Senile dementia of the neurofibrillary tangle type (SD-NFT): a clinical, neuropathological and molecular genetic study

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Introduction

A subset of senile dementia is characterized by numerous neurofibrillary tangles (NFTs) in the hippocampal region, similar to Alzheimer’s disease (AD), but with absence or scarcity of senile plaques (SPs) throughout the brain [1]. These cases have been reported as an atypical or NFT-predominant form of AD [2]. We studied demented elderly patients with such neuropathological features [3, 4], compared them with age-matched AD patients in clinico-pathological and genetic aspects, and investigated whether the senile dementia characterized by NFTs was just a subtype of AD or an independent disease entity [4]. Our results indicated that this neuropathological condition represents a disease entity with a pathogenetic process different from that of AD [4]. Therefore, we have proposed the term, “senile dementia of the NFT type (SD-NFT)”, which is distinguished from late-onset AD, i.e., senile dementia of the Alzheimer type [4]. Thereafter, the identical neuropathological condition has been recently reported under terms such as NFT-dominant form of senile dementia [5], senile dementia with tangles [6], and limbic neurofibrillary tangle dementia [7].

We report here the incidence, clinical and neuropathological features, and genetic aspects of SD-NFT in comparison with AD.

Incidence of SD-NFT

We performed neuropathological examinations of the 105 patients who developed dementia at age 70 or later in an autopsy series of elderly Japanese at Yokufukai Geriatric Hospital, Tokyo.

The causes of dementia were AD in 57 patients (54.3%), vascular dementia in 31 (29.5%), SD-NFT in 5 (4.8%), dementia with Lewy bodies in 5 (4.8%) and others [4].
Clinical and neuropathological features of SD-NFT

The clinical features of SD-NFT were compared with AD [4]. The patients with SD-NFT were characterized clinically by very late-onset (average age, 89.4 years) of dementia in which memory disturbance was predominant with relative preservation of the other cognitive functions. Ages at onset and death in SD-NFT were significantly higher than those in AD. All the patients with SD-NFT had been diagnosed as having late-onset AD.

Neuropathological features of SD-NFT were compared with AD [4]. SD-NFT was characterized neuropathologically by abundant NFTs in the hippocampal region and scarcity of SPs throughout the brain. A large number of NFTs with neuropil threads were found in the hippocampal regions, including the hippocampus (CA1 > CA2), subiculum and entorhinal and transentorhinal regions, associated with neuronal loss and gliosis, while NFTs were scarce in the neocortical regions. The distribution of NFTs in SD-NFT corresponds to the Limbic Stages (Stages III and IV) of Braak and Braak’s Classification [8]; however, the density of the NFTs in SD-NFT far exceeds the Limbic Stages. Electron-microscopically, the structure of paired helical filaments (PHF) of NFTs in SD-NFT was similar to that in AD [3]. NFTs and neuropil threads in SD-NFT were immunohistochemically labelled with antibodies to phosphorylated (AT8, AT100, AT180 and AT270) and non-phosphorylated epitopes (TAU-2 and anti-human tau) of tau (Fig. 1) and an antibody to ubiquitin [9]. There was no significant difference in the immunoreactivities of NFTs with the anti-tau antibodies between SD-NFT and AD [9].

Aβ deposits (SPs and amyloid angiopathy) were absent or scarce in SD-NFT in contrast with AD [4, 9].

We have proposed criteria for neuropathological diagnosis of SD-NFT (Tab. 1).

Comparisons of SD-NFT with AD and centenarians

To elucidate the mechanism of neurodegeneration in SD-NFT, we morphometrically analyzed the hippocampal lesion of SD-NFT for the atrophy, neuronal cells, NFTs, presynaptic terminals and astroglial and microglial changes in comparison with AD, using immunohistochemistry with antibodies to synaptophysin, Aβ, tau, glial fibrillary acidic protein (GFAP), and KiM1P (a microglial marker) in addition to routine neuropathological stainings [9].

The densities of hippocampal NFTs in SD-NFT were significantly higher than those in age-matched AD patients; in contrast, the hippocampal atrophy, synaptic loss and proliferation of astrocytes and microglia in SD-NFT were significantly mild compared with AD [9].

The results indicated that the neurodegenerative process with NFT formation of the hippocampal region in SD-NFT would be different from that in AD. We speculate that neuronal death without NFT formation may be important in the disease progression of AD compared with SD-NFT.

Furthermore we compared neuropathological findings of 13 centenarians without obvious dementia [10] with those of AD and SD-NFT. The patterns of NFT distribution, Aβ deposition, synaptic loss and glial changes in the centenarians were different from those of AD.