

Diabetes Linked to ALS Risk

Pauline Anderson | June 05, 2015

A new study finds an association between type 2 diabetes and a lower risk for amyotrophic lateral sclerosis (ALS), while type 1 diabetes was associated with a higher risk.

Along with other recent research that points in a similar direction, the findings should help move the field forward to improve understanding of the relationship between diabetes and ALS, said lead author Marianthi-Anna Kioumourtzoglou, ScD, Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts.

Part of this effort will involve identifying what, if any, environmental factors in type 2 diabetes might be protective and what aspects of type 1 diabetes could be harmful, said Dr Kioumourtzoglou.

"This might help in developing some prevention guidelines and maybe even treatments in future," she told *Medscape Medical News*.

The study was published online June 1 in *JAMA Neurology*.

Strong Protective Effect

The retrospective, population-based study used the Danish National Patient Register to identify 3650 patients aged 20 years and older who were diagnosed with ALS between January 1, 1982, and December 31, 2009. The mean age at ALS diagnosis was 65.4 years.

For every case, researchers selected 100 controls, matched for sex and year of birth, from the Danish Civil Registration System.

On the basis of hospital discharge codes, the investigators identified 9294 diabetes cases at least 3 years before the index date, which was the date of ALS diagnosis or the same date in controls. Researchers concentrated on diabetes discharges at least 3 years before the ALS diagnosis to minimize the chance that the association with diabetes could be due to undetected ALS.

The mean age at first diabetes-related diagnosis was 59.7 years, and there was no significant difference between cases and controls. Among the 55 patients with both diabetes and ALS, the first diabetes-related admission occurred a mean of 9.8 years before the ALS diagnosis.

The researchers uncovered a strong protective association between prior diabetes related admissions and ALS; the crude odds ratio (OR) was 0.59 (95% confidence interval [CI], 0.45 - 0.77).

Adjustment for socioeconomic status, marital status, region of residence, and prior chronic obstructive pulmonary disease (COPD; an indicator of smoking) did not change the effect estimates, nor did adjustment for obesity (OR, 0.61; 95% CI, 0.46 - 0.80).

The ORs were similar after exclusion of diabetes in the 5 or 7 years before the index date (OR, 0.66 [95% CI, 0.50 - 0.88] and 0.69 [95% CI, 0.50 - 0.96], respectively).

The researchers identified 4536 patients with obesity at least 3 years before the index date. Because these were hospital related and not based on a body mass index of 30 kg/m² (the typical definition of obesity), it likely reflects a more severe obesity problem, said Dr Kioumourtzoglou.

In models adjusting for socioeconomic status, COPD, marital status, and residence of diagnosis, effect estimates for obesity were similar to those for diabetes. However, when diabetes was included in the model, the association was weakened and no longer significant.

Age at Diagnosis

Use of hospital codes is problematic in terms of differentiating diabetes types, said Dr Kioumourtzoglou. There's a significant amount of misclassification, with type 1 patients often also having a code for type 2 diabetes. Because this might affect outcomes, researchers looked at the effect of age at diagnosis.

(Type 1 diabetes, formerly known as juvenile-onset diabetes, is in most cases autoimmune in cause and is associated with complete or almost complete absence of insulin. Type 2 diabetes "is characterized by insulin resistance and occurs later in life as a syndrome of mainly overweight adults," the authors note.)

Their sensitivity analysis of the age at ALS diagnosis showed that until about age 51 years, development of diabetes increased ALS risk (OR, 1.68), although this didn't reach statistical significance.

"ALS happens in older ages and we didn't have many younger cases, but still, it was a harmful risk," said Dr Kioumourtzoglou.

After about age 50, the risk "dropped down" significantly, indicating a protective effect, she said. For example, at age 65, the OR was 0.65 (95% CI, 0.50 - 0.85).

A second sensitivity analysis showed that a diabetes diagnosis before age 40 years had an "almost significant harmful association" with ALS (OR, 1.66), while getting diagnosed after age 40 was "significantly protective" ($P = .002$, with an OR 0.52), said Dr Kioumourtzoglou.

The mechanism tying type 1 diabetes to ALS is unclear. However, diabetes is typically autoimmune related, and research shows that autoimmunity may also be involved in ALS.

Similarly, there are no proven mechanisms by which type 2 diabetes might protect against ALS. Although the study found no link between lipid abnormalities and ALS, the researchers didn't have data on actual blood cholesterol levels. It's possible, said Dr Kioumourtzoglou, that protection is through obesity and lipid levels, which are highly correlated with type 2 diabetes.

"Part of this could be that we are seeing this whole protective effect of these other vascular risk factors."

Another mechanism could involve uric acid. People with type 2 diabetes have relatively high levels of uric acid, which is protective in other neurodegenerative diseases, said Dr Kioumourtzoglou.

High blood glucose could be another possible link. While patients with type 1 diabetes are typically receiving insulin, those with type 2 diabetes often try to control their disease through lifestyle modifications, such as losing weight.

"They may have increased glucose blood levels," said Dr Kioumourtzoglou. "I think with type 1 diabetes, people are more careful with their medication; it's more likely that they would have hypoglycemic episodes instead of hyperglycemic episodes."

Dr Kioumourtzoglou sees the new study as "the beginning of a big discussion" about the role of diabetes and energy metabolism in general, and about how these might affect ALS.

Low Prevalence

The results fit nicely with a study published earlier this year in the journal *Muscle & Nerve* that uncovered a very low prevalence of type 2 diabetes among patients with ALS, not only in clinical trial populations that might be biased because of selection criteria but also in regular clinic populations.

This finding, said lead author of that paper, Sabrina Paganoni, MD, PhD, assistant professor, physical medicine and rehabilitation, Harvard Medical School, was "striking."

Dr Paganoni and her coauthors stressed the need for a large, prospective study to determine whether type 2 diabetes affects ALS risk.

"Then, sure enough, this other study came afterwards and was totally consistent with our findings," Dr Paganoni told *Medscape Medical News*. "I was very excited to see the findings."

Because people with high body mass index are also less likely to be diagnosed with ALS, "I think there is some metabolic connection here, but we don't know exactly what it is," said Dr Paganoni. "So it's something to look at."

According to Dr Paganoni's study, diabetes is not associated with ALS prognosis, but this could be because of other things going on, she said. "That doesn't mean that diabetes is not somehow associated with something that has to do with ALS risk."

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