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CASE REPORT

Hippocampal sclerosis with four-repeat tau-positive round inclusions in the dentate gyrus: a new type of four-repeat tauopathy

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Abstract Hippocampal sclerosis is defined as selective neuronal loss and gliosis of the hippocampus with heterogeneous etiologies, including neurodegenerative tauopathies. We report a 78-year-old woman who presented with depression, in whom postmortem examination revealed almost complete loss of neurons with gliosis in the subiculum and CA1-3 regions of the hippocampus and abundant neuronal cytoplasmic inclusions in the dentate gyrus. The inclusions were round, slightly basophilic and argyrophilic, resembling Pick bodies. However, they were Gallyas- and 4-repeat tau-positive, and 3-repeat tau- and ubiquitin-negative. To our knowledge, the histopathological features in this case were different from those in hippocampal sclerosis or 4-repeat tauopathies reported previously. It is likely that this case is a new variant of 4-repeat tauopathy presenting with hippocampal sclerosis.

Keywords Dentate gyrus · Four-repeat tau · Hippocampal sclerosis · Pick body-like inclusion · Tauopathy

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Introduction

Hippocampal sclerosis (HS) is defined as selective neuronal loss and gliosis of the hippocampus, with a predilection for the CA1 region and subiculum [11] and is associated with degenerative dementias like tauopathies [6, 11, 20] and frontotemporal lobar degeneration with TDP-43-positive inclusions (FTLD-TDP) [7, 16, 21]. Tauopathies are now known to be divided into three categories by the biochemical composition of tau in the respective inclusions, these being predominant three-repeat tau (3R-tau) pathology, predominant four-repeat tau (4R-tau) pathology and mixed 3R/4R-tau pathology. HS is frequently associated with 3R/4R tauopathies [5, 6, 8, 11, 19, 20, 30, 31, 39], including Alzheimer's disease (AD) [5, 6, 8, 11, 20], sporadic multisystem tauopathy [6] and limbic tauopathy with features of FTLD-TDP [31] (Table 1). However, HS is less frequently associated with 4R tauopathies, including progressive supranuclear palsy (PSP) [6], corticobasal degeneration (CBD) [33] and argyrophilic grain disease (AGD) [6, 11] (Table 1). Recently, we encountered a case of HS with numerous 4R-tau-positive, ubiquitin-negative inclusions in the dentate gyrus, in whom tau pathology was restricted to the medial temporal lobe and the histological features did not meet the pathological criteria of PSP, CBD, AGD and other 4R tauopathies previously reported. We feel that the present case is a new type of HS or a variant of 4R tauopathy.

Case report

A 75-year-old Japanese woman visited a psychiatrist. Depression was diagnosed and treatment with antidepressant was initiated, which was beneficial. Although the

Table 1 Types of hippocampal sclerosis with tauopathies

3R/4R tauopathies
Alzheimer's disease [5, 6, 8, 11, 20]
Sporadic multisystem tauopathy [6]
Limbic tauopathy with features of FTLD-TDP [31]
Parkinsonism-dementia complex of Guam [30]
Senile dementia of the neurofibrillary tangle type [39]
4R tauopathies
Progressive supranuclear palsy [6]
Corticobasal degeneration [33]
Argyrophilic grain disease [6, 11]

3R three repeat, *4R* four repeat, *FTLD-TDP* frontotemporal lobar degeneration with TDP-43-positive inclusions

neuropsychological state was not fully evaluated by neurologists, her family members and some of her friends did not notice any impairment in her cognitive function. The patient could carry out housework until she died of subarachnoid hemorrhage due to a dissection of the right middle cerebral artery at the age of 78 years. A CT scan at the time of hospitalization (4 days prior to death) showed no brain atrophy. She had no family history of dementia. *MAPT* gene mutations was not screened because of no family history.

