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Sleep Deprivation May Promote Amyloid-Beta Build-Up

BY RICHARD J. CASELLI, M.D.

Sleep deprivation over long periods of time appears to increase the level of amyloid-beta in the interstitial fluid of the hippocampus, potentially contributing to the eventual deposition of amyloid-beta plaques associated with Alzheimer's disease, according to a study of transgenic mice that express mutated forms of the amyloid-precursor protein.

"Sleep disturbances, in addition to being prominent in neurodegenerative diseases, could exacerbate a fundamental process leading to neurodegeneration, and optimization of sleep time could potentially inhibit aggregation of toxic proteins and slow the progression of AD," said Jae-Eun Kang, Ph.D., of Washington University, St. Louis, and her colleagues (Science 2009 Sept. 24;doi:10.1126/science.1180962).

They found that amyloid-beta (Abeta) levels in the interstitial fluid of wild-type and human amyloid precursor protein (APP) transgenic mice were negatively correlated with the amount of time they spent asleep, especially during non-REM sleep. In light periods, when the mice spent most of their time asleep, Abeta levels in the interstitial fluid were about 75% of the levels during dark periods. This dip in the level of Abeta in interstitial fluid during the low level of synaptic activity during sleep agrees with previous research showing how synaptic activity regulates Abeta release from neurons into the interstitial fluid. This diurnal fluctuation in Abeta levels in brain interstitial fluid was also seen in the CSF of 10 healthy patients who had lumbar catheters in place for 33 hours.

Mice that were forced to stay awake for an additional 6 hours during their normal 12-hour light period had significantly higher Abeta levels in interstitial fluid, compared with the levels in the same period 24 hours before. However, the researchers proved that the increase in Abeta levels was not due to stress mediated by corticotrophin-releasing factor, which is known to increase interstitial Abeta acutely.

When the researchers infused the wakefulness-regulating molecule orexin into the hippocampus (where orexin receptors reside) for 6 hours at the beginning of the light period at a dose that induces wakefulness in rodents, Abeta levels again significantly rose beyond the previous day's levels in the same period. They next showed the diurnal variation in Abeta interstitial levels could be erased with infusion of an orexin receptor antagonist and then reinstated when the antagonist was removed.

The researchers restricted the sleep of two different types of APP transgenic mice for 20 hours daily on 21 consecutive days, which greatly increased their Abeta plaque burden. But systemic administration of the orexin receptor antagonist once daily for 8 weeks significantly decreased the formation of Abeta plaques at an age when they were beginning to form. They suggested that the differences in synaptic activity (mediated by orexin) that change the interstitial levels of Abeta by 20%-25% on an hourly basis during sleep and wake states may be enough to block the development and growth of plaques. The study was funded by the National Institutes of Health, the Cure Alzheimer's Fund, the Alzheimer's Association Zenith Award, and Eli Lilly & Co.

Dr. Caselli's comment: Study hard, have a good diet, exercise regularly, and get plenty of rest. We might also add avoid getting hurt and do not take (recreational) drugs. This advice would sound very familiar to any parent reading this editorial. But as research into Alzheimer's disease prevention progresses, it seems everything we really do need to know we learned in kindergarten. Previous studies have examined the effects of mental activity (JAMA 2002;287:742-8), the Mediterranean diet (JAMA 2009;302:638-48), physical activity and fitness (JAMA 2008;300:1027-37), the adverse role of diabetes mellitus and other cardiovascular risk factors (Dement. Geriatr. Cogn. Disord. 2007;24:185-92), and the adverse effects of repetitive head injuries (Nat. Med. 2009;15:377-9). In contrast, every supplement studied from vitamin E (N. Engl. J. Med. 2005;352:2379-88) to *Ginkgo biloba* (JAMA 2008;300:2253-62) has failed to show any meaningful benefit.

The current study has shown a remarkable association between Abeta levels and the sleep-wake cycle. It shows that rest (particularly non-REM sleep) cuts Abeta levels and probably amyloid plaques, one of the cardinal neuropathologic features of AD.

Abeta seems to be produced quickly in response to a variety of stresses, including sleep deprivation, emotional stress, brain trauma, cerebral hypoxia and ischemia, and energy failure (mitochondrial impairment). Some pharmacologic agents seem to cut the Abeta-generating effects of at least some of these stresses, yet clinical trials of agents that collectively interfere with the production of Abeta have failed to show anything therapeutically remarkable in regard to reducing dementia progression. Possibly targeting sleep, cortisol, or other amyloid-provoking stimuli might prove more effective. Until then, perhaps we should pass on our parents' advice to our patients: Keep your mind active, eat good food, exercise, control cardiovascular risk factors (yes, nonrecreational medications can be used), try not to bump your head, avoid recreational drugs (and unproven supplements), and get enough rest. ■

Clinical perspective by DR. CASELLI, *chair of neurology at the Mayo Clinic, Scottsdale, Ariz., and professor of neurology at the Mayo Medical School, Rochester, Minn.*

Research report by Jeff Evans, clinical news editor.

