkers

Figure 2. Normal/pathological CSF tau and APOE genotypes


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