Materials and methods

For routine histological examination, 4-μm-thick, formalin-fixed, paraffin-embedded sections from multiple cortical and subcortical regions were stained with hematoxylin and eosin or by the Klüver–Barrera, Bodian's and Gallyas–Braak method. Multiple anterior to posterior blocks of the medial temporal lobe were taken from both the left and right hemispheres. We also examined paraffin-embedded sections immunohistochemically using the following primary antibodies: anti-ubiquitin (1B3; MBL, Nagoya, Japan; 1:2,000), anti-phosphorylated tau (AT8; Innogenetics, Ghent, Belgium; 1:1,000), anti-3R-tau (clone 8E6/C11; Upstate, NY, USA; 1:500), anti-4R-tau (clone 1E1/A6; Upstate; 1:100), anti-TDP-43 (10782-1-AP; ProteinTec Group, Inc., Chicago, IL, USA; 1:5,000), anti-phosphorylated α-synuclein (#64; WAKO, Osaka, Japan; 1:5,000), anti-phosphorylated neurofilament (SMI31; Sternberger Immunochemicals, Baltimore, MD, USA; 1:10,000) and anti-non-phosphorylated neurofilament (SMI32; Sternberger Immunochemicals; 1:1,000). Diaminobenzidine was used as the chromogen. The sections were counterstained with hematoxylin.

In addition to the conventional electron microscopy, immunoelectron microscopy was performed by pre-embedding method. Vibratome sections of the dentate gyrus were blocked with normal goat serum and incubated with AT8 (1:1,000) for 2 days at 4°C, followed by incubation with a 1.4 nm gold-coupled Fab′ fragment of goat anti-mouse IgG (Nanoprobes, Yaphank, NY, USA). The sections were visualized by silver enhancing kit (BBInternational, Cardiff, UK). The immunolabeled sections were postfixed in 1% osmium tetroxide, stained with uranyl acetate, dehydrated in ethanol, embedded in epoxy resin, and then sectioned and viewed with a Hitachi H-300 electron microscope.

Results

At autopsy, the brain weighed 1,390 g before fixation and fresh subarachnoid hemorrhage was found in the right Sylvian fissure. Microscopically, almost complete loss of neurons with gliosis was found in the subiculum and CA1-3 regions of the posterior hippocampus, bilaterally (Fig. 1). Moderate gliosis was also evident in the CA4 region. No obvious neuronal loss was noted in the dentate gyrus, entorhinal cortex and amygdaloid nucleus as well as in the cerebral neocortex, basal ganglia and brainstem. Moreover, numerous intracytoplasmic inclusions were found in the dentate granule cells. They were slightly basophilic in sections stained with hematoxylin and eosin (Fig. 2a) and showed argyrophilia with Bodian's method (Fig. 2b). Staining with the Gallyas–Braak method and AT8-immunostaining revealed that the inclusions appeared round, crescent or circular in shape (Fig. 2c, d). Similar inclusions were scattered in the CA3-4 regions. Neurofibrillary tangles and pretangles were found in the medial temporal cortex and amygdaloid nucleus (Braak stage III). Only a few senile plaques were found in the cerebral cortex (Braak stage A). No argyrophilic grains were observed in the limbic system. Although thorn-shaped astrocytes were distributed in the periventricular area of the mediobasal temporal lobe [34], other glial tau pathology (tufted astrocytes, astrocytic plaques and coiled bodies) was absent.

Immunohistochemistry with monoclonal antibodies directed against 3R- or 4R-tau isoforms revealed that the inclusions in the dentate gyrus and CA3-4 regions of the posterior hippocampus were exclusively stained with 4R-tau antibody (Fig. 2e, f), whereas neurofibrillary tangles observed in the anterior hippocampus, entorhinal cortex and amygdaloid nucleus were stained with both 3R- and 4R-tau antibodies (Fig. 2g, h). The inclusions in the dentate granule cells were immunonegative for ubiquitin, neurofilament, α-synuclein and TDP-43. However, TDP-43-immunoreactive neuronal cytoplasmic inclusions were occasionally found in the entorhinal and transentorhinal cortex (Fig. 2i). A few neuronal intranuclear, but not intracytoplasmic, inclusions were found in the dentate gyrus (Fig. 2j).

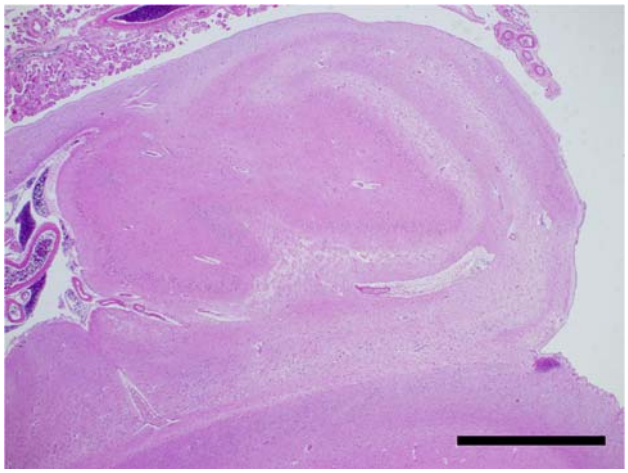

Fig. 1 The right hippocampus showing almost complete loss of pyramidal neurons in the subiculum and CA1-3 regions. *Bar* 2 mm

Ultrastructurally, the inclusions in the dentate gyrus were composed of randomly oriented straight filaments, 12–15 nm in diameter (Fig. 3).

