NEWS FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE

In Late Life, Low Blood Pressure Reportedly Increases Dementia Risk

BY LISA J. BAIN

ARTICLE IN BRIEF

At the Alzheimer's Association International Conference, several teams of investigators reported that low blood pressure in late life can increase the likelihood of brain atrophy and cognitive impairment, but only in people who had hypertension during mid-life.

VANCOUVER, BC—Although hypertension is widely believed to elevate the risk of developing dementia, data presented here at the Alzheimer's Association International Conference in July, have added to a growing chorus of voices suggesting that in older individuals, low blood pressure may be an even bigger problem.

Majon Muller, MD, PhD, an epidemiologist and geriatrician at the VU University Medical Center in Amsterdam, the Netherlands, and currently a visiting fellow at the NIH National Institute on Aging (NIA), reported results from the AGES Reykjavik Study, which showed that low blood pressure in late life can increase the likelihood of brain atrophy and cognitive impairment, but only in people who had hypertension during mid-life.

AGES (Age, Gene/Environment Susceptibility), a collaboration between the NIA and the Icelandic Heart Association, is an extension of the longitudinal Reykjavik study, which gathered mid-life cardiovascular risk data on more than 20,000 participants between 1967 and 1994. Between 2002 and 2006, surviving members from the original study, by then in their 70s, 80s, and 90s, were enrolled in AGES Reykjavik. Dr. Muller and colleagues analyzed data from 4,306 non-demented elderly participants from this cohort who had undergone MRI scans of their brain.

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> 'What we may see is that a retained diastolic blood pressure may actually be a measure of vascular health as we get older.'

After adjusting for age, sex, intracranial volume, other cardiovascular risk factors, and the presence of brain white matter lesions and infarcts on MRI, they reported that lower late-life diastolic blood pressure (DBP), and to a lesser extent systolic blood pressure (SBP), was associated with more brain atrophy and memory impairment among those individuals who had a history of hypertension in mid-life, but not in those with no history of mid-life hypertension.

Among subjects with mid-life hypertension, those with late-life DBP below 65mmHg had a 1.5 percent reduction in total brain (TB) or gray matter (GM) volume and a 4.4 percent increase in memory impairment compared with those with late-life DBP greater than 80mmHg (p=0.009, p=0.06, respectively). In comparison, subjects with no mid-life hypertension who had low late-life DBP had no reduction in total brain volume or increased memory impairment.

A RISK FACTOR OR INDICATOR?

Dr. Muller speculated that high mid-life blood pressure could increase the risk of cerebral hypoperfusion through microvascular pathology and changes in autoregulatory mechanisms in the brain that are intended to protect the brain against high blood pressure. These mechanisms, she said, could make the brain more vulnerable to lower blood pressure later in life, whether that lower blood pressure resulted from treatment with antihypertensive medication or from reduced cardiac output or arterial stiffness.

"It's quite complicated. If you've been healthy all your life and you have low

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MORE AAIC STUDY DATA ON LOW BLOOD PRESSURE & DEMENTIA

• Hadassa Jochemsen, MD, PhD-student in epidemiology at the University Medical Center in Utrecht, the Netherlands, reported that among late middle-aged patients with arterial disease, lower diastolic blood pressure was related to more progression of global and subcortical brain atrophy, suggesting that vascular disease makes patients more vulnerable to lower diastolic blood pressure and subsequent neurodegeneration. Subcortical brain volume was reduced by 0.8 percent, adjusted for intracranial volume in patients with low diastolic blood pressure (<70mmHg) compared to patients with high diastolic blood pressure (>90mmHg). Lower systolic blood pressure was not significantly associated with a reduction in brain volume.

• Among the oldest old, hypertension either by history or measurement, was shown to correlate with a reduced risk of dementia, although this this association was not mediated by the presence of either Alzheimer's disease (AD) or vascular pathologies, reported Maria Corrada, SciD, associate adjunct professor of neurology at University of California, Irvine. After adjustment for the presence of AD or vascular pathology, the odds ratio (OR) for hypertension and dementia was 0.27. The association between dementia and hypertension or pre-hypertension did not change after adjustment for pathology.

• Compared to people who were never diagnosed with hypertension, midlife hypertension was associated with increased risk of cortical and subcortical infarctions in late life, Rosebud Roberts, MBChB, professor of epidemiology at Mayo Clinic in Rochester, MN, reported. Midlife hypertension was associated with 14 percent increase in white matter hyperintensity volume (p=.01). Midlife hypertension was associated with a two-fold increased risk of having subcortical infractions (p=.01). Midlife hypertension was associated with a 1.7-fold increased risk of having cortical infarctions (p=.01).

• In people with a history of hypertension, reduced blood pressure was associated with an increase in the neurodegeneration biomarker CSF phospho-tau, as well as in deterioration of episodic memory, Lidia Glodzik, MD, research assistant professor of radiology and psychiatry at the New York University Langone Medical Center reported. A decrease in mean arterial pressure (MAP) — MAP=1/3 SBP + 2/3 DBP — over ~ two years was associated with an increase in CSF phospho-tau181 (r=-0.5, p=.01). A decrease in MAP was associated with poorer performance on tests of verbal episodic memory (r=0.46, p=.03).

—Lisa J. Bain

CT Radiation

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ARTICLE IN BRIEF

Investigators reported that CTs elevated the risk of brain cancer and leukemia. But because these cancers are relatively rare, the increase in the number of cases remains small, with no more than one excess brain tumor and one excess case of leukemia expected per 10,000 head CT scans for each 10 milligray.

The study, led by researchers at the National Cancer Institute and the Institute of Health and Society at Newcastle University in England, examined rates of brain cancer and leukemia in people younger than 22 who received CT scans between 1985 and 2002 in Great Britain. Seventy-four out of 178,604 of them developed leukemia, and 135 out of 176,587 developed a brain tumor.

The authors concluded that a dose of about 60 milligray (mGy) — about two or three CT scans — might triple the risk of brain cancer, while a dose of about 50 mGy might triple the risk of leukemia. However, because these cancers are relatively rare, the increase in the number of cases remains small, with no more than one excess brain tumor and one excess case of leukemia expected per 10,000 head CT scans for each 10 mGy. The US annual rates for brain tumor and leukemia through age 21 are 2.9 and 4.3 per 100,000 respectively, according the NIH.

The results for leukemia coincided with the Life Span Study, which estimates cancer risk from radiation exposure by extrapolating data from survivors of atomic bomb blasts in Hiroshima and Nagasaki. However, for brain tumors, *The Lancet* study risk estimate was about four times higher than the Life Span Study's estimate, with an excess relative risk of 0.023 per mGy vs. 0.0061. Some of the excess risk might be due to the inclusion of patients who had CT scans for symptoms of a brain tumor not yet detectable, the authors said. Also, X-radiation from CT scans can be more biologically active than the gamma rays produced by the atomic bombs.

In an accompanying editorial to *The Lancet* study, Andrew J. Einstein, Victoria and Esther Aboodi assistant professor of medicine (in radiology) at Columbia University, wrote that the cancer risks of low-dose medical radiation can be minimized with the help of new technology and techniques. He encourages clinicians to adopt the "three As" — awareness (of radiation risks vs. benefits), appropriateness of each procedure, and audit of the imaging process to make sure it meets the standards of good practice.

"Pearce and colleagues confirm that CT scans almost certainly produce a small cancer risk," Dr. Einstein wrote in

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DENTAL X-RAYS AND MENINGIOMA

The dangers of radiation reported in *The Lancet* echo results reported in the current issue of *Cancer* from what is believed to be the largest case-control study to date examining the correlation between dental x-rays and the risk of meningioma. The study compared 1,433 patients with intracranial meningioma diagnosed between the ages of 20 and 79 to 1,350 controls, and found that the cancer patients were more than twice as likely to report receiving dental X-rays. The results also show that patients who reported having annual "bitewing" X-rays have a 40-90 percent greater risk of meningioma. The risk was higher in people who received panoramic X-rays when they were younger than 10.

"Our findings suggest that dental x-rays, particularly when obtained frequently and at a young age, may be associated with an increased risk of intracranial meningioma," the authors stated.

The authors of the *Cancer* study reaffirm the American Dental Association's statement discouraging the use of dental x-rays to search for occult disease in asymptomatic patients, or to obtain routine dental studies from all patients at pre-set intervals. (The American Dental Association recommends dental X-rays for teenagers and adults every 18 months to three years.) The lead researcher, Elizabeth B. Claus, MD, PhD, of Yale University School of Medicine and Boston's Brigham and Women's Hospital, also pointed out that the X-rays reported may have been made with higher levels of ionizing radiation than those used today.

—Tom Valeo

Low Blood Pressure, Dementia

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blood pressure later in life, it's good. But when you have high blood pressure levels all your life, and later in life they are lower, it might be a problem because the brain is not set on these lower blood pressure levels, and this low blood pressure might be inadequate for healthy cerebral perfusion," she said.

DR. MAJON MULLER: "It's quite complicated. If you've been healthy all your life and you have low blood pressure later in life, it's good. But when you have high blood pressure levels all your life, and later in life they are lower, it might be a problem because the brain is not set on these lower blood pressure levels, and this low blood pressure might be inadequate for healthy cerebral perfusion."

The fact that low DBP is linked to brain atrophy could mean that arterial stiffness is to blame for the phenomenon, said Dr. Muller. "But it could also be that these people with high mid-life and low late-life blood pressure have more comorbidity, such as more heart problems." In other words, low blood pressure could be a risk indicator rather than a risk factor.

Neurologist Charles DeCarli, MD, director of the Alzheimer's Disease Center at the University of California, Davis, who was not involved with the study, said that there is evidence to suggest that the vascular system gets less compliant with age. "So the drop in diastolic blood pressure is because there is something wrong with the pipes. What we may see is that a retained diastolic blood pressure may actually be a measure of vascular health as we get older."

THE JURY IS STILL OUT

Despite numerous studies linking low blood pressure to an elevated risk of dementia — see "More AAIC Study Data on Low Blood Pressure & Dementia" — Dr. Muller said more data are needed to demonstrate a causal relationship. One way to do this would be with antihypertensive treatment trials where participants randomized to achieve more and less stringent blood pressure targets are evaluated to see if the brain is affected to different degrees when the blood pressure is higher or lower.

"Ideally you want to have a clinical trial randomizing older people with a history of hypertension, and treat them with the current guidelines, which is the lower the better; and a less stringent target, say 150/90, and see if there is a difference. But that's a difficult trial to do because you need a lot of people. So probably the first step is to do a longitudinal study and see if low blood pressure is causing progression of brain atrophy or a decline in cognition, and to investigate which older individuals are particularly susceptible to these lower systemic blood pressure levels."

Dr. DeCarli suggested a different kind of trial. "One of biggest impediments for looking at optimal blood pressure management is having surrogate markers of health in the heart, kidney, and brain," he said. "I would like to see the development of a clinical trial in hypertension management that would simultaneously look at all of those things." Such a trial could start in 30- or 40-year-olds to test not cognition but whether controlling blood pressure results in improved health of these organs. "Then we could move to an older age group and do the same sort of thing," Dr. DeCarli said.

DR. CHARLES DECARLI: "One of biggest impediments for looking at optimal blood pressure management is having surrogate markers of health in the heart, kidney, and brain. I would like to see the development of a clinical trial in hypertension management that would simultaneously look at all of those things."

"Our interventions may not be as good for the brain as we expected them to be, and that needs further study," said Dr. DeCarli. "We need to be aggressive early in life, but later in life we need to think more carefully. The whole point is that therapy needs to be tailored." •