MARY S. EASTON CENTER for Alzheimer's Disease Research at UCLA
DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA

David Geffen School of Medicine

Autumn 2021

E-Newsletter

The Mary S. Easton Center for Alzheimer's Disease Research at UCLA has very active teams working on basic research, drug discovery, biomarkers for early diagnosis and clinical activity including clinical trials, cognitive testing, and patient care.

Anti-seizure Medication Improves Cognitive Function in Alzheimer's Patients with Epileptic Activity

By: Keith Vossel, MD, MSc

In the Sept. 27th issue of JAMA Neurology,[1] we published the highly anticipated results of a phase 2a clinical trial of levetiracetam for patients with Alzheimer's disease. Levetiracetam is an inexpensive anti-seizure medication that is widely used to treat epilepsy. We found that it markedly improves learning and memory and other cognitive functions in Alzheimer's patients who have epileptic activity in their brains.

Alzheimer's disease is the leading cause of dementia worldwide. Early symptoms include short-term memory loss, decline in problem solving, word-finding difficulties, and trouble with spatial navigation. Among Alzheimer's patients, an estimated 10-22% develop seizures, while an additional 22-54% exhibit silent epileptic activity, which is seizure-like brain activity without the associated physical convulsions.

We showed in earlier studies that patients who experience silent epileptic activity in their brains have a more rapid decline in cognitive function. We chose to test the anti-seizure medication levetiracetam, which is approved by the FDA because it performed well in animal models of Alzheimer's disease. Now available as a generic, levetiracetam costs around $70 per year. The dose tested in the trial was 125 mg twice a day, far less than a typical dose used for epilepsy.

In the study, 54 patients with mild Alzheimer's symptoms were screened for silent epileptic activity using an electroencephalogram (EEG) to monitor them overnight, as well as an hour-long magnetoencephalogram (MEG) to record magnetic waves generated from electrical activity. MEG can detect epileptic activity that EEGs miss because it's looking at a different population of brain cells.

Among the patients screened for the study, 34 patients were eligible to participate, with nearly 40% having epileptic activity, and the remainder having no epileptic activity (patients on anti-seizure medications due to preexisting seizure disorders were excluded prior to screening).

Patients were then divided into two groups with one group receiving placebo for four weeks, followed by a 4-week period of receiving no drug and then a 125 mg dose of levetiracetam twice a day for four weeks. The second group received these same treatments in reverse order. This crossover design allowed the intervention to be tested on all participants with neither the patients nor the researchers knowing whether the patient was taking the actual drug on any given week.

During the study period, we tested skills like the patients' abilities to problem solve, reason, remember words and how well they could navigate. For example, using a driving simulator on a computer monitor, participants learned to navigate a street route through a virtual city.

We found that the patients treated with levetiracetam showed trends toward improvement in cognitive function, but when the patients were separated into those with silent epileptic activity and those without, the patients with silent epileptic activity showed clear benefit from being on the drug.

These clear differences between the groups indicates that there is a subtype of Alzheimer's disease, consider it an epileptic variant, that's quite common, occurring in approximately 60% of patients. Patients with this form of Alzheimer's disease show symptomatic improvement with levetiracetam.

When doctors diagnose Alzheimer's disease, they do not typically test for silent seizures, so findings from the study will prompt them to consider whether a patient is potentially experiencing epileptic activity.

There are some clinical features that indicate Alzheimer's patients are more likely to be having silent epileptic activity. The main one is being under the age of 65 when symptoms begin. In fact, the drug also benefited younger patients even if they didn't have detectable epileptic activity.

Patients in the study were already taking currently approved medications for Alzheimer's, and this study demonstrates that levetiracetam improves cognitive function better than current treatments alone. Future studies will see if the drug can help slow the disease course over longer periods. The Easton Center will collaborate with investigators in the UCLA Epilepsy program. We will focus on recruiting a more diverse study population, applying advanced brain wave recordings, testing additional anti-seizure medications, and studying additional neurodegenerative diseases related to Alzheimer's disease.

References:

1. **Vossel K**, Ranasinghe KG, Beagle AJ, et al. Effect of Levetiracetam on Cognition in Patients With Alzheimer's Disease With and Without Epileptiform Activity: A Randomized Clinical Trial. JAMA Neurol 2021. PMC8477304

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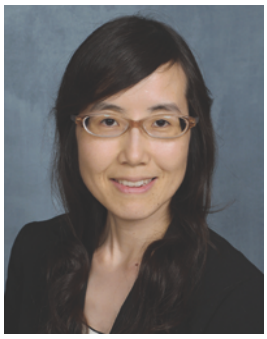
Neuropathology in the Study of Neurologic Diseases



By: Shino Magaki, MD, PhD

Neuropathology is the study of diseases of the brain, spinal cord and peripheral nerve (the central and peripheral nervous system) as well as skeletal muscle, through the examination of tissue obtained at surgery or autopsy. There are descriptions of the brain in ancient Egyptian and Greek documents, and Pythagoras considered the brain central to cognition and mental diseases. However, the modern history of Neuropathology began at the turn of the last century when clinician-scientists in Psychiatry and Neurology sought to understand the pathogenesis of diseases in their patients. At the same time, there were advances in anatomic and histologic techniques, including stains that highlighted the cellular features of neurons, which allowed for a more detailed study of nervous tissue. In the United States today, Neuropathology is a subspecialty of Anatomic Pathology, the study of diseases of the entire body using similar methodology. Neuropathology works closely with Neurology, Neuroradiology and Neurosurgery, less so with Psychiatry despite close ties in the beginning due to the difficulty in detecting changes in the brains of individuals with psychiatric diseases using currently available techniques, although that will likely change in the future.

Neuropathologic studies of autopsy brains have been instrumental in many of the breakthroughs in the understanding of neurologic diseases, especially neurodegenerative disease. One of the most famous examples is Alzheimer's disease. In 1906, Dr. Alois Alzheimer described the clinical and neuropathologic findings of a dementing disorder, later known as Alzheimer's disease, in a 55-year-old female patient at a meeting of Psychiatrists in Germany. Clinical features of the disease had been documented as far back as ancient Greek times, and plaques had been described previously several years earlier, but he was the first to describe neurofibrillary tangles that he observed in her brain. Decades later, by studying autopsy brains, researchers discovered that amyloid-beta was the major component of plaques and tau comprised neurofibrillary tangles (Figures A and B). These plaques and tangles are considered pathological hallmarks of Alzheimer's disease. Autopsy studies performed in England during the late 1960s also played a key role in showing that Alzheimer's disease, considered up to that time to be a rare cause of dementia, was in fact the most common brain disease leading to dementia. Neuropathology has played an important role in the characterization and understanding of many other neurodegenerative diseases including the discovery of alpha-synuclein in Lewy bodies (Figure C), the pathologic hallmark of Parkinson disease and dementia with Lewy bodies, and more recently, different types of tau, TDP-43 and other proteins involved in frontotemporal dementias and amyotrophic lateral sclerosis. These proteins are thought to be central to the origins of these diseases. Such discoveries have led to studies using biochemical methods and animal models to provide mechanistic insights into the disease process as well as potential treatments.

There has been great progress in imaging, laboratory studies and neuropsychological testing that allows for quite accurate diagnoses of Alzheimer's disease and other dementias during life. However, the gold standard remains neuropathologic examination at autopsy where, not infrequently, unexpected findings that would have affected neurologic function are detected. Ironically, at this time, when the technological advances in molecular biology and genetics have revolutionized medicine and expanded the potential of studying diseases in human tissue as never before, the rate of autopsies, a major source of human tissue for research, have declined worldwide. This is likely to be exacerbated in the US by the elimination of the autopsy requirement for hospitals by the Centers for Medicare and Medicaid Services in 2019. The implications are that centers, such as the Mary S. Easton Center, and research participants at these centers will become even more critical in the continued research on Alzheimer's disease and other neurodegenerative disorders.

(A) (B) (C)

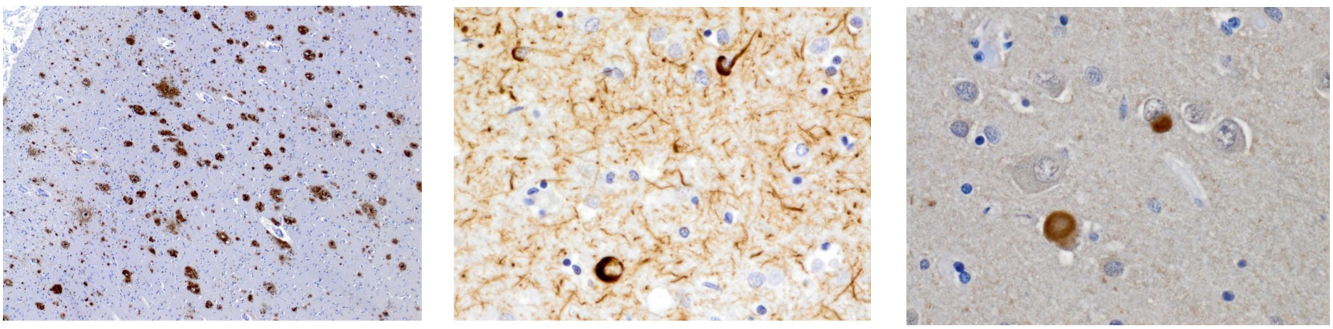


Figure A. Amyloid Plaques (Alzheimer's disease)
Figure B. Neurofibrillary Tangles (Alzheimer's disease)
Figure C. α-Synuclein Aggregates (Parkinson's disease)

