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CONTACT: Alzheimer's Association AAIC Press Office, 416-585-3701, media@alz.org
Niles Frantz, Alzheimer's Association, 312-335-5777, niles.frantz@alz.org

FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2016

NEW RESEARCH SUGGESTS MEN RECEIVE DEMENTIA-RELATED MISDIAGNOSIS MORE OFTEN THAN WOMEN

- May explain some of difference in Alzheimer's prevalence between the sexes -
- Autopsies suggest same frequency of Alzheimer's in men and women overall, but differences between age ranges -

TORONTO, July 26, 2016 – Among the 5.2 million Americans age 65 or older with Alzheimer's disease, nearly two-thirds (3.3 million) are women. However, new data presented today at the Alzheimer's Association International Conference 2016 (AAIC 2016) in Toronto, suggests a high number of men are not accurately diagnosed during their lifetime. In addition, the investigators found that there may be a relationship between sex and the age of onset of Alzheimer's.

Researchers from the Mayo Clinic in Jacksonville, Florida, queried the State of Florida brain bank for Alzheimer's cases and identified 1,606 individuals ranging in age from 37 to 102. Demographic and clinical data were collected, including education, family history, age of onset, disease duration, cognitive test results, and presence of known Alzheimer's risk genes. The purpose of the study was to examine the frequency, as well as the pathologic, demographic, clinical, and genetic features of women and men with autopsy-confirmed Alzheimer's.

Results showed that women with Alzheimer's in the study had lower education and older age at death. Men in the study were younger at age of onset, had a shorter disease duration, and more commonly had an atypical clinical diagnosis (e.g., corticobasal degeneration, aphasia).

The study also revealed a spike in the frequency of Alzheimer's in men in their 60s; whereas the frequency of women with AD was overrepresented in their 70s, 80s and 90s.

The study showed key sex differences in disease pathology with Alzheimer's pathology in men in the study more often sparing the hippocampal region of their brain that coordinates memory, whereas women were more often affected in the limbic area of the brain, which includes the hippocampus.

"This study goes much deeper than just looking at the difference between the number of women and men diagnosed. It calls attention to the process of diagnosis and other lifelong factors that may influence diagnosis and timing and duration of the disease," said Maria C. Carrillo, PhD, chief science officer, Alzheimer's Association. "An accurate and timely diagnosis can provide individuals and their families with more and better opportunities to receive the best possible care at the earliest time point."

"While it is well accepted that age is the strongest risk factor for Alzheimer's, there is an enormous need to understand additional factors that contribute to the development of the disease," said Melissa E. Murray, PhD, Assistant Professor at the Mayo Clinic and presenting author of the new research at AAIC 2016. "Our study demonstrates that there may be an interaction between age of onset and sex-based differences."

"In our study population, neuropathologically diagnosed Alzheimer's was observed at the same frequency overall in both sexes, but occurred quite differently depending on the age range being examined. Atypical clinical presentations were more common in men, suggesting that their lower reported prevalence of Alzheimer's may be a result of the disease not being accurately recognized in life," Murray added.

Misdiagnosis of Alzheimer's: Inconsistencies between the clinic and neuropathology

A second study reported at AAIC 2016 - presented by a team from Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, Ontario, Canada - also focused on issues related to diagnosis and misdiagnosis of Alzheimer's disease.

The researchers looked at inconsistencies between clinical and neuropathological diagnoses in 1,073 people from the National Alzheimer's Coordinating Center database.

- 841 (78.4%) had a clinical diagnosis and autopsy confirmation of Alzheimer's using the NIA-Reagan criteria.
- 116 (10.8%) were diagnosed with Alzheimer's in the clinic but, on autopsy, did not have the brain changes necessary for an Alzheimer's diagnosis ("false positives"). In other words, some disease or condition other than Alzheimer's was causing their dementia.
- 116 (10.8%) had Alzheimer's changes in their brains, but were not clinically diagnosed with Alzheimer's ("false negatives").

The correct clinical diagnosis of Alzheimer's disease was made in 78.4 percent of cases (83.5 percent if possible pathological diagnosis of Alzheimer's is accepted), with equal rates of false negatives and false positives.