Discussion

Hippocampal sclerosis usually shows selective neuronal loss and gliosis in the CA1 region and subiculum of the hippocampus [8, 11, 20]. However, an extension of the lesions to the CA2-4 regions, dentate gyrus, entorhinal cortex or entire parahippocampal gyrus and to the amygdala has been reported [1, 2, 11, 24, 31]. The present case showed almost complete loss of neurons with gliosis in the subiculum and CA1-3 regions of the hippocampus and no obvious neuronal loss in other brain areas. On the basis of the distribution of neuronal loss, we considered the present case to be an example of HS.

Tauopathies are classified as predominant 3R-tau pathology (Pick's disease type), mixed 3R/4R-tau pathology (AD type) and predominant 4R-tau pathology (PSP type). The most striking finding in the present case is the occurrence of Gallyas- and 4R-tau-positive, and 3R-tau- and ubiquitin-negative round inclusions in the dentate gyrus. They were similar to Pick bodies in sections stained with conventional methods such as hematoxylin and eosin and

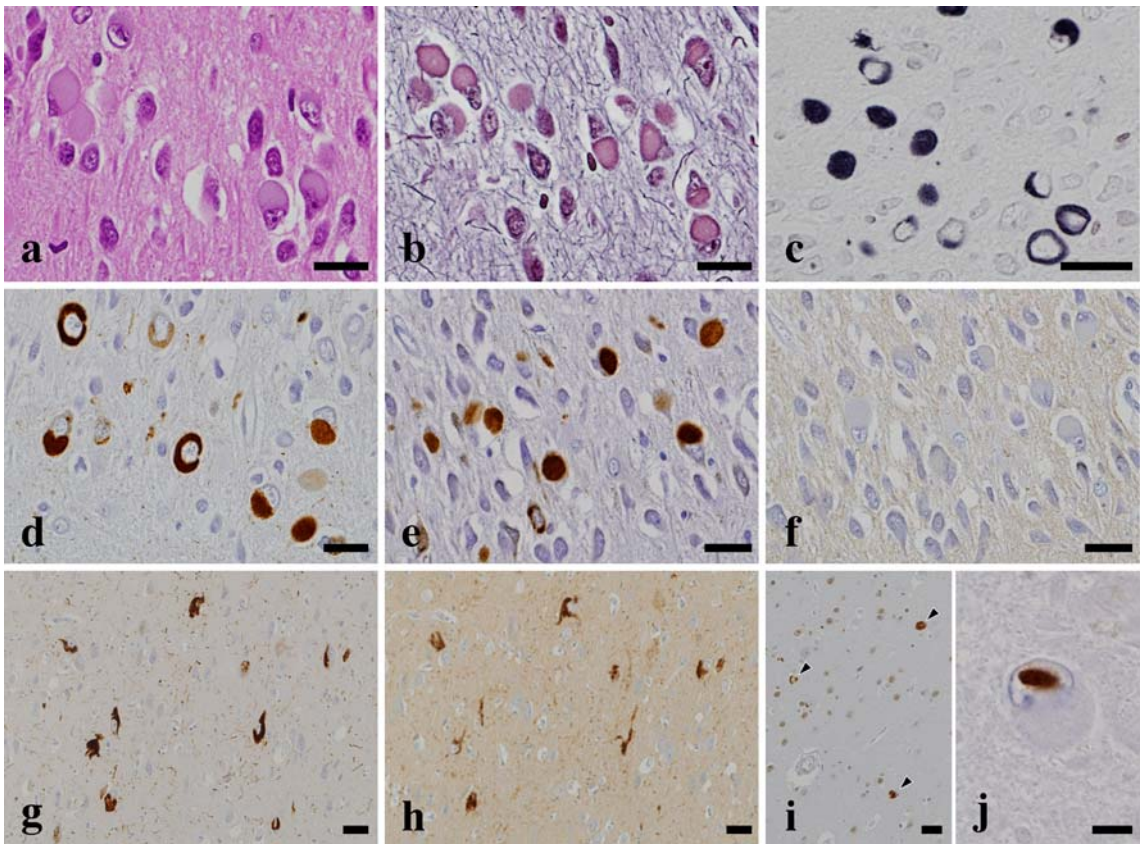

Fig. 2 **a–f** Neuronal intracytoplasmic inclusions in the dentate gyrus. They are stained with 4-repeat-tau antibody (**e**), but not with 3-repeat-tau antibody (**f**). **g**, **h** Neurofibrillary tangles in the anterior hippocampus. They are stained with both 4-repeat- (**g**) and 3-repeat-tau antibodies (**h**). **i** TDP-43-immunoreactive neuronal cytoplasmic inclusions in the entorhinal cortex (*arrowheads*). **j** TDP-43-immunoreactive lenticular inclusions in the dentate granule cell nuclei. Hematoxylin and eosin stain (**a**), Bodian's method (**b**), Gallyas–Braak method (**c**), AT8 (**d**), 4-repeat-tau (**e**, **g**), 3-repeat-tau (**f**, **h**), TDP-43 (**i**, **j**). *Bars* 20 μm for (**a–i**) and 5 μm for (**j**)

