Hippocampal sclerosis in senile dementia of the neurofibrillary tangle type

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Abbreviations

AD, Alzheimer's disease
GTs, ghost tangles
HS, hippocampal sclerosis
LATE, limbic-predominant age-related TDP-43 encephalopathy
NFTs, neurofibrillary tangles
PART, primary age-related tauopathy
p-TDP-43, phosphorylated transactive response DNA-binding protein 43
SD-NFT, senile dementia of the neurofibrillary tangle type

Abstract

Introduction: Senile dementia of the neurofibrillary tangle type (SD-NFT) is a subset of dementia in elderly individuals. Recent studies have reported a correlation between hippocampal sclerosis (HS) and aging. This study aimed to investigate the relationship between HS and SD-NFT.

Methods: We conducted a clinical and neuropathological review of Japanese patients diagnosed with SD-NFT. Hematoxylin–eosin and Klüver–Barrera staining, Gallyas silver impregnation, and immunohistochemistry were employed. Pathological assessments focused on identifying HS, neuritic plaques, and phosphorylated transactive response DNA-binding protein 43 (p-TDP-43)-positive inclusions. Additionally, we quantified the densities of neurofibrillary tangles (NFTs) and ghost tangles (GTs) within the hippocampal CA1 region.

Results: Nine patients met the criteria for SD-NFT from the patients who underwent consecutive autopsies from 1994 to 2022 at our institute. The mean ages at onset and death were 84.0 ±6.8 years (range, 76–94 years) and 91.0 ± 7.0 years (range, 79–101 years), respectively. The mean dementia duration was 7.0 ± 4.0 years (range, 1–13 years). All patients exhibited memory loss although none were diagnosed with SD-NFT during their lifetime. The mean brain weight was 1124.2 ± 132.1 g (range, 980–1390 g). Three patients displayed HS. NFT and GT densities were significantly higher in patients with HS than in those without HS. No significant correlation was found between HS and p-TDP-43 inclusions in the medial temporal lobe.

Conclusion: In SD-NFT, NFTs are more strongly associated with HS. This finding enhances our understanding of the pathological underpinnings of HS in SD-NFT.

Keywords: hippocampal sclerosis, neurofibrillary tangles, ghost tangles, senile dementia of the neurofibrillary tangle type, phosphorylated transactive response DNA-binding protein 43

1. Introduction

Senile dementia of the neurofibrillary tangle type (SD-NFT) is a dementia characterized by memory loss and is associated with brain aging [1, 2, 3, 4]. Typically, patients with SD-NFT develop symptoms in advanced age, with a gradual clinical progression [1, 2, 3, 4]. 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 [1, 2, 3]. A distinct pathological feature of SD-NFT is the presence of numerous ghost tangles (GTs) in the entorhinal cortex. NFT deposition in SD-NFT is concentrated predominantly in the medial temporal lobe, giving rise to alternative terms, including limbic NFT dementia, tangle-predominant senile dementia, senile dementia with tangles, tangle-only dementia, and NFT-predominant dementia [2].

Building on SD-NFT criteria, Crary et al. introduced the concept of primary age-related tauopathy (PART) [5]. PART is described as a neuropathological state characterized by NFTs in the medial temporal lobe in the absence of amyloid β deposition. NFT Braak stages remain in the limbic region in almost all patients with PART-type pathology [5]. PART is a pathological concept; thus, some patients remain cognitively unaffected, while others have dementia [5, 6]. Recent findings have suggested that SD-NFT represents a form of cognitive impairment associated with PART pathology [6].

Hippocampal sclerosis (HS) for aging is defined as neuronal loss and astrogliosis in the hippocampal CA1 and/or subiculum [7]. Recent studies have reported a correlation between HS and aging [7], and it is associated with cognitive impairment [8]. In previous studies, 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) [9]. Some research has examined the distribution and morphology of NFTs in the hippocampal CA1 region in SD-NFT cases [10]. However, 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.

2. Methods

2.1. Participants

We analyzed the data stored in the Brain Bank of the Department of Neuropathology, Institute for Medical Science of Aging, Aichi Medical University. We investigated deceased Japanese patients who underwent consecutive autopsies from 1994 to 2022. We included patients diagnosed with SD-NFT. We excluded patients with other neurodegenerative diseases, such as cerebrovascular dementia, as well as those with early-onset psychiatric conditions. Additionally, patients with argyrophilic grain pathology in the entorhinal, transentorhinal, and insular cortices were excluded [11], along with cases with Lewy body pathology in the limbic and diffuse neocortical stages [12].

The patients' relatives provided informed consent before all autopsies, and the Research Ethics Committee of Aichi Medical University approved all procedures.

2.2. Clinical analysis

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.

2.3. Tissue preparation

The tissues (left cerebral hemisphere, entire cerebellum, and whole brainstem) were fixed in 20% formalin for a minimum of 2 weeks [13]. The left cerebral hemisphere was first sectioned coronally at a thickness of 8 mm using a brain knife and standardized slicer. The brainstem was cut transversely, and the cerebellum was sectioned sagittally at a thickness of 5 mm. Subsequently, regions of interest were trimmed for embedding, while entire hemispheric sections were occasionally embedded in paraffin without trimming. Sections 9 μm in thickness were prepared for hematoxylin–eosin (H&E) staining, Klüver–Barrera staining, and Gallyas silver impregnation, while sections 4.5 μm in thickness were prepared for immunohistochemical analysis. Immunostaining was conducted on selected paraffin sections using anti-phosphorylated tau (1:1000, mouse monoclonal, clone AT-8; Innogenetics, Ghent, Belgium), amyloid-β (1:1000, mouse monoclonal, clone 12B2; UBL, Gunma, Japan), and p-TDP-43 (1:4000, rabbit polyclonal, clone pS409/410; CosmoBio, Tokyo, Japan). A standard avidin-biotin complex technique was applied, with diaminobenzidine used as the chromogen.

2.4. Neuropathological investigation

SD-NFT diagnosis was based on the following clinical and pathological criteria [2]: we pathologically confirmed a high density of NFTs in the hippocampal region, particularly in the entorhinal and transentorhinal cortices and the subicular and CA1 regions of the anterior hippocampus and a poor amyloid β deposition. No definitive criteria exist regarding the neuritic plaque phase; therefore, we included cases where amyloid β deposition extended within the cerebral neocortex and hippocampus, classified as Thal phase 2 [14]. This approach aligns with the PART criteria [5].

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 [7], which makes hippocampal atrophy. HS was assessed in the anterior hippocampus using H&E staining (Figure 1). Astrogliosis was evaluated based on the apparent reactive astrocyte and rarefaction of neuropil using H&E and Klüver–Barrera staining (Figure 1). We assessed qualitatively the atrophy of the hippocampus with loupe images of H&E staining and immunostaining for anti-phosphorylated tau (Figure 2). When the volume of anterior hippocampus was clearly small at a glance, we regarded hippocampal atrophy as positive.

