Check for updates

DOI: 10.1002/alz.052465

BASIC SCIENCE AND PATHOGENESIS

POSTER PRESENTATION

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Degeneration of human orexinergic neurons across Braak stages of Alzheimer's disease: Implication for pathogenesis, sleep dysfunction, and therapy

Eva Larsen[1] | Jun Yeop Oh[1] | Mihovil Mladinov[1,2] | Caroline Lew[1] | Song Li[1] | Thomas Neylan[1,3] | William W. Seeley[1] | Salvatore Spina[1] | Christine M Walsh[1] | Lea T. Grinberg[1,4,5]

[1] Weill Institute for Neurosciences and Memory and Aging Center, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA

[2] Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA

[3] Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA

[4] Global Brain Health Institute, San Francisco, CA, USA

[5] Brain Bank of the Brazilian Brain Aging Study Group, São Paulo, Brazil

Correspondence
Eva Larsen, Weill Institute for Neurosciences and Memory and Aging Center, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA.
Email: eva.larsen@ucsf.edu

Abstract

Background: Sleep disturbances are common precognitive symptoms of Alzheimer's disease (AD). Wake-promoting orexinergic neurons (Oxe) in the lateral hypothalamic area (LHA) are key regulators of sleep-wake states. We recently reported a major loss of Oxe in the terminal stages of AD. This was unexpected, because clinical research shows elevated orexin levels in the cerebrospinal fluid (CSF) of AD patients. In line with this finding, suvorexant, an orexin receptor antagonist, was recently the first drug approved for insomnia in patients with mild-to-moderate AD. The aim of our current study was to understand the biological basis of these findings and elucidate the still unknown pattern of orexinergic neuron degeneration in the course of AD.

Methods: We performed a postmortem study of 15 subjects with different AD stages and controls. Patients with contributing pathologies other than AD were excluded from the study. Using double immunohistochemistry and unbiased stereology, we estimated the number of total neurons, Oxe and tau-inclusions in the LHA along the Braak stages of AD.

Results: Examined participants' mean age was 70± 12 years, 47% female. Along AD progression, there was an increase of tau inclusions in Oxe, with 0.1% of tau-positive neurons at Braak stage 0 and 23% at stage 6 (Fig. 1). Further, we observed a substantial decrease of ONs from Braak stage 0 to stage 6 (Fig. 2). Along other Braak stages the decrease of orexinergic neuronal number was slower.

Conclusion: We provide evidence of tau-accumulation in Oxe as early as Braak stage 0 and significant orexinergic neuronal loss from Braak 1. This correlates well with clinical data showing that in many patients sleep-wake disorders precede the cognitive symptoms, which typically emerge with Braak 3-4 stages. Further, we conclude that elevated orexin levels in the CSF of AD patients may represent a compensatory mechanism for the loss of Oxe in the early and middle disease stages, whereas in the terminal stage the compensatory capacity may be lost. The practical consequence is that during treatment, disease stages should be considered and symptomatic therapy should be adjusted accordingly. Further studies are necessary to develop better targeting / therapeutics for sleep disturbances in AD.

© 2021 the Alzheimer's Association

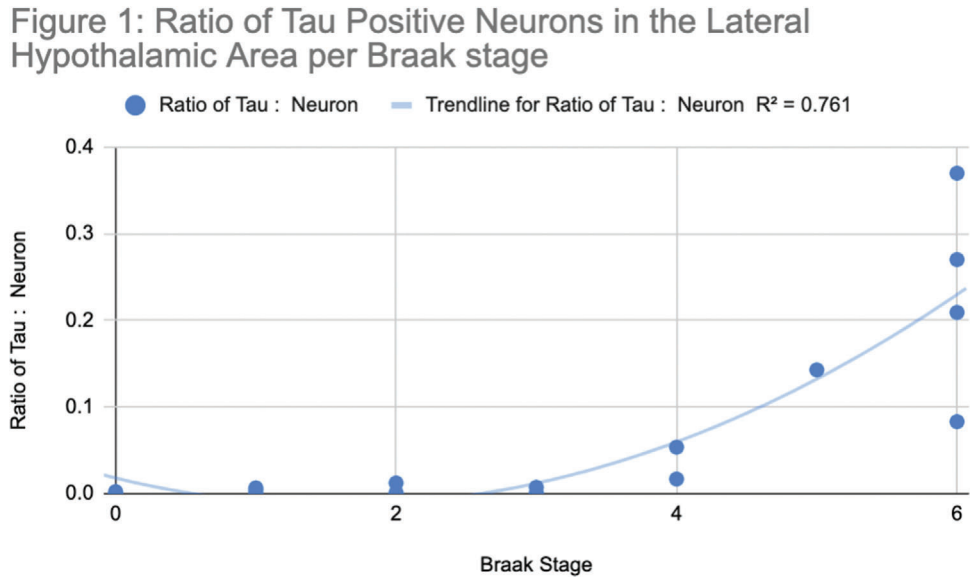


FIGURE 1

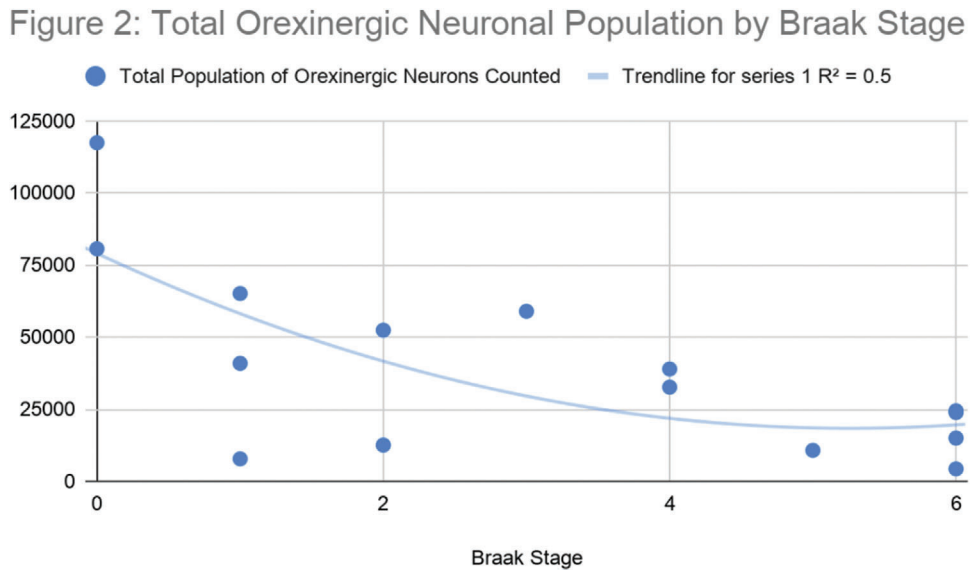


FIGURE 2

15525279, 2021, S3, Downloaded from https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.053465 by University College London UCL Library Services, Wiley Online Library on [27/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License