Type 2 Diabetes Linked to Tau Tangles in Brain

Pauline Anderson | |September 09, 2015

Older people with type 2 diabetes have an elevated level of tau protein in their cerebrospinal fluid (CSF) whether they have normal cognition, mild cognitive impairment (MCI), or dementia, a new study has shown.

As higher levels of tau in the CSF reflect greater accumulation of tau tangles in the brain, the results suggest that type 2 diabetes may contribute to this build-up of tangles, said author Velandai Srikanth, PhD, associate professor, medicine, and head of the Stroke and Aging Research Group, Monash University, Melbourne, Australia.

The finding might help explain why patients with type 2 diabetes have almost a two-fold increased risk for dementia and Alzheimer disease (AD), he said. "Tau pathology is an avenue that needs to be pursued as a potential mechanism."

Their results were published online September 2 in *Neurology*.

Dr Velandai Srikanth

Comparing Biomarkers

The study used data from the Alzheimer's Disease Neuroimaging Initiative, which was launched in 2003 to identify biomarkers of potential progression of MCI to early AD dementia. The biomarkers used in this study include MRI and positron emission tomography (PET) neuroimaging with the ligand C Pittsburgh compound B (PiB), as well as markers in CSF.

Researchers compared these biomarkers in 124 patients with type 2 diabetes (mean age, 75.5 years) and 692 participants without type 2 diabetes (mean age, 74.1 years). Type 2 diabetes was defined as fasting blood glucose level of 7.0 mmol/L or greater.

The study excluded patients with a high Hachinski ischemic score, who would be at higher risk for stroke or cerebrovascular disease. As Dr Srikanth explained, this was an effort to prevent confounding the relationship between type 2 diabetes and various neurodegeneration biomarkers. This exclusion may explain the lower prevalence of type 2 diabetes in study participants (17% in cognitively normal participants), which would be expected in a US sample of a similar age (25%).

In the 415 participants for whom CSF measurements were available, type 2 diabetes was associated with greater CSF total tau (β = 16.06; 95% confidence interval [CI], 1.10 - 31.02; P = .035), and p-tau (hyperphosphorylation of tau) (β = 5.84; 95% CI, 0.95 - 10.73; P = .02) when adjusted for age, sex, *APOE* 4 status, and cognitive diagnosis.

There was no association between type 2 diabetes and β amyloid (Aβ). "We looked at PET scans, and spinal levels of β amyloid and in both we did not find a correlation," said Dr Srikanth. He suggested, however, that the number of people in the sample might not have been large enough to detect a correlation if there was one.

Other research did find a link between diabetes and amyloid, but these were mainly postmortem studies that looked at whether the participants had type 2 diabetes before death. "In those studies, the subjects have reached the point of death, and there are several events that might happen prior to death that could confound the relationship," said Dr Srikanth.

When stratified by cognitive diagnosis, type 2 diabetes was associated with greater CSF p-tau only among those with MCI; it was not associated with CSF total tau or Aβ in any of the cognitive diagnostic groups.

Cortical Thickness

As expected, in the 816 participants with available measures, cortical thickness was greatest in those with normal cognition, followed by those with MCI and then those with AD dementia. After adjustments, type 2 diabetes was associated with lower total cortical thickness but not with hippocampal volume, presence of infarcts, or white matter hyperintensity volume.

Cortical thinning related to diabetes was observed in frontal and parietal cortices rather than the mesial temporal predilection for AD-related atrophy, noted the authors.

In the 102 participants for whom C-PiB PET scans were available, standardized uptake value ratio (SUVR), a measure of PiB uptake or binding, increased across groups, from normal cognition through MCI to AD dementia, again as expected. There was no significant association between type 2 diabetes and PiB PET-SUVR after adjustments.

Additive Effects

The authors concluded that the neurodegenerative effects of diabetes may be independent and possibly additive to those of AD and driven by pathways that promote neuronal tau more than Aβ.

How diabetes might increase levels of tau isn't clear. "No one really knows exactly why, but there's a strong feeling that low-level neuroinflammation might be set off by type 2 diabetes," said Dr Srikanth.

Type 2 diabetes causes low-grade inflammation in most organ systems, for example, cardiovascular systems, he added. "It may be that a similar low-grade inflammatory process is appearing in the brain."

It's important to learn more about the route leading from type 2 diabetes to dementia to help target interventions, said Dr Srikanth. "If we are to find specific therapies that might reduce the risk of dementia, we need to know the pathways."

He added that identifying people at higher risk for dementia might yield a group on which researchers might test new therapeutics to prevent cognitive decline.

But for now, the new study results should "enhance the awareness of physicians that older people with type 2 diabetes may have changes occurring in their brain that may contribute to the risk of dementia in the future," said Dr Srikanth.

Physicians should also ensure that patients with diabetes keep as healthy as possible, particularly in midlife since there's a long lead time to developing dementia. "A key thing physicians can do is advise these patients to adopt healthy lifestyles to potentially minimize complications from diabetes, for example maintaining good control of high blood pressure," said Dr Srikanth.

Not including patients with a high probability of vascular disease is a limitation of the study in that it didn't allow an explanation of potential vascular mechanisms. But this could also be a strength in that it facilitates better control for the confounding effects of vascular disease, said the authors.

Not "Front Page"

Steven DeKosky, MD, visiting professor, neurology and radiology, University of Pittsburgh, Pennsylvania, said that in his view, the connection the study uncovered between type 2 diabetes and phospho-tau tangles "is interesting but not a front page finding."

He pointed out that the numbers in the study were small "when you get down to the individual groups."

And, he said, it's not surprising that if you have two diseases — diabetes and dementia — the effects on the brain may be greater than having only one disease.

"Several large studies have shown that when the brains of people with Alzheimer's disease are examined postmortem, the number of people with 'pure' Alzheimer's disease — no other diagnosable brain diseases other than Alzheimer's — is about 25%," he told *Medscape Medical News*. "The majority of the cases have other things, including vascular disease, dementia with Lewy bodies. Most researchers believe that several different pathological processes combine to allow greater or heightened effects on brain function."

Another interesting finding of the study, said Dr DeKosky, was that it found no relationship between diabetes and amyloid. He's convinced there is a mechanism by which diabetes mellitus might increase amyloid deposition.

"The enzyme that breaks down insulin, insulin degrading enzyme or IDE, also breaks down β amyloid. In a diabetic with elevated levels of insulin because of insulin receptor insensitivity, the hypothesis is that excess insulin would occupy the IDE and less β amyloid would be broken down, allowing it to slowly accumulate."

Although much of this work has been done in animal models, the related principle "fits nicely with the idea that it's a potential mechanism of the elevated prevalence of Alzheimer's in diabetics," added Dr DeKosky.

The study needs to be repeated in another population, and with more controls, he said. "And it would be great to be able to test this in animals."

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