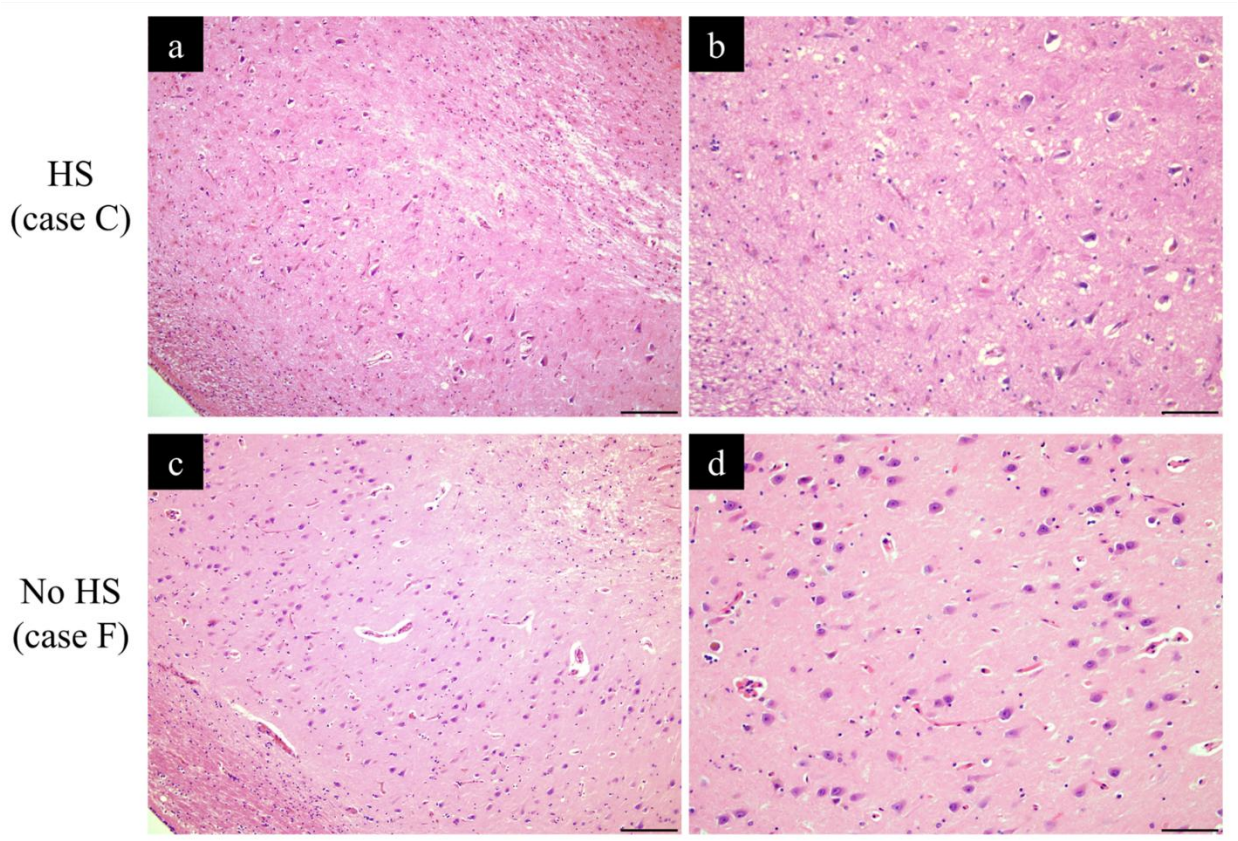

Figure 1: Hippocampal sclerosis (HS) versus non-HS cases, with hematoxylin–eosin staining. Images represent the study's patients. (a) HS showing severe gliosis and neuronal loss. (b) Higher magnification of (a) reveals gemistocytic astrocytes with eosinophilic-stained. (c) Non-HS cases exhibit mild gliosis and no significant neuronal loss. (d) Higher magnification of (c) facilitates detailed assessment. H&E staining, scale bars: (a, c) 100 µm, (b, d) 50 µm.

