Neuropathology of Dementia Differs Across Age Groups — Less Pathology Evident in Oldest Ages

BY ELIZABETH STUMP

ARTICLE IN BRIEF

The neuropathology of dementia in cognitively impaired people, 90-107 years old, appears different from that of 60-to 80 year old demented patients — there are increased NP and NFT lesion densities in younger demented people but this increase in densities is absent in the demented oldest patients.

The neuropathology of dementia in cognitively impaired people, 90-107 years old, appears different from that of 60-to 80 year old demented patients, a new study published in the September *Archives of Neurology* reports.

The study, led by Vahram Haroutunian, PhD, professor of psychiatry and director of clinical and biological studies of early AD at the Mount Sinai School of Medicine, set out to explore the relationship between cognitive dysfunction and neurofibrillary tangles (NFTs) and neuritic plaques (NPs) — the hallmark lesions of Alzheimer disease and dementia in the elderly.

The investigators examined postmortem tissue of 317 people, grouped by age at death — the youngest-old (60-80 years), middle-old (81-89 years), and oldest-old (90-107 years). They compared data on severity of dementia — measured by the Clinical Dementia Rating (CDR) scale — and the density of NPs and NFTs. [A CDR score of 0 means nondemented, 0.5 is questionably demented, and 1 to 5 reflects increasing levels of severity of dementia.]

STUDY FINDINGS

Investigators observed increased NP and NFT densities in postmortem brain tissue of moderately to severely demented 60- to 80-year-olds (with CDR scores of 2-5), but not in those older than 90 years — even when the oldest-old had CDR scores indicating marginal or mildest dementia, Dr. Haroutunian said.

The data were reported as the ratio of NP and NFT densities in each dementia and age category relative to the densities of NPs and NFTs in the same age group with no significant dementia.

Dr. Haroutunian noted that the nondemented oldest subjects did not have greater NP and NFT lesion densities than their younger counterparts.

EXPERTS COMMENT

David S. Knopman, MD, professor of neurology at the Mayo Clinic College of Medicine in Rochester, MN, who was not involved in the study, said he was impressed by the data. He noted, however, that the oldest cognitively-intact (normal) group may have a much higher burden of AD pathology than the 60- to 80-year-old normals, so the ratio of the amount of lesions in the normal group to the lesions in the severely demented group is attenuated in the oldest-old.

DR. VAHRAM HAROUTUNIAN said that the current age-associated scale may have to be reconsidered because the association may not be linear — instead, the association of NPs and NFTs with age and dementia may only hold up to a certain age, such as 85.

The difference in the ratios is entirely driven by the very small amount of AD pathology in young normals, even though the amount in the demented group was almost the same. In other words, older people have more AD pathology even if not demented, and therefore there is less of a parallel of AD pathology and severity of clinical evidence of dementia. That in turn affects how the different age groups can be compared. (Higher disease burden means more pathology: more plaques and tangles.)

He pointed out that in the current study less AD pathology was seen with severe dementia in the oldest group. As noted by the authors, he said, the oldest people had other pathology, such as occlusive microvascular disease and synaptic loss that could be attributed to aging or other diseases, reducing the threshold for cognitive impairment; that is, less AD pathology was could lead to severe dementia.

William E. Klunk, MD, PhD, professor of psychiatry and neurology at the Uni-

Continued on page 32

Schizophrenia

Continued from page 28

more genes that are in the deleted region."

Dr. St. Clair and others explained that these microdeletions can be inherited or occur *de novo* (as new mutations) at conception, which is why someone can develop schizophrenia without any family history. That these mutations occur at a high rate in the population (about one percent) could explain why the incidence of schizophrenia remains at one percent, even though many patients do not go on to have children of their own.

The genes they linked to schizophrenia seem to have a variety of functions in brain development and neuronal signaling. "These findings establish beyond a doubt that genetic abnormalities can cause schizophrenia and they explain why some cases seem sporadic because there is no family history," Dr. St. Clair added.

In an additional data set of 3,285 cases and 7,951 controls, the association was even stronger. Seven of 4,213 cases had one of the chromosome 15 deletions (15q13.3) compared to 8 of 39,800 controls. One of the genes in this region is the alpha-7 nicotinic receptor gene that the authors said is "targeted to axons by neuregulin 1, and has been implicated in both schizophrenia and mental retardation."

