

Exercise Provides Cognitive Benefit in Patients With AD

Pauline Anderson | June 26, 2015

BERLIN, Germany — In the first study of its kind, Danish researchers have shown that intensive aerobic exercise has a positive cognitive effect in patients with Alzheimer's disease (AD).

The single-blinded, randomized, controlled study demonstrated the training intervention was feasible in that few patients dropped out, and it had a dose effect in that the most adherent patients who achieved a high maximum heart rate fared the best, said Gunhild Waldemar, MD, director, Danish Dementia Research Center, and professor, neurology, Copenhagen University Hospital, Denmark.

Dr Waldemar presented the new data at the first Congress of the European Academy of Neurology (EAN).

To date, some epidemiologic studies have found that midlife physical activity in healthy people lowers later dementia risk, the authors note. Studies in mice have shown that exercise reduces Alzheimer pathology, and other research has demonstrated that moderate physical activity improves cognition in older adults who are at high risk for dementia. But there is little evidence of the effect of physical exercise in people who already have dementia, said Dr Waldemar.

"This is the first rigorously conducted study of moderate- to high-intensity aerobic exercise in mild to moderate AD," she said.

The study included 200 patients at eight memory clinics in Denmark, which collaborated with seven research units across the country. None of the participants had any serious medical or psychiatric illnesses. Most were receiving antedementia treatment and were stable on this therapy for at least 3 months.

Researchers randomly assigned these patients to one of two groups. The intervention group (n = 107) underwent exercise training for 4 months and the control group (n = 93) received treatment as usual but could train for 1 month after the end of the 4-month study period.

The groups were similar in terms of age (median, 72 years for the control group and 70 years for the intervention group) and cognitive status (Mini-Mental State Examination score of 24.1 in the control group and 23.8 in the intervention group; Symbol Digit Modalities Test [SDMT] score of 25.4 and 27.1, respectively).

Most, about 72% in each group, lived with a caregiver. "Notably," said Dr Waldemar, many of the patients reported that they were already physically active.

Researchers randomly assigned new groups of participants to the participating centers every 6 months over a period of 2.5 years, from January 2012 to July 2014.

Patients in the intervention group trained under the supervision of a therapist for 1 hour, three times a week for 16 weeks. During the first 4 weeks, they did adaptation exercises (strength plus aerobic exercises), after which they concentrated on aerobic exercises.

Participants wore a pulse watch and aimed at a training intensity of at least 70% to 80% of maximum heart rate. Therapists validated exercise frequency and logged exercise intensity.

The primary outcome was the SDMT, a cognitive test that assesses mental speed and attention. Dr Waldemar explained that researchers chose this test because of positive results in a small randomized controlled trial of patients with mild cognitive impairment (MCI).

High Attendance

Only five patients dropped out of each group during the study. "We were very pleased with the very high attendance rate," commented Dr Waldemar.

Although in the intention-to-treat population the difference in SDMT score between the intervention and control groups was not significant at 16 weeks, neuropsychiatric symptoms significantly differed in favor of the intervention group, said Dr Waldemar.

In addition, there was a significant outcome in a per protocol analysis of the SDMT score in 66 patients who had at least an 80% attendance rate (38 or more of the 48 training sessions) and trained to at least 70% of their maximum heart rate. The difference was -4.2% (-7.9% to -0.45% ; $P = 0.03$) through use of linear regression models accounting for clustering, missing data, and differences in baseline values.

"When we compare that group to the control group, there was indeed a significant effect in favor of the intervention in the SDMT," said Dr Waldemar. "This is a per protocol analysis and is not the primary analysis, but still, that may indicate a possible dose effect of physical activity."

Dr Waldemar said it was "surprising" that such a large group of patients met the criteria for the per protocol analysis.

The adverse event rate was very low. Only one serious adverse event occurred, a case of atrial fibrillation that was possibly related to the intervention, "but of course, it's hard to know" said Dr Waldemar.

The researchers have not yet completed the analysis of the secondary outcomes, which included other cognitive measures, depression, psychiatric symptoms, functional levels, health-related quality of life, and cost-effectiveness.

In a subgroup of patients, the researchers collected plasma samples before and after training and carried out imaging studies, which will allow them to investigate various biomarkers, according to Dr Waldemar. This, she said, might help determine the physiology behind the effect of exercise on cognition.

"Stay tuned," she told her audience. "Perhaps while waiting for a cure for Alzheimer's disease, health care providers could consider implementing supervised physical exercise sessions for patients."

Asked by a delegate why the study duration was restricted to 3 months, Dr Waldemar acknowledged that had the study continued for longer — 6 months, for example — there might have been "a more clear signal" for better results.

"But I can assure you that conducting this study for even 4 months in these very complex patients was not an easy task, so this was a compromise," she said.

Another delegate wondered why the researchers didn't do the SDMT, which is a simple test to administer, more often, say once a month. Dr Waldemar explained that the "test/retest effect" was a concern.

"With training, more and more patients get better even if they are not getting any intervention, but maybe we could have done it one more time."

Responding to a query by session co-chair Ana Verdelho, MD, Department of Neurosciences, Santa Maria Hospital, University of Lisbon, Portugal, about the statistical power of the study, Dr Waldemar said there were no similar studies to use "as background," so she and her colleagues based their power analysis on that small randomized controlled trial in patients with MCI.

"The SDMT is perhaps better suited for patients with MCI than patients who already have AD dementia," she noted.

Another meeting delegate asked whether the effect seen in patients with the highest attendance could be explained by those with the highest attendance also having milder AD. Dr Waldemar said she hasn't looked at that. "That's a very good question."

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