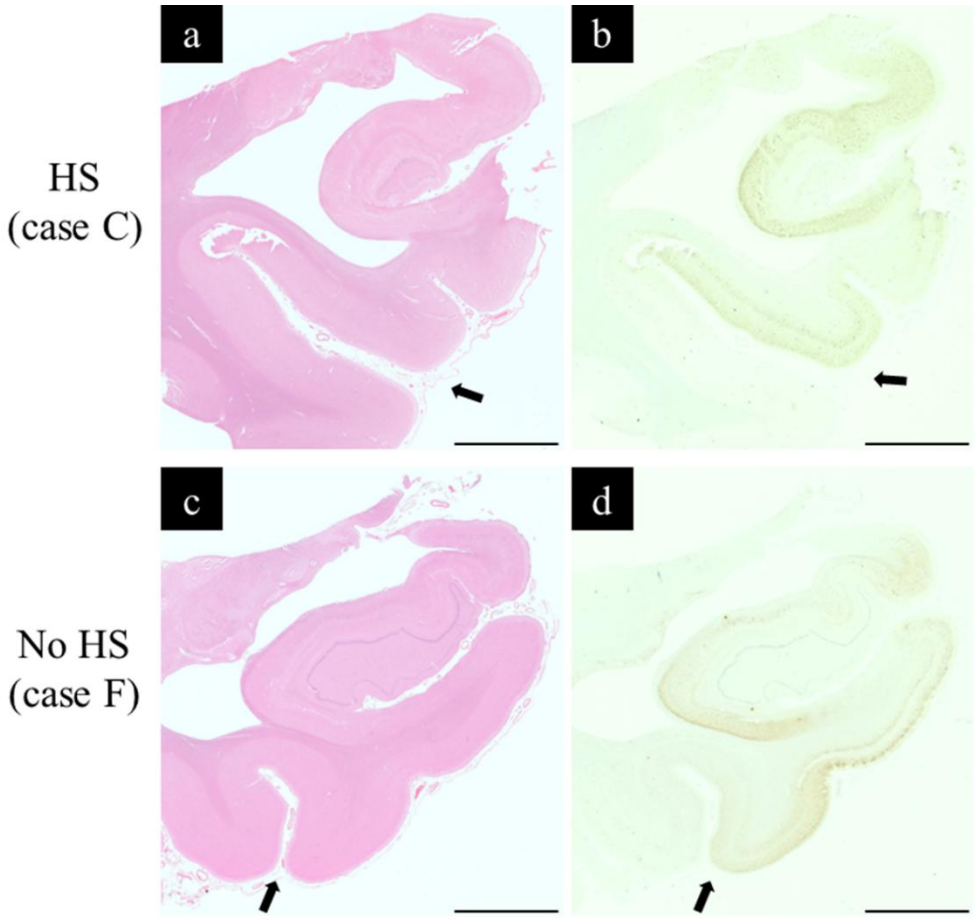

Figure 2: Hippocampal atrophy in cases with hippocampal sclerosis (HS) (a); in contrast, non-HS cases showed no hippocampal atrophy (c). In senile dementia of the neurofibrillary tangle type (SD-NFT) cases, neurofibrillary tangles extended into the occipitotemporal gyrus, observable on loupe images, regardless of the presence of HS (b, d). The arrow indicates the sulcus collateralis. (a, c): H&E staining, (b, d): immunostaining for anti-phosphorylated tau, scale bar: 5 mm.

NFTs were identified through immunostaining for phosphorylated tau and were scored according to Braak staging criteria [15] and PART classification [5]. Amyloid β deposition was observed via immunostaining for amyloid-β and scored according to the Thal phase [14]. Neuritic plaques were observed via Gallyas silver impregnation and scored according to the CERAD score [16].

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, corresponding to the following three specific areas within CA1: adjacent to CA2, the central region of CA1, and the area near the subiculum in the anterior hippocampus (Figure 3). Next, we selected three arbitrary ×200 fields obtained using the Gallyas method for each area. We distinguished between pretangle materials, NFTs, and GTs by stainability and forms (Figure 4). Pretangle materials are at a stage prior to NFT, and they were pale argyrophilic and their shape was swollen, while NFTs were argyrophilic and flame-shaped [15]. GTs were extracellular structure and getting less argyrophilic [15, 17]. We

counted the number of NFTs and GTs in the CA1 region of the hippocampus using ImageJ software (National Institutes of Health, Bethesda, MD, USA) and calculated the density of NFTs and GTs (Figure 4). We did not contain pretangle materials in NFTs. The GT-to-NFT ratio was calculated by dividing the density of GTs by that of NFTs.