DR. THOMAS LEHNER: "These findings are all exciting but we don't have definite answers yet. We need to take a comprehensive look at all the factors that contribute to schizophrenia."

The International Schizophrenia Consortium (ISC) found genetic deletions associated with schizophrenia in chromosomes 1,15, and 22. "As a group, these may be rare events, but individually these copy number variants may confer a large increased risk for schizophrenia," said Shaun Purcell, PhD, of Massachusetts General Hospital, who led the study.

> 'These findings establish beyond a doubt that genetic abnormalities can cause schizophrenia and they explain why some cases seem sporadic because there is no family history.'

He said that people with large deletions in these regions may have a ten-fold increased risk for schizophrenia. The largest effect was found on chromosome 22, with a 20-fold increased risk.

Dr. Lehner remains optimistically cautious about these findings. "We are still missing the environment and other factors that influence how these genes are expressed." He suspects that complex psychiatric conditions, including schizophrenia, are disorders of genetic dysregulation that work in concert with environmental triggers.

"We now have the technology and the large sample sizes. In a few years, we will have the answers." •

REFERENCES:

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Dopamine System Defects Implicated in Two Forms of Epilepsy

BY KURT SAMSON

ARTICLE IN BRIEF

Investigators in Australia and Sweden used PET and specially irradiated molecules (radioligands) to examine defects in binding and signaling activity associated with dopamine delivery in patients with autosomal dominant nocturnal frontal lobe epilepsy and juvenile myoclonic epilepsy.

Researchers have identified molecular mutations in cell receptors associated with dopamine in two inherited forms of epilepsy — one a rare form of the disease that causes sleep-related seizures and the other, a very common type of juvenile epilepsy.

In two small studies published in the Sept. 9 *Neurology*, researchers in Australia and Sweden used PET and specially irradiated molecules (radioligands) to examine defects in binding and signaling activity associated with dopamine delivery. One team looked at dopamine defects in patients with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), and the other in patients with juvenile myoclonic epilepsy (JME).

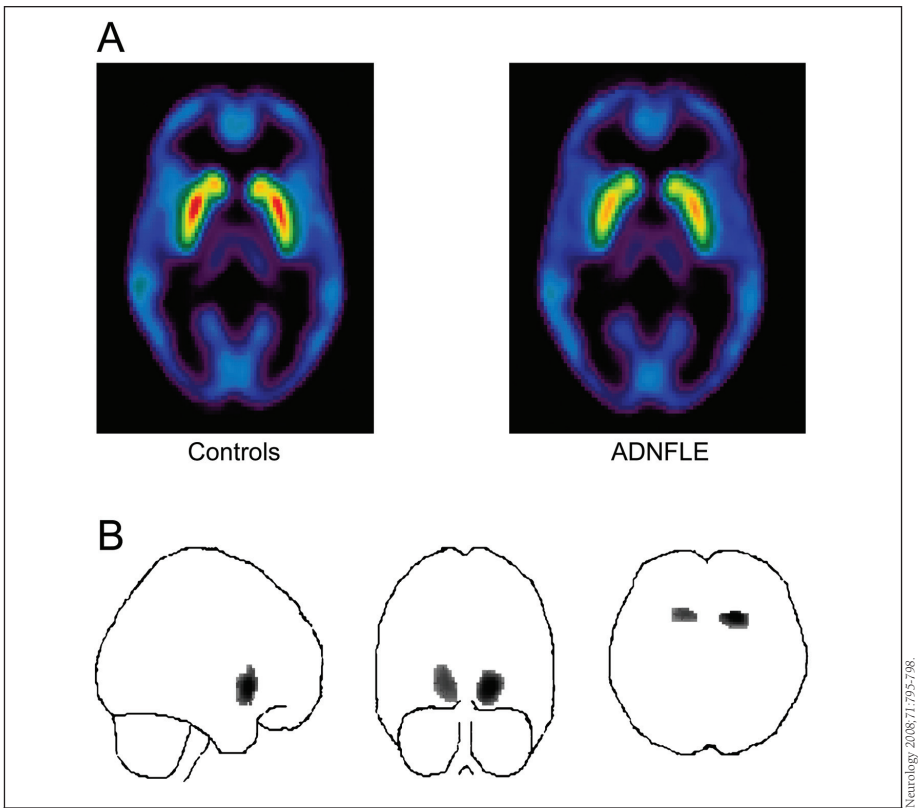
Ligands are molecules that interact with proteins by binding to specific receptors on cell membranes. In the dopamine transport system, these ligand receptors include D1, D2, and D3. The development of receptor-specific radioligands have enabled scientists to look more closely than ever before at the dopaminergic system in different parts of the brain.

NOCTURNAL FRONTAL LOBE EPILEPSY

In the first paper, a team led by Marco Fedi, MD, and David C. Reutens, MD, at Monash Medical Center in Victoria, Australia, examined a mutation of presynaptic neuronal nicotinic acetylcholine (nACh) binding in 12 patients with ADNFLE, which causes sudden convulsions during sleep. They compared dopamine levels in different parts of the brain and compared them with those in a similar group of normal controls.

Specifically, the team zeroed in on a specific mutation (a4-Ser248Phe), known to be involved in nACh binding, and measured extracellular dopamine at the D1 receptor site, a key transfer point for dopamine in the striatum and putamen. Patients with the

Continued on page 33



Neurology 2008;71:795-798.

Images of [11C]-SCH23390 binding demonstrating reduced striatal D1 receptor binding in 12 subjects with the alpha4-Ser248Phe mutation compared to 19 healthy volunteers. The voxel-based analysis detected a cluster of reduced [11C] SCH23390 binding in patients with autosomal dominant nocturnal frontal lobe epilepsy in the right putamen.

Neuropathology, Dementia

Continued from page 30

versity of Pittsburgh, said he drew different conclusions from the data than did the authors.

He plotted the lesion data by CDR score and found that in those aged 90 and older, there is a clear increase in NPs in those with scores of CDR 0-1 — the most clinically important range, because the diagnosis of AD and the initiation of treatment almost always occurs in these stages — and in NFTs from stages with CDR scores 0.5-5, which was very similar to the pattern is seen in the younger groups.

"The most striking differences I can discern in the oldest age group are a lower ceiling for plaque (NP) count above CDR 3 and a higher NFT count in the non-demented (CDR=0) group," he said. (Lower ceiling means that the plaque count in the 90 and older group levels off at lower numbers of plaques than seen in the 60- to 80-year-old group.) In other words, the clinical severity and pathological severity run parallel for a while and then severity of pathology hits a maximal level.

"The lower plaque ceiling may be due to the expected lower prevalence of

DR. WILLIAM KLUNK agreed with the study's suggestion that there may be other physiological and molecular substrates of dementia that have yet to be uncovered in the very old.

apolipoprotein E 4 [*ApoE4*, the AD risk gene] in this very late-onset group — that is, *ApoE4* causes earlier onset and heavier plaque burden, thus the younger AD group has a higher plateau," Dr. Klunk said. "The higher NFT count in the oldest non-demented subjects is also not surprising given the well-known increase of limbic NFTs with age in non-demented cohorts."

Dr. Klunk agreed with the study's suggestion that there may be other physiological and molecular substrates of dementia that have yet to be uncovered in the very old. It makes "great sense that other factors that allow or add to the expression of clinical symptoms accumulate with age," he said.

In response to Dr. Klunk's comments, Dr. Haroutunian said that it is true that despite the lack of significant increase in lesion density, there was an association, albeit small, between CDR and NP and NFT density.

"This was within the context of very few lesions even in the maximally demented subjects," Dr. Haroutunian said. "As noted astutely by Dr. Klunk, this association does raise the question of lesion threshold. It is quite possible that the density of lesions needed to impair cognition in the oldest-old may be substantially less than the necessary lesion load for cognitive impairment in those 60- to 80-year- olds. This is why we suggest re-evaluating the contribution of age to the criteria for the neuropathological diagnosis of AD in the oldest-old."

The current age-associated scale may have to be reconsidered because the association may not be linear — instead, the association of NPs and NFTs with age and dementia may only hold up to a certain age, such as 85, Dr. Haroutunian said.

Dr. Knopman agreed, adding: "Dementia is a clinical diagnosis, and the pathological basis for the dementia, while critical for therapeutic decisions, should not change the way dementia is diagnosed."

The study raises the key issue of the approach to therapy, he said, suggesting that "anti-AD therapies may be less specific for persons over age 90." •

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