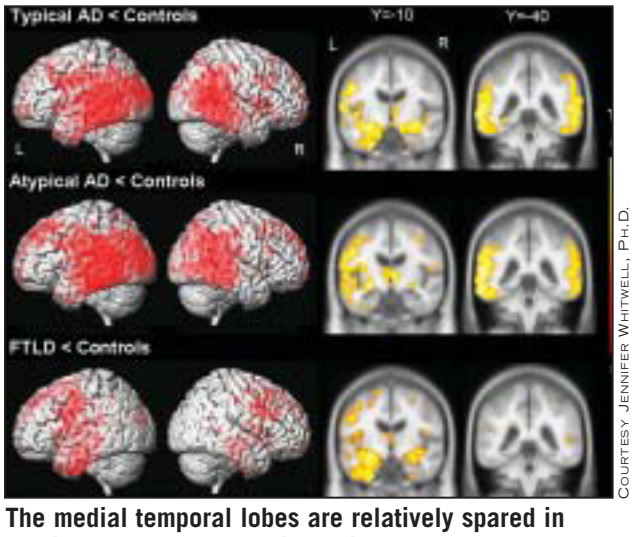
Temporoparietal Atrophy May Be Specific Marker for AD

BY JEFF EVANS

BALTIMORE — Atrophy in the temporoparietal cortex might be a common identifier of Alzheimer's disease patients that differentiates individuals who have atypical clinical presentations of the disease from those who have other types of dementia, according to a small MRI scanning study.

Patients with Alzheimer's disease (AD) who do not show its typical clinical characteristics—loss of episodic memory, executive dysfunction, language dysfunction, and visuospatial and perceptual deficits—are usually diagnosed with a frontotemporal dementialike syndrome, progressive aphasia syndrome, or a corticobasal syndrome characterized by asymmetric, extrapyramidal, and cortical dysfunction. However, patients with those symptoms most frequently have a type of frontotemporal lobar degeneration (FTLD), Dr. Keith A. Josephs said at the annual meeting of the American Neurological Association.

Differentiating AD from other dementias is important if future treatments for AD differ from FTLD, "which is likely, given the fact that the proteins that are deposited in Alzheimer's disease differ from the ones in FTLD," said Dr. Josephs of the department of neurology at the Mayo Clinic, Rochester, Minn.



COURTESY JENNIFER WHITWELL, PH.D.

The medial temporal lobes are relatively spared in atypical AD, compared with typical AD and FTLD.

To predict AD pathology in patients who present with a range of atypical AD clinical syndromes, Dr. Josephs and his colleagues looked at the gross structure of the brain with volumetric MR imaging.

They found 14 patients at the Mayo Clinic in Rochester who had a diagnosis of atypical AD dementia. These patients were evaluated by a behavioral neurologist and determined not to have a typical presentation of AD but were pathologically confirmed to have a high-probability diagnosis of AD according to National Institute on Aging–Reagan Institute Consensus Conference criteria (Braak stage V or VI).

Of the 14 patients with atypical AD, 6 had aphasic dementia, 5 had a corticobasal syndrome, and 3 had a clinical diagnosis of behavioral-variant frontotemporal degeneration. Dr. Josephs and his associates compared the atypical AD patients with 14 patients with pathologically diagnosed FTLD who had the same clinical dementia syndromes.

They also compared the atypical AD patients with 14 patients who had both the typical clinical symptoms and pathological signs of AD and 20 healthy control patients.

In each group, patients had a mean age of about 64 years at disease onset with a mean of 3.4 years from disease onset to the time of the MRI scan. Half of the patients in each group were women.

In comparisons between the groups, both typical AD and FTLD patients had more hippocampal atrophy than did atypical AD patients. The atypical AD patients showed more putamenal atrophy than did typical AD patients. The atypical AD patients also had more temporoparietal atrophy than did the FTLD patients.

Patterns of atrophy also tended to vary across the dementia syndrome subtypes found among the atypical AD patients when compared with the healthy control patients, but all of the atypical AD patients had temporoparietal atrophy in common.

In individual analyses of each patient, typical AD and FTLD patients had significantly more hippocampal atrophy than did individual atypical AD patients.

However, individuals with either typical or atypical AD had significantly more temporoparietal atrophy than did FTLD patients. The pattern of atrophy was not driven by one clinical dementia subtype.

In discriminating atypical AD from FTLD, volume loss from the hippocampus gave an area under the receiver operating characteristic curve (AUC) of 0.74, compared with 0.81 for the temporoparietal cortex. The ratio of hippocampal to temporoparietal volume loss provided the best result with an AUC of 0.93.

The study was funded by grants from the National Institutes of Health and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation. Dr. Josephs had no disclosures to report. ■