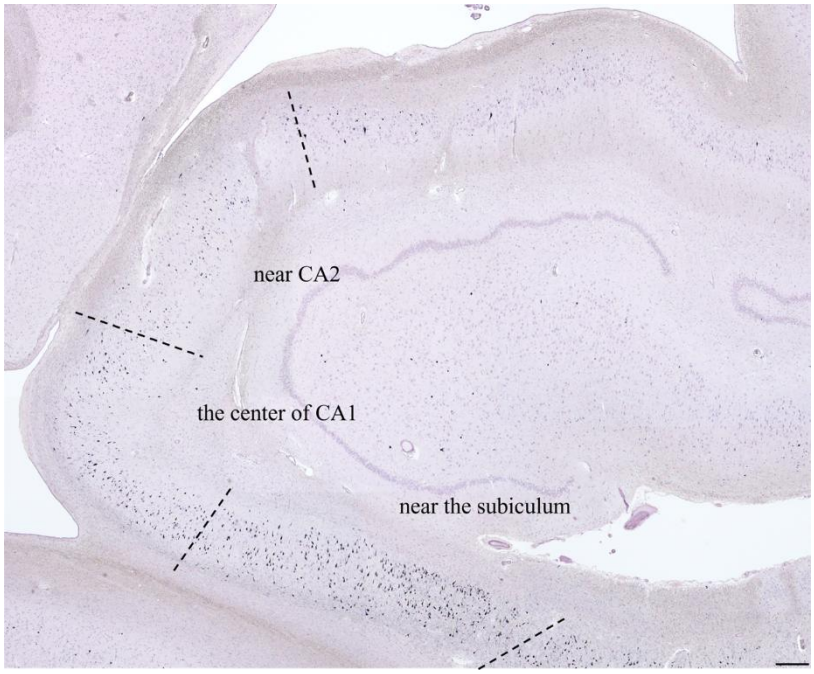

Figure 3: Distribution of neurofibrillary and ghost tangles within CA1. Using Gallyas silver impregnation, CA1 was divided into the following three sections: near CA2, the center of CA1, and near the subiculum in the anterior hippocampus. Three arbitrary fields were selected from each of these sections. Gallyas silver impregnation, scale bar: 200 μm.

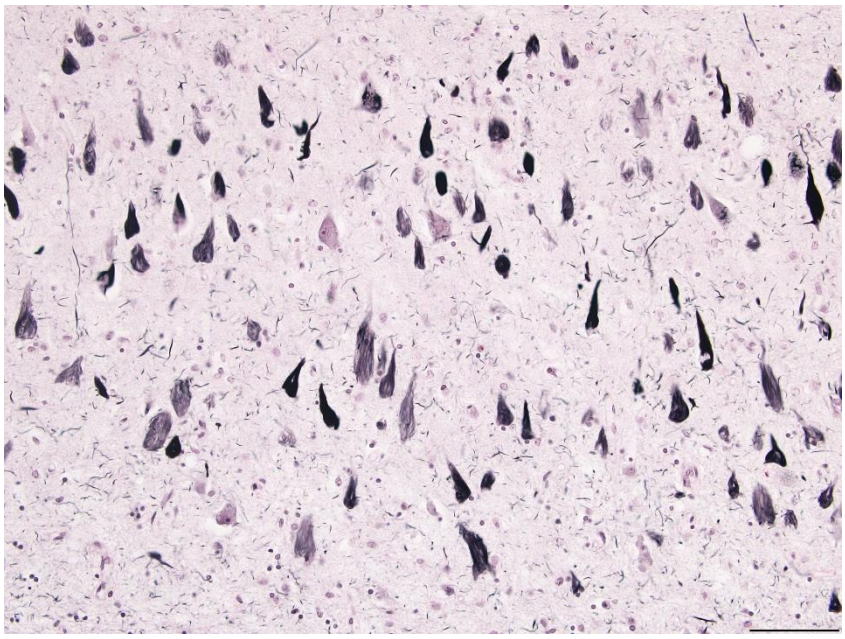

Figure 4: For Gallyas silver impregnation, we assessed neurofibrillary tangles (NFTs) and ghost tangles (GTs). NFTs appeared black within neuronal cells, while ghost tangles appeared gray with visible fine fibers. We measured NFTs and GTs in the CA1 region of the hippocampus using ImageJ software in three arbitrary ×200 fields obtained with Gallyas silver impregnation for each area. Gallyas silver impregnation, scale bar: 50 μm.

p-TDP-43-positive neuronal inclusions were identified through immunostaining for p-TDP-43 and scored using a simplified staging system for diagnosing limbic-predominant age-related TDP-43 encephalopathy (LATE) [18]. We excluded p-TDP-43-positive findings associated with other structures, such as NFTs and granulovacuolar degeneration. p-TDP-43-positive inclusions were assessed within hippocampal dentate gyrus granule cells at ×400 magnification and were categorized as follows: –, no cells with p-TDP-43-positive inclusions; and +, one positive cell visible in some fields.