References:

1. Henry JM. Neurons and nobel prizes: A centennial history of neuropathology. Neurosurgery 1998;42:143–56.
2. Del Bigio MR, Hainfellner JA, McLean CA, et al. Neuropathology training worldwide - Evolution and comparisons. Brain Pathol 2014;24:285–98.

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New Additions to the Easton Center

Please join us in welcoming new staff members to the Easton Center.

Photo: Jaila Coleman, BA, Clinical Research Coordinator

Jaila received her Bachelor of Arts Degree in Psychology from Marquette University in 2019. During her undergraduate studies, she worked in a research lab that focused on aging, imaging, and memory in Alzheimer's disease, and in a different lab as a clinical research assistant developing the early stage of a new study, focused on heart rate variability and mild traumatic brain injury. Before joining the Easton Center, she was a Clinical Research Coordinator at the Stanford/VA Aging Clinical Research Center located in Palo Alto, California. Jaila was the lead Clinical Research Coordinator for the Alzheimer's Disease Neuroimaging Initiative study and oversaw the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) clinical trial study. Outside of work, she enjoys exploring the city and attending yoga classes. Jaila is excited to continue her work in the research of Alzheimer's disease.

Photo: Jessica Morales, BA, Clinical Research Coordinator

Jessica graduated from UCLA in 2020 with a Bachelor's degree in Psychology. As an undergraduate student, she volunteered and worked in an education and psychology lab, an addictions lab, and a geriatrics lab. After graduating, Jessica gained valuable research experience working with Dr. Mario Mendez, where she helped manage two research projects investigating Alzheimer's disease and frontotemporal dementia. She's passionate about clinical research and advancing treatments and diagnosis for diseases such as Alzheimer's.

Jessica is excited to join the Kagan Clinical Trials Program at the UCLA Easton Center. Outside of research, Jessica enjoys spending time with her family, listening to music, and reading.

Photo: Samantha Shah, BS, Project Manager

Samantha (Sam) received her B.S. degree in Psychology from the University of Illinois at Urbana Champaign with a minor in Social Work. As an undergraduate, she had a keen sense for research and completed her own research project, which she wrote up as thesis that earned distinction. Sam's passion for research has continued after graduation. She previously worked at Northwestern University as a Clinical Researcher, and is a Project Manager for Dr. Tim Chang in the UCLA Easton Center. Sam is excited to learn more about Alzheimer's disease and various movement disorders. Outside of research, she enjoys staying active outdoors, reading, and exploring new restaurants and food throughout LA.

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Clinical Research Opportunities

If you would like to advance Alzheimer's disease research, please consider being a study participant. Below are the current recruiting trials. For a complete list of enrolling studies, visit our website at www.eastonad.ucla.edu.

EASTON CENTER KAGAN CLINICAL TRIALS PROGRAM

- Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3) Protocol

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For more information on our upcoming lectures and events, please visit the Easton Center Community Calendar.

Making Memories Festival: A Celebration of LA Food and Music

Date: Sunday, November 14, 2021
Time: 12:00 P.M. – 6:00 P.M. (PST)
Location: LA State Historic Park

https://connect.alzheimersla.org/event/making-memories-festival-2021/e344000 for more information and to purchase tickets.

Care.Cure.Prevent

Date: Wednesday, November 17, 2021
Time: 3:00 P.M. – 4:00 P.M. (PST)
Virtual Forum

Join Dr. Leila Parand, Cedars Sinai, USC, UCSF, Stanford and Kensington Senior Living for a women-led virtual panel on everything brain health and the care, cure and prevention of Alzheimer's disease; moderated by Lauren Miller Rogen.
Please register in advance to receive a confirmation email containing access information:
https://us02web.zoom.us/webinar/register/WN_Twi3tU14RXO6kLyzt11UOA

Update on Alzheimer's Disease Research and Clinical Trials

Date: Wednesday, December 1, 2021
Time: 6:00 P.M. - 7:30 P.M. (PST)
Virtual Forum

In partnership with CAPS Adult Day Center Pasadena
Questions, please email Monica Moore at mrmoore@mednet.ucla.edu or Elizabeth Nadeau at enadeau@heritageclinic.org
https://heritageclinic.zoom.us/j/82047532263

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