Of the false positives, 35 (30.2%) had primary vascular pathology, 14 (12.1%) had Lewy body pathology, 12 (10.3%) had medial temporal lobe sclerosis, 10 (8.6%) had FTD-related pathology (4-progressive supranuclear palsy, 3-frontotemporal dementia, 2-corticobasal degeneration, 1-Pick's disease), 14 (12.1%) had another form of tauopathy (e.g. tangle-only dementia and argyrophilic grain dementia), and 17 (14.7%) had mixed pathology (two or more of the previous).

The false negative group included 51 (44.0%) diagnosed with possible Alzheimer's, 42 (36.2%) with dementia with Lewy bodies (DLB), 12 (10.3%) with vascular dementia, and 11 (9.5%) with Parkinson's disease dementia.

"Vascular pathology was the most common cause of a false positive clinical Alzheimer's diagnosis while dementia with Lewy bodies was the most common cause of a false negative diagnosis. Multiple overlapping pathologies may have contributed to the discrepancy," said Winnie Qian, BSc, Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, Canada.

"Diagnostic errors can have important implications for patient treatment and outcome. We need assessment tools with higher sensitivity and specificity to reduce diagnostic errors in Alzheimer's," Qian added.

The term "mixed dementia" is most commonly applied when the hallmark brain changes of Alzheimer's disease and vascular dementia coexist, but can also describe Alzheimer's and coexisting pathology of other forms of dementia. These pathologies may interact in important ways to increase likelihood of clinically significant cognitive decline. Mixed dementia prevalence may also become more common with increasing age.

"Recent studies suggest that the prevalence of mixed dementia is greater than previously thought," said Carrillo, "and this study illustrates how it can complicate the process of getting a diagnosis."

No drugs are currently approved by the FDA to treat mixed dementia. According to Carrillo, "since some of the drugs approved to treat Alzheimer's have shown a similar benefit in treating vascular dementia, there is reason to believe they may also be of help in mixed dementia. More research is needed in this area."

Taking Steps to Increase Diagnostic Accuracy

The Alzheimer's Association supports research that helps improve diagnosis of Alzheimer's disease and other dementias. For example, the Association leading the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study (http://www.ideas-study.org/). The four-year study, with an estimated budget of $100 million, will determine the clinical usefulness and value in diagnosing Alzheimer's and other dementias of a brain positron emission tomography scan that detects a core feature of Alzheimer's disease. IDEAS is led by the Alzheimer's Association and managed by the American College of Radiology and American College of Radiology Imaging Network.

About AAIC

The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.
AAIC 2016 home page: www.alz.org/aaic/
AAIC 2016 newsroom: www.alz.org/aaic/press.asp

About the Alzheimer's Association®

The Alzheimer's Association is the leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit alz.org or call 800.272.3900.

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- Melissa Murray, PhD, et al. Alzheimer's Disease May Not be More Common in Women; Men May be More Commonly Misdiagnosed. (Funder(s): Florida Department of Health; Gerstner Family Foundation)
- Winnie Qian, BSc, David Munoz, MD, FRCPC, et al. Misdiagnosis of Alzheimer's disease: inconsistencies between clinical diagnosis and neuropathological confirmation (Funder(s): University of Toronto; Canadian Institutes of Health Research)

Proposal ID: O3-04-04
Oral session: Tuesday July 26, 2016: 2:00-3:30 PM
Theme selection: Neuropathology

Alzheimer's Disease May Not be More Common in Women; Men May be More Commonly Misdiagnosed

Presenting author: Melissa Murray, PhD
Mayo Clinic, Jacksonville, Florida, USA
murray.melissa@mayo.edu

Senior author: Neill Graff-Radford, MBBCh, FRCP
Mayo Clinic, Jacksonville, Florida, USA
graffradford.neill@mayo.edu

Background: Women reportedly make up two-thirds of the Alzheimer's disease (AD) sufferers (Herbert Neurology 2013). Many estimates regarding AD, however, are based on clinical series lacking autopsy confirmation. The purpose of this study was to examine the frequency, as well as the pathologic, demographic, clinical, and genetic features of women and men who were autopsy-confirmed AD cases.

Methods: The State of Florida brain bank was queried for AD cases with a total of 1606 cases identified ranging in age from 37 to 102 years. Demographic and clinical data were collected, including education, family history, age of onset, disease duration, and Mini-Mental Status Examination (MMSE). MAPT and APOE were examined for genetic differences across cases.

Results: Women had lower education and were older at death (see Table). Men were younger at age onset, had a shorter disease duration, and more commonly had an atypical clinical diagnosis (e.g. corticobasal degeneration, aphasia). Braak tangle stage and TDP-43 positivity was higher in women, but Thal amyloid phase did not differ. Men were more commonly classified as hippocampal sparing AD, whereas limbic predominant AD was more common in women. Neither MAPT haplotype, nor APOE genotype differed between men and women. The frequency of men and women across decade-long intervals revealed two inverse U-shaped curves, with the inflection identified at approximately 70 years old.

Conclusions: Our data suggest neuropathologically diagnosed AD in women is observed at the same frequency overall, but quite differently depending on what age range is being examined. Atypical clinical presentations were more common in men, suggesting that their lower reported frequencies may be a result of not being recognized as AD dementia in life.

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Oral session: Tuesday July 26, 2016: 2:00-3:30 PM
Theme selection: Neuropathology

Misdiagnosis of Alzheimer's disease: inconsistencies between clinical diagnosis and neuropathological confirmation

Presenting author: Winnie Qian, BSc
Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, Canada
winnie.qian@mail.utoronto.ca

Senior author: David Munoz, MD, FRCPC (preferred contact for news media)
Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, Canada
munozd@smh.ca

Background: Despite consensus on clinical diagnostic criteria, some patients with Alzheimer's disease (AD) may be misdiagnosed as other forms of dementia, and conversely, other dementias may be misdiagnosed as AD. Misdiagnosis is a roadblock in clinical management because different dementia types require different treatment approaches. Moreover, clinical misdiagnosis impedes the ability to find new treatments in clinical trials because inclusion of incorrectly diagnosed patient groups can dilute or obscure important effects. The current study aimed to investigate inconsistencies between clinical and neuropathological diagnoses in AD.

Methods: Using data from the National Alzheimer's Coordinating Center database, we compared the clinical ("Probable AD" using the NINCDS-ADRDA criteria) and neuropathological diagnosis ("High Likelihood" on the NIA-Reagan) in patients presenting with AD and in patients with confirmed neuropathological diagnosis of AD at autopsy.

Results: We identified 1073 subjects from the NACC database who met criteria. Of these subjects, 841(78.4%) had a clinical diagnosis as well as neuropathological confirmation of AD; 116(10.8%) presented with AD clinically but did not have confirmed AD pathology ("false positives"); and 116(10.8%) had AD pathology but were not clinically diagnosed with AD ("false negatives"). Of the false positives, 35(30.2%) had primary vascular pathology, 14(12.1%) had Lewy body pathology, 14(12.1%) had another form of tauopathy, 12(10.3%) had medial temporal lobe sclerosis, 10(8.6%) had FTD-related pathology(4 with progressive supranuclear palsy, 3 with frontotemporal dementia, 2 with corticobasal degeneration, and 1 with Pick's disease), and 17(14.7%) had mixed pathology (two or more of the previous). The false negative subset included 51(44.0%) diagnosed with possible AD, 42(36.2%) with dementia with Lewy bodies (DLB), 12(10.3%) with vascular dementia, and 11(9.5%) with Parkinson's disease dementia.

Conclusions: The correct clinical diagnosis of AD was made in 78.4% of cases (83.5% if possible AD is accepted), with equal rates of false negatives and false positives. Vascular pathology was the most common cause of a false positive clinical AD diagnosis while DLB was the most common cause of a false negative diagnosis. Multiple overlapping pathologies may have contributed to the discrepancy. Diagnostic errors can have important implications for patient treatment and outcome. Perhaps we need assessment tools with higher sensitivity and specificity to mitigate diagnostic errors in AD.

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