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SHORT REPORT

Neuropathology of patients with preclinical or early clinical Alzheimer's disease with pathogenic *PSEN1_p. L392V*: Comparison of advanced siblings

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Abstract

INTRODUCTION: Neuropathological investigation of presymptomatic or early symptomatic presenilin-1 (*PSEN1*) mutation carriers in familial Alzheimer's disease (AD) is extremely scarce.

METHODS: We report the autopsy findings of brothers with familial AD. Case 1 is a 45-year-old man without obvious cognitive impairment, who committed suicide. Case 2 is a 57-year-old older brother of Case 1 with advanced AD symptoms, who died of hypothermia during wondering.

RESULTS: In both cases, abundant amyloid plaques positive for amyloid β (Aβ) were found throughout the brain. Progression of neuronal loss and increasing amount and extension of neurofibrillary tangle pathology were evident in Case 2. Genetic investigation revealed a *PSEN1*_p. L392V mutation in both cases.

DISCUSSION: The present study shows a possible neuropathological boundary between symptomatic and preclinical AD with pathogenic *PSEN1* mutation. Additional clinicopathological investigation for familial AD-related mutation carriers may be significant to explore the association between familial AD and suicide.

KEYWORDS
amyloid-β, autopsy, familial Alzheimer's disease, immunohistochemistry, neurofibrillary tangle, presenilin 1, suicide

1 | INTRODUCTION

The pathological hallmark, which includes amyloid-β (Aβ) protein-containing neuritic plaques and hyperphosphorylated tau-containing paired helical filaments in the neurofibrillary tangles (NFTs), is common in both familial and sporadic Alzheimer's disease (AD). Familial AD is characterized by the alteration of specific genes, including the presenilin 1 gene (PSEN1, 14q24.2), presenilin 2 gene (PSEN2, 1q42.13), and amyloid precursor protein (APP, 21q21.3).[1] *PSEN1* mutations are the most frequent, with > 300 mutations having been identified.[2]

The neuropathological investigation for presymptomatic or early symptomatic mutation career may be significant for exploring the etiology of dementia and other associated symptoms in familial AD, similar to other neurodegenerative diseases.[3] However, such investigations is extremely scarce.[4] Here, we showed the neuropathological appearance of the forensic autopsy cases of two brothers with the same

PSEN1 mutation. One patient had advanced AD symptoms, whereas the other patient died before clear symptoms suggesting AD appeared.

Research in context

1. **Systematic review**: Neuropathological investigation of presymptomatic or early symptomatic presenilin-1 (*PSEN1*) mutation carriers in familial Alzheimer's disease (AD) is extremely scarce. There was only one case report.
2. **Interpretation**: Case 1 is a 45-year-old man without obvious cognitive impairment, who committed suicide. Case 2 is a 57-year-old older brother of Case 1 with advanced AD symptoms, who died of hypothermia during wondering. In both cases, abundant amyloid plaques positive for amyloid β (Aβ) were found throughout the brain. Progression of neuronal loss, and increasing amount and extension of neurofibrillary tangle pathology were evident in Case 2. Genetic investigation revealed a *PSEN1*_p.L392V mutation in both cases.
3. **Future directions**: Neuropathological investigation targeting the AD pathology and genetic investigation may be significant in young and middle-aged forensic autopsy cases to explore the association between preclinical/early clinical familial AD and suicide.

2 | METHODS

2.1 | Patients

Case 1 died from drowning at 45 years old. Police investigation showed that the manner of death was suicide due to poverty. No individuals concerned noticed his inebriated state, which included speech disturbance, movement disorders, and cognitive dysfunction, although they knew that he was worried with his economic situation. At his death, no obvious family history was noted.

Case 2 was a 57-year-old man who was an older brother of Case 1. He was found dead in a multi-use building on a winter day. The cause of death was judged as hypothermia by medicolegal autopsy. He was diagnosed with juvenile AD 5 years before death and a few years after death of Case 1 because of significant cognitive impairment. The Score of the Hasegawa Dementia Scale—Revised of this patient was 19/30. His Mini-Mental State Examination score 3 years prior to his death death was 20/30. During the disease course, his neuropsychiatric symptoms, memory deficit, space disorientation, and abnormal behavