Oxidative Stress May Induce Amyloid Accumulation

BY KERRI WACHTER
Senior Writer

PORTO, PORTUGAL — The hallmark amyloid accumulation in Alzheimer's disease may actually be the body's response to neuronal oxidative stress, according to data presented at the Fourth International Congress on Vascular Dementia.

Attempts to remove amyloid plaque may have the unintended effect of increasing neuronal oxidative damage, said Dr. Akihiko Nunomura of Asahikawa (Japan) Medical College.

Evaluation of immunoreactions in the hippocampal regions of the brains of patients with Alzheimer's disease (AD) has revealed an inverse relationship between amyloid-β 42—the protein believed to be responsible for the formation of amyloid plaques in the brain—and the nucleoside 8-hydroxyguanosine—a product of RNA oxidation that serves as a biomarker of neuronal oxidative stress, he said.

Dr. Nunomura and his colleagues evaluated postmortem tissue samples from the hippocampal region of 16 subjects (aged 65-93 years at time of death) previously diagnosed with AD using Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria.

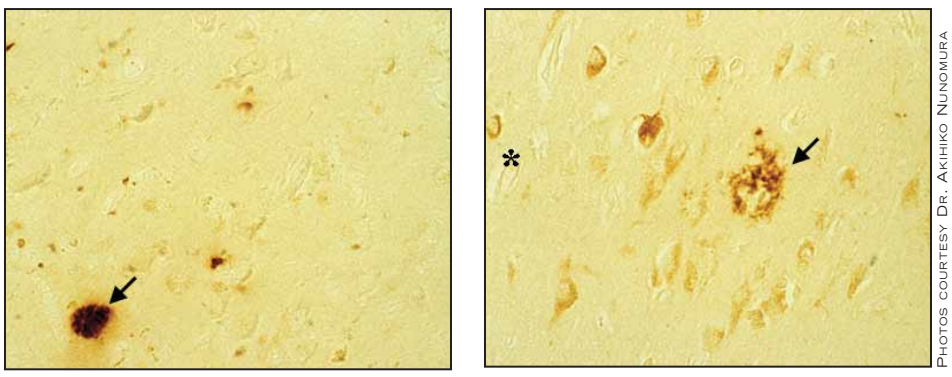
Optical density measurements were done on tissue samples that had been immunochemically stained for 8-hydroxyguanosine, amyloid-β 40, and amyloid-β 42.

Intraneuronal amyloid-β 42 and 8-hydroxyguanosine immunoreactions were observed in the hippocampal pyramidal neurons in all of the subjects. Neurons positive for 8-hydroxyguanosine were more widely distributed compared with those positive for amyloid-β 42. However, immunoreaction of intraneuronal amyloid-β 40 was faint in most of the subjects, compared with that of amyloid-β 42.

"When we focused on the relationship between intraneuronal 8-hydroxyguanosine and amyloid-β 42 immunoreactivities, we found several cases with high 8-hydroxyguanosine and low amyloid-β 42, as well as [several cases with] low 8-hydroxyguanosine and high amyloid-β 42," said Dr. Nunomura.

Relative optical density measurements confirmed the inverse relationship between 8-hydroxyguanosine and amyloid-β 42 immunoreactivities but there was no significant relationship between 8-hydroxyguanosine and amyloid-β 40.

The inverse relationship between 8-hydroxyguanosine and amyloid-β 42 suggests "that extra- and intraneuronal accumulation of amyloid-β 42 is related to a compensatory response to neuronal oxidative stress in AD," said Dr. Nunomura.



PHOTOS COURTESY DR. AKIHIKO NUNOMURA

Faint intraneuronal A-β 42 immunoreactivity in the hippocampus is shown in an 82-year-old AD patient (left). Intense intraneuronal A-β 42 immunoreactivity in a 77-year-old patient with AD (right). Arrow indicates extraneuronal A-β deposition.

While the mechanism at work is unclear, the researchers hypothesize that amyloid-β 42 accumulates as a response to oxidative stress and that 8-hydroxyguanosine is also downregulated, coauthor George Perry, Ph.D., said in an interview. Dr. Perry is a professor of pathology and neurosciences and Case Western Reserve University in Cleveland.

The researchers previously reported an inverse relationship between percent area of amyloid-β 42 plaque burden and immunointensity of neuronal 8-hydroxyguanosine in subjects with Down syndrome. In addition, both intraneuronal amyloid-β accumulation and oxidative stress precede amyloid-β deposition both in patients with Down syndrome and in transgenic mice models of AD.

Taken together with previous data, these findings suggest that excessive removal of amyloid-β may lead to increased neuronal oxidative damage in AD, said Dr. Nunomura.

The researchers are now focusing on better understanding the mechanism behind the amyloid-β/8-hydroxyguanosine relationship, said Dr. Perry. ■

Airway Pressure Enhances Cognitive Function in Alzheimer's Patients

BY BRUCE JANCIN
Denver Bureau

DENVER — Continuous positive airway pressure improved both excessive daytime sleepiness and—in a particularly encouraging finding—cognitive function in a randomized trial involving Alzheimer's disease patients with obstructive sleep apnea, investigators reported at the annual meeting of the Associated Professional Sleep Societies.

"This is preliminary, but it seems to be quite promising. If in fact we can do anything to at least slow down deterioration of cognition—if not actually improve it—then that might postpone institutionalization, which will save billions of dollars as well as improving quality of life for these patients," observed Sonia Ancoli-Israel, Ph.D., professor of psychiatry at the University of California, San Diego.

Sleep-disordered breathing is exceedingly common in Alzheimer's disease patients. Various studies have put the prevalence of obstructive sleep apnea (OSA) in patients with dementia at 50%-90%.

Moreover, demented patients with severe OSA have significantly worse dementia and individuals with severe dementia have more sleep-disordered breathing.

"Clearly there is some association between how much one can breathe at night and how much dementia one might have. Do I think that sleep apnea causes dementia? No, I don't—but I do think that if someone is already demented and you add hypoxia and disturbed sleep on top of that, it's likely to make the dementia worse," Dr. Ancoli-Israel explained.

She reported on 40 noninstitutionalized patients with mild to moderate Alzheimer's disease and OSA who were randomized in double-blind fashion to true continuous positive airway pressure (CPAP) or to a control group given a counterfeit respiratory assistance protocol—"affectionately known as CRAP," she said. After 3 weeks of CRAP, patients in the control group were switched to 3 weeks of CPAP. Those already on CPAP continued on the therapy for an additional 3 weeks. A comprehensive neuropsychological test battery was administered at baseline, at 3 weeks, and after 6 weeks.

'Clearly there is some association between how much one can breathe at night' and dementia.

DR. ANCOLI-ISRAEL

The first noteworthy finding, Dr. Ancoli-Israel said, was that these Alzheimer's disease patients—mean age 78 years—tolerated CPAP "reasonably well," using the equipment for an average of 5 hours per night. "That's really not that different from what we see in our clinic patients."

The patients' mean respiratory disturbance index, a measure of OSA severity, decreased in the CPAP group from a baseline of 30.4 events per hour to 7.2 after 3 weeks and 4.9 per hour after 6 weeks. No significant change was seen in the CRAP group until 3 weeks after those patients had been switched to real CPAP.

Composite neuropsychological test scores improved significantly after 3 weeks of CPAP; no further improvement was seen during the second 3 weeks on the therapy. There was no improvement in neuropsychological test scores after sham therapy, but a significant gain was documented following the switch to CPAP.

"The kinds of changes that we're seeing are actually not that different from the changes one sees when patients are put on cognition-enhancing drugs. So this might be an additional way to treat the patient," she said. ■

Testosterone Replacement May Boost Quality of Life

BY MARY ANN MOON
Contributing Writer

Testosterone replacement improved the quality of life for men with Alzheimer's disease and low serum testosterone levels in a small preliminary study, reported Po H. Lu, Psy.D., and associates at the University of California, Los Angeles, David Geffen School of Medicine.

Testosterone therapy has been shown to improve mood, muscle mass, strength, bone density, libido, and certain cognitive functions in hypogonadal men who are otherwise healthy, but this is the first study to report that testosterone may exert positive effects in Alzheimer's disease (AD), the researchers said (Arch. Neurol. 2006;63:1-9).

They assessed testosterone's effects on a variety of cognitive, behavioral, mood, and quality of life (QOL) measures in 16 men with mild to moderate AD and 22 healthy elderly men who served as controls. The study subjects were randomly assigned to apply either testosterone patches (7 patients and 10 controls) or placebo patches (9 patients and 12 controls) every day for 6 months.

Five of the AD patients and six of the control subjects were hypogonadal at baseline, with serum testosterone levels below 298 ng/dL.

As a group, the AD patients who received testosterone showed a significantly better QOL, as assessed by their caregivers using the 13-item Quality of Life-Alzheimer's Disease scale, than AD patients who received placebo. This effect occurred because the testosterone recipients showed a nonsignificant trend toward improved QOL over the 6-month study period, while the placebo group showed significant declines.

Similarly, the AD patients who received testosterone showed either greater improvement or less decline in three measures of visual-spatial cognitive functioning, compared with the placebo group and the control groups.

Both the improved QOL and the improved cognitive functioning were correlated with increased serum testosterone levels.

Two AD patients and four control subjects withdrew from the study because of adverse effects, including skin rash at the testosterone patch application site. ■