2.5. Statistical analyses

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 $p < 0.05$. Analyses were conducted using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria; version 4.2.2) [19].

3. Results

3.1. Clinical analysis

Nine Japanese patients had SD-NFT. The clinical and pathological information of the patients with SD-NFT used in this study is presented in Table 1.

Table 1: Clinicopathological profile of participants with senile dementia of neurofibrillary tangle type

Case	A	B	C	D	E	F	G	H	I
Age of onset (years)	80	94	89	77	76	80	82	-	94
Age of death (years)	93	100	101	79	82	87	91	91	95
Duration of dementia (years)	13	6	12	2	6	7	9	-	1
Sex	F	F	F	F	M	M	F	M	F
Clinical diagnosis	AD	AD	AD	NPH	AD	AD	paranoid disorder	AD	AD
Brain weight (g)	1025	980	1100	1185	1070	1390	1008	1300	1060
AT-8 NFT stage	3	4	3	3	4	3	3	3	3
CERAD stage	0	A	A	0	0	0	A	0	0
Thal phase	1	1	1	0	2	1	1	0	0
PART stage	possible	definite	possible	definite	possible	possible	possible	definite	definite
HS	+	+	+	-	-	-	-	-	-
Density of GTs in the hippocampus CA1 (/mm^2)	361.6	117.5	303.8	49	49.3	62.6	86.3	20.4	50.7
Density of NFTs in the hippocampus CA1 (/mm^2)	29	31.5	28.8	35.5	70.2	45.1	156.1	47.7	34.2
Ratio of GTs in the hippocampus CA1 (GTs/NFTs)	12.5	3.7	10.5	1.4	0.7	1.4	0.6	0.4	1.5
p-TDP-43 inclusion in the hippocampal dentate gyrus granule cell	-	-	+	-	-	+	-	-	-
LATE stage	0	0	1	0	0	1	0	1	0
Combined neuropathological change			Lacunar infarction in putamen	AG		CNS-DLBCL		Brain abscess	Subdural hematoma

Abbreviations: AD, Alzheimer's disease; AG, Argyrophilic grain; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CNS-DLBCL, diffuse large B-cell lymphoma of the central nervous system; GTs, ghost tangles; HS, hippocampal sclerosis; LATE, limbic-predominant age-related TDP-43 encephalopathy; NFT, neurofibrillary tangle; NPH, normal pressure hydrocephalus; PART, primary age-related tauopathy; p-TDP-43, phosphorylated transactive response DNA-binding protein 43; SD, standard deviation

The participants comprised three males and six females. 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). Patient H had dementia; however, its duration was not recorded. All patients recorded dementia symptoms, such as memory loss; seven of the nine patients were diagnosed with "AD," and patient D was diagnosed with normal pressure hydrocephalus based on the clinical course and imaging studies. None of the patients were diagnosed with SD-NFT while alive. Patient G had severe psychiatric symptoms following the development of dementia. She complained of discomfort in the nasopharynx and dizziness, although no functional problems were detected clinically. The patient was diagnosed with a paranoid disorder.

3.2. Neuropathological investigation

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. Patient D had argyrophilic grains, which were observed in the ambient gyri.

3.3. Comparison between hippocampal sclerosis and no hippocampal sclerosis

Three of the nine patients (33.3%) had HS, while six (66.7%) did not have HS (Table 2).

Table 2: Comparison of age at death, disease duration, clinical diagnosis, brain weight, densities of ghost tangles (GTs), and neurofibrillary tangles (NFTs) in hippocampal CA1 and p-TDP-43 inclusion in hippocampal dentate gyrus granule cells between patients with and without hippocampal sclerosis.

	SD-NFT with HS (n=3)	SD-NFT with no HS (n=6)	*p*-value
Age at death, years	98±3.6 (93–101)	88.6±5.4 (79–95)	0.072[a]
Duration of disease, years	10.3±3.1 (6–13)	4.8±3.3 (1–9)	0.229[a]
Clinical diagnosis			1[b]
Alzheimer's disease	3	3	
Normal pressure hydrocephalus	0	1	
Paranoid disorder	0	1	
Brain weight, g	1035±49.5 (980–1100)	1188.6±142.9 (1008–1390)	0.25[a]
Density of ghost tangles in the hippocampus CA1, /mm^2	261.0±104.2 (117.5–361.6)	53.1±19.6 (20.4–86.3)	0.024[a]

Density of NFTs in the hippocampus CA1, /mm^2	29.7±1.2 (28.8–31.5)	64.8±42.5 (34.2–156.1)	0.024[a]
Density of NFTs and ghost tangles in the hippocampus CA1, /mm^2	290.7±103.0 (149.0–390.6)	117.9±58.1 (68.1–242.4)	0.048 [a]
Ratio of ghost tangle in hippocampus CA1 (ghost tangles/NFTs)	8.9±3.8 (3.7–12.5)	1.0±0.4 (0.4–1.5)	0.024 [a]
LATE stage (mean)	0.33	0.33	1 [a]
p-TDP-43 inclusion in hippocampal dentate gyrus granule cells			
+	1	1	1 [b]
–	2	5	

Data are expressed as mean ± standard deviation (range) or number. [a] Mann–Whitney U test, [b]Fisher's exact test
Abbreviations: HS, hippocampal sclerosis; LATE, limbic-predominant age-related TDP-43 encephalopathy; NFTs, neurofibrillary tangles; p-TDP-43, phosphorylated transactive response DNA-binding protein 43; SD-NFT, senile dementia of the neurofibrillary tangle type

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. Among HS cases, patient C had p-TDP-43 inclusions in the amygdala, while patient F without HS had p-TDP-43 inclusions in the hippocampal dentate gyrus granule cells.

4. Discussion

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 the following two neuropathological changes: neuronal loss and astrogliosis in CA1 and subiculum [20]. Several conditions, other than aging, can result in neuronal loss and astrogliosis in the hippocampus, including hypoglycemia and hypoxia, epilepsy, and frontotemporal lobar degeneration [20, 21]. Thus, it is essential to distinguish HS due to aging from tissue damage caused by these conditions. In this study, none of the patients had any histories and neuropathological findings of hypoglycemia, hypoxia, and epilepsy; the nuclei initially appeared pyknotic and became more eosinophilic, indicating hypoglycemia in the caudate nucleus and putamen [17] and hypoxia in Purkinje cells [17]. Additionally, the absence of neuronal loss in the subiculum was not observed in epilepsy [21]. Furthermore, we did not observe the degeneration of frontotemporal lobes. Thus, we believe neuronal loss and astrogliosis in the hippocampus observed in this study are indicative of HS related to aging.

HS can combine with neurodegenerative disorders, including AD, argyrophilic grain disease, Parkinson's disease, corticobasal degeneration, and progressive supranuclear palsy [9, 22, 23]. 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 [24] compared to <10% of those without AD [7]. In this study, slightly more patients (33%) had HS. Both AD and SD-NFT are related to aging [2, 6, 17, 18]; 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 [22, 24]. 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. NFTs are neuronal inclusions comprising hyperphosphorylated tau proteins [17]. GTs represent remnants of NFTs following neuronal loss due to phosphorylated deposition [17, 26]. 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 [27]. For example, there are some hypotheses that NFTs have toxicity that impairs normal cellular functions or influences normal tau function [28]. 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 [9, 18]. Recently, it has been reported that HS has been associated with p-TDP-43 inclusion, with TDP-43 inclusions observed in 86% of patients with HS, and approximately 80% of them had AD [22]. In AD, patients with HS had p-TDP-43 inclusion in hippocampal dentate gyrus granule cells [9]. AD and p-TDP-43 inclusions appear to be related, partly because amyloid β and p-TDP-43 inclusion co-existed in AD [25]. The relationship between tau and p-TDP-43 inclusion was unclear in AD [29]. 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.

In conclusion, HS and p-TDP-43 inclusions are generally connected [7, 9, 18]; 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. Neuropathological assessment through autopsy remains essential for understanding dementia.

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Declarations of interest

The authors declare no conflicts of interest.

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