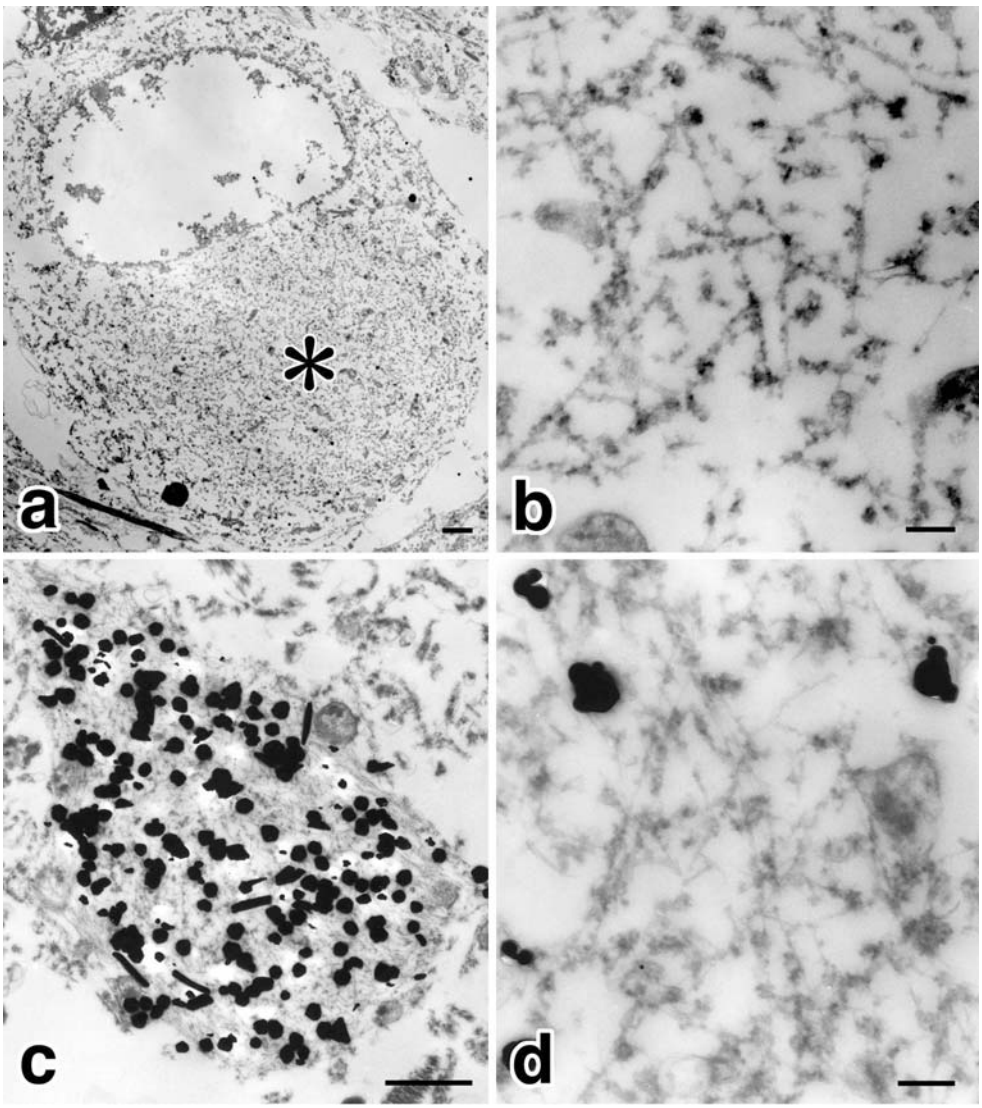

Fig. 3 **a** Electron micrograph of the inclusions in the dentate granule cells. **b** Higher magnification view of the area indicated by *asterisk* in **a** showing randomly arranged straight filaments coated with electron-dense granules. The filaments are about 12–15 nm in diameter. **c** Immunoelectron microscopy of the dentate gyrus inclusions labeled with AT8 showing silver enhanced gold particle on the constituent filaments. **d** Higher magnification view of another inclusion showing granule-coated straight filaments. *Bars* 1 μm for **a** and **c**, and 200 nm for **b** and **d**

Bodian's method. However, they were different from Pick bodies, because Pick bodies are immunohistochemically positive for 3R-tau [9, 40] and ubiquitin [25] and not stained with Gallyas–Braak method [36]. Although Pick body-like inclusions also occur in the dentate granule cells in patients with advanced stage of AD [10, 38], they are immunoreactive for both 3R- and 4R-tau [9] and are immunolabeled with anti-ubiquitin [18]. Pick body-like inclusions have also been described in 4R tauopathies such as PSP [38], CBD [17] and frontotemporal lobar atrophy with 4R-tau predominant tauopathy [40, 41] as well as in frontotemporal dementia with parkinsonisim linked to chromosome 17 [12, 23, 27, 32]. However, the distribution of Pick body-like inclusions and the extent of neuronal and glial tau pathology in these cases are much more severe and widespread than those in the present case. In AGD, tau pathology is restricted to the limbic system. However, no argyrophilic grains were noted in the present case. Ishizawa et al. [19] have demonstrated that all but 1 of 21 cases with selective neurofibrillary degeneration of the hippocampal CA2 region were 4R tauopathies, including PSP, CBD and AGD. However, HS was not noted in these atypical cases of 4R tauopathies. Therefore, the histological and antigenic features in the present case are different from those in HS and 4R tauopathies reported previously. It is likely that the present case is a new type of HS or a variant of 4R tauopathy.

Ultrastructurally, the inclusions in the dentate gyrus observed in the present case were composed of randomly

arranged straight filaments, 12–15 nm in diameter. Although neurofibrillary tangles in the cerebral cortex in mixed 3R/4R tauopathy (AD) are composed of twisted tubules [35], those in the dentate granule cells are mainly composed of straight tubules [10, 22, 38]. Moreover, tau-positive inclusions in the dentate gyrus in 3R tauopathy (Pick's disease) [26] and 4R tauopathy (PSP) [38] are also composed of straight tubules. These findings suggest that tau-positive inclusions in the dentate gyrus are predominantly composed of straight tubules irrespective of the tau isoforms.

TDP-43 is a major disease protein in ubiquitinated inclusions in amyotrophic lateral sclerosis and FTLD-TDP with or without motor neuron disease [4, 29]. In our case, TDP-43-positive inclusions were found in the dentate gyrus, hippocampus and entorhinal cortex. This finding is consistent with the results of recent studies that TDP-43 is deposited in more than 70% of cases with HS [3, 31]. However, TDP-43-immunoreactive neuronal inclusions were restricted to the hippocampal formation and the motor neuron system was not involved in our case. TDP-43 is also deposited in the brain of patients with Guam parkinsonism-dementia complex [14, 15] as well as in a significant proportion of cases with AD [3], Lewy body diseases [28], Pick's disease [13] and CBD [37]. These findings suggest that TDP-43 may deposit secondarily in tauopathy lesions, especially in the hippocampal formation.

Hippocampal sclerosis is one of the causes of dementia in the elderly [24]. Although dementia was not noted in our patient, she was diagnosed as having depression 3 years prior to death. Corey-Bloom et al. [8] reported that depression was noted in 5 of 8 patients pathologically diagnosed as HS. Beach et al. [6] reported that 2 of 11 patients with HS showed depression as clinical features at presentation. These findings suggest that depression may be an initial symptom in some patients with HS.

In conclusion, the present case is a HS with 4R tauopathy restricted to the posterior hippocampus. The histological features are different from those in HS and 4R tauopathies reported previously. The present case may be a new type of HS or a variant of 4R tauopathy.

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