Amyloid Angiopathy Heaviest in Occipital Region

BY KERRI WACHTER
Senior Writer

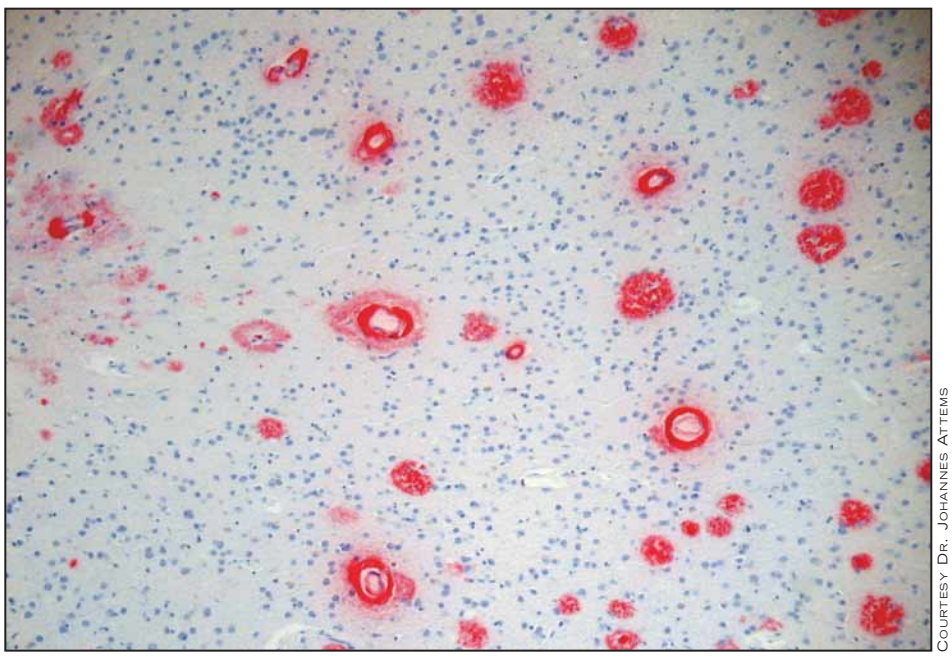
PORTO, PORTUGAL — Cerebral amyloid angiopathy appears to disproportionately affect the occipital region, according to findings presented at the Fourth International Congress on Vascular Dementia.

In a study involving the postmortem neuropathologic evaluation of brains from 113 subjects (61% women), the incidence and severity of cerebral amyloid angiopathy (CAA) was highest in the occipital region, followed by the frontal, hippocampal, and frontobasal areas. The occipital region was significantly more frequently and more severely affected than the other regions, said Johannes Attems, M.D., of the Otto Wagner Hospital in Vienna.

Cerebral amyloid angiopathy (CAA) is defined by the deposition of amyloid-β peptide in cerebral vessels and has been associated with Alzheimer's disease (AD). Despite the association with AD, CAA has been shown to be an independent risk factor for cognitive decline.

Dr. Attems and his colleagues looked at the topographical distribution of CAA in the vessels of the brain, as well as the relationship between CAA and AD. In all, 63 patients had a clinical diagnosis of dementia and 50 were nondemented. Dementia was assessed retrospectively from hospital charts based on ICD-10 criteria of a Mini-Mental State Examination score less than 20. Subjects ranged in age from 54 to 102 years at the time of death.

Neuropathologic assessment of AD was performed using Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria, Braak stages, and National Institute on Aging/Reagan Institute (NIA-Reagan) criteria. In this cohort, 43 subjects had high-grade AD pathology, 16 with medium-grade AD pathology, 37 with low-grade AD pathology, and 17 with no AD pathology.



COURTESY DR. JOHANNES ATTEMS

Immunostaining of tissue with cerebral amyloid angiopathy using modified Bielschowsky silver stain shows severe thickening of the cortical vessel walls.

Sections were immunostained with modified Bielschowsky silver stain and a commercially available monoclonal human amyloid-β antibody for the detection of amyloid-β in cerebral vessels. The severity of amyloid-β deposition in vessels—and CAA—was semiquantitatively assessed in the frontal, frontobasal, hippocampal, and occipital regions. The researchers used a 5-point scoring system. A grade of 0 signified no amyloid-β was present, while grade 4 signified severe amyloid-β deposition.

Within a region, scores were totaled separately for meningeal and cortical vessels. These values were totaled for a regional score. A mean overall score was then calculated using the regional values. For a better estimate of the relative contribution of the separate regional scores, the overall score was subtracted from each regional score to yield relative scores.

CAA was present in 77 cases. In these subjects, "Independent of the region, meningeal vessels were always affected more frequently and more severely than cortical vessels," said Dr. Attems. However, the differences between meningeal and cortical vessels were only statistically significant in the occipital region.

"CAA prevalence was significantly higher in cases with high-grade AD pathology, compared with cases with no to medium pathology," said Dr. Attems. Overall CAA severity increased with increasing AD pathology. This was true in all of the regions, though only the relative contribution of CAA in the occipital region increases significantly with increasing AD pathology.

"This means that—at least statistically—increasing AD pathology shifts the topographic distribution of CAA even more toward the occipital cortex," said Dr. Attems.

Interestingly, of the brains with no AD pathology, 24% had evidence of CAA. Conversely, 24% of brains with AD pathology showed no evidence of CAA. "We have cases with severe CAA but without any AD pathology and on the other hand, case with high AD pathology completely lacking CAA," said Dr. Attems. This suggests that neuritic AD pathology and CAA might represent different entities.

Demented subjects more frequently showed signs of CAA and CAA total scores were greater than in nondemented patients. This finding suggests a significant association between CAA and dementia, said Dr. Attems. However, after controlling for clinical criteria, the association was no longer statistically significant.

"The combination of AD pathology and CAA might synergistically contribute to the development of clinical dementia," said Dr. Attems.

Interestingly, among patients with a CAA total score greater than 0, there was no difference in the prevalence of CAA between cases with high versus low AD pathology. Also the CAA total score did not increase with increasing AD pathology in this subgroup. ■

Removal of Amyloid May Increase Neuronal Oxidation

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 Akihiko Nunomura, M.D., 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.

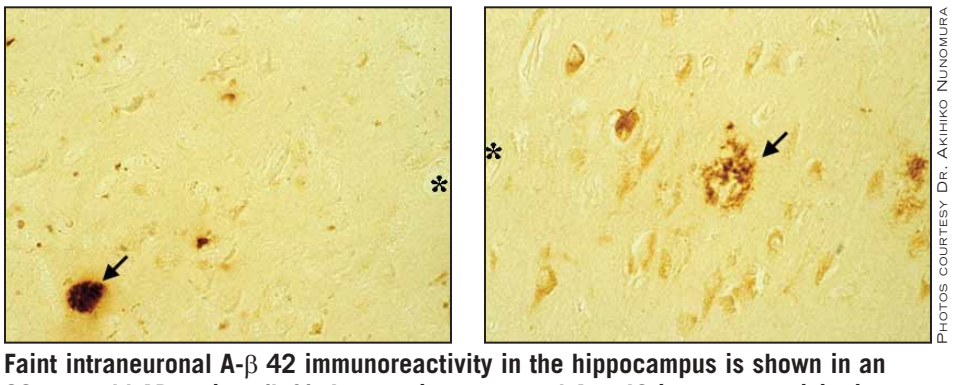
Dr. Nunomura and his colleagues evaluated postmortem tissue samples from the hippocampal region of 16 subjects (aged 65-93 years at time of death) who had been previously diagnosed with AD using Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria.

Optical density measurements were performed 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.



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.

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.

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. ■