Estrogen Therapy Linked to Brain Atrophy in Women With Diabetes

BY MICHELE G. SULLIVAN

WASHINGTON — Women with type 2 diabetes who take estrogen therapy showed lower total gray matter volume, with atrophy particularly evident in the hippocampus.

A new analysis of the Women's Health Initiative Memory study suggested that these hormone therapy–related decrements in brain volume seem to stabilize in the years after treatment ends. However, said Christina E. Hugenschmidt, PhD, of Wake Forest University, Winston-Salem, NC, the findings also suggested caution when considering a prescription for estrogen therapy for a woman with emerging or frank diabetes.

"The concern is that prescribing estrogen to a woman with diabetes could increase her risk of brain atrophy," she said at the Alzheimer's Association International Conference 2015.

Dr. Hugenschmidt reviewed data from the Women's Health Initiative Memory Study–MRI (WHIMS-MRI). The parallel placebo-controlled trial randomized women 65 years and older to placebo, or 0.625 mg conjugated equine estrogen with or without 2.5 mg progesterone. They were all free of cognitive decline at baseline.

Dr. Hugenschmidt focused on 1,400 women who underwent two MRI brain scans: one 2.5 years after beginning the study and another about 5 years after that. The primary outcomes were total brain volume, including any ischemic lesions, total gray matter, total white matter, frontal lobe and hippocampal volume, and ischemic white matter lesion load.

At enrollment, the women were a mean age of 70 years old; 124 had type 2 diabetes. About 42% had long-standing disease of 10 years or longer. Not surprisingly, there were some significant differences between the diabetic and nondiabetic groups: Body mass index, waist girth, and waist/hip ratio were all significantly larger in the women with diabetes.

Diabetes = Less Brain Volume

At the first scan, women with diabetes who had been randomized to estrogen therapy had about 18 cc less total brain volume than those without diabetes. The brain volumes of women with diabetes who were taking placebo were nearly identical to those of the nondiabetic women, regardless of what treatment they were taking.

The difference seemed to be driven by a loss of gray matter, Dr. Hugenschmidt said. There was no significant effect on white matter. The hippocampus appeared to have a similar amount of shrinkage. However, she added, there were no differences in cognitive scores on the Mini Mental State Exam.

Insulin use didn't appear to ameliorate the findings of smaller brain volume among those with diabetes. Atrophy didn't progress, however; findings at the same scan were similar.

Interrupted Brain Metabolism

The findings may be linked to the suppression of a natural process that occurs during the perimenopausal transition, Dr. Hugenschmidt said. Estrogen is crucial in maintaining the brain's energy metabolism. It works by increasing glucose transport and aerobic glycolysis. But during this time of life, as estrogen wanes, it becomes uncoupled from the glucose metabolism pathway. The female brain then begins to use ketone bodies as its primary source of energy. Intact estrogen levels normally downregulate the use of alternative energy sources before menopause; supplementing them seems to prevent this transition from occurring.

"Among older women with diabetes for whom the glucose-based energy metabolism promoted by estrogen is already compromised, this downregulation of alternative energy sources may lead to increased atrophy of gray matter, which has a greater metabolic demand relative to white matter," Dr. Hugenschmidt and her colleagues wrote in an article published online ahead of print in *Neurology* (2015 July 10 [doi:10.1212/WNL.0000000000001816).

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