# 学 位 論 文 の 要 旨

氏名　田原　奈生

学　位　論　文　名　Hippocampal Sclerosis in Senile Dementia of the Neurofibrillary Tangle Type

発　表　雑　誌　名　Journal of the Neurological Sciences
(**471**, 123437, 2025)
（巻，初頁～終頁，年）

著　　者　　名　Nao Tahara, Daisuke Tahara, Akio Akagi, Yuichi Riku, Jun Sone, Hiroaki Miyahara, Atsushi Nagai, Mari Yoshida, Yasushi Iwasaki

## 論 文 内 容 の 要 旨

### INTRODUCTION

Senile dementia of the neurofibrillary tangle type (SD-NFT) is a dementia associated with brain aging. Neuropathologically, SD-NFT is defined by neurofibrillary tangles (NFTs) in the hippocampal region and a minimal presence of neuritic plaques throughout the brain in elderly individuals. A characteristic pathological feature of SD-NFT is the presence of numerous ghost tangles (GTs) in the entorhinal cortex.

Hippocampal sclerosis (HS) for aging is defined as neuronal loss and astrogliosis in the hippocampal CA1 and/or subiculum. Recent studies have reported a correlation between HS and aging, and it is associated with cognitive impairment. HS in aging patients has been linked to phosphorylated transactive response DNA-binding protein 43 (p-TDP-43) expression in the hippocampal dentate gyrus, particularly in Alzheimer's disease (AD). To the best of our knowledge, in SD-NFT, which is also related to aging, no comprehensive studies have investigated HS. Therefore, in this study, we aimed to investigate the presence of HS in patients with SD-NFT.

### MATERIALS AND METHODS

We investigated deceased Japanese patients who underwent consecutive autopsies in our institute. The study protocol was approved by the Research Ethics Committee of Aichi Medical University. We included patients diagnosed with SD-NFT. We excluded patients with other

neurodegenerative diseases, and with early-onset psychiatric conditions.

We retrospectively investigated patients' sex, age at onset, duration of dementia, age at death, clinical diagnosis, and brain weight. Clinical data were obtained from medical records and clinicopathological conferences.

SD-NFT diagnosis was based on the clinical and pathological criteria. We included cases where amyloid β deposition extended within the cerebral neocortex and hippocampus, which approach aligns with the PART (primary age related tauopathy) criteria.

We pathologically evaluated HS, NFTs, amyloid β deposition, and p-TDP-43-positive neuronal inclusions. HS is defined as neuronal loss and severe astrogliosis in subiculum and/or hippocampal CA1 region, which makes hippocampal atrophy. p-TDP-43-positive inclusions were assessed within hippocampal dentate gyrus granule cells.

Additionally, we counted the number of NFTs and GTs in the hippocampal CA1 region using the Gallyas method. Hippocampal CA1 was divided into three equal sections. Next, we selected three arbitrary fields for each area. We distinguished between pretangle materials, NFTs, and GTs by stainability and forms. We counted the number of NFTs and GTs and calculated the density of NFTs and GTs. The GT-to-NFT ratio was calculated by dividing the density of GTs by that of NFTs.

Data are presented as means ± standard deviations (ranges). Fisher's exact test was used to compare categorical variables, and the Mann–Whitney U test was applied for continuous and ordinal variables. Statistical significance was set at $p < 0.05$.

## RESULTS AND DISCUSSION

Nine Japanese patients had SD-NFT. The participants comprised three males and six females (patient A to I). The mean ages at onset and age at death were 84.0 ± 6.8 years (range, 76–94 years) and 91.0 ± 7.0 years (range, 79–101 years), respectively. The mean duration of dementia was 7.0 ± 4.0 years (range, 1–13 years). All patients recorded dementia symptoms, such as memory loss; seven of the nine patients were diagnosed with "AD," and one patient was diagnosed with normal pressure hydrocephalus. Another patient had severe psychiatric symptoms and was diagnosed with a paranoid disorder. None of the patients were diagnosed with SD-NFT while alive.

The mean brain weight of all patients was 1124.2 ± 132.1 g (range, 980–1390 g). All patients had Braak stage III or IV based on immunostaining. One (11.1%), five (55.6%), and three (33.3%) patients had Thal phases 2, 1, and 0, respectively. Four (44.4%) and five (55.6%) patients were classified as having definite and possible PART, respectively. Five patients (55.6%) had additional neuropathological findings.

Three of the nine patients (33.3%) had HS, while six (66.7%) did not have HS. None of the patients had a history of epilepsy, seizures, hypoxia, or ischemia. No significant differences were found in age at death, duration of dementia, or brain weight between patients with HS and those without HS. Three of the nine patients (33.3%) had p-TDP-43-positive neuronal inclusions in the medial temporal lobe, classified as LATE stage 1.

This study examined HS in patients with SD-NFT. Approximately 30% of the included patients had HS, and patients with HS had more NFTs and GTs than those without HS in hippocampal CA1.

HS related to aging is defined by neuronal loss and astrogliosis in CA1 and subiculum. Several conditions, other than aging, can result in neuronal loss and astrogliosis in the hippocampus, including hypoglycemia and hypoxia, epilepsy, and frontotemporal lobar degeneration. In this study, none of the patients had any histories and neuropathological findings of hypoglycemia, hypoxia, epilepsy and the degeneration of frontotemporal lobes. Thus, neuronal loss and astrogliosis in the hippocampus observed in this study are indicative of HS related to aging.

HS can combine with neurodegenerative disorders. The studies of the HS in these disorders are limited; however, patients with AD are relatively more studied. Moreover, 24% of the patients with AD have HS compared to <10% of those without AD. In this study, slightly more patients (33%) had HS. Both AD and SD-NFT are related to aging; thus, more patients would tend to have HS. Significant differences have been found in the age of death and duration of dementia between patients with HS and those without HS. However, no such differences were found in our study. We believe this may be due to the small number of patients with SD-NFT.

In this study, one of the characteristic neuropathological findings in patients with SD-NFT combined with HS was the number of NFTs. Neuronal loss can lead to HS, and we observed a significant difference in GT and NFT densities between HS and non-HS cases. The specific mechanisms underlying NFT-related gliosis remain unclear; however, tau protein is known to exert toxic effects on neurons. The presence of numerous NFTs and GTs may contribute to hippocampal gliosis, a characteristic of HS in SD-NFT.

TDP-43 inclusion was found in patients with amyotrophic lateral sclerosis and frontotemporal lobar degeneration, as well as in aged individuals with AD and/or HS without amyotrophic lateral sclerosis and frontotemporal lobar degeneration. Recently, it has been reported that HS has been associated with p-TDP-43 inclusion. AD and p-TDP-43 inclusions appear to be related, partly because amyloid β and p-TDP-43 inclusion co-existed in AD. The relationship between tau and p-TDP-43 inclusion was unclear in AD. In the present study, NFTs were significantly more numerous in HS than no-HS group whereas p-TDP-43 inclusions did not significantly differ among two groups. In SD-NFT, minimal amyloid β deposition may be related to less p-TDP-43 inclusions regardless of HS. We believe that in SD-NFT, HS is more related to NFTs than p-TDP-43 inclusions.

## CONCLUSION

HS and p-TDP-43 inclusions are generally connected; however, there may be a group where HS and NFTs are related. In SD-NFT, HS appears to be associated with NFTs, and NFT deposition contributes to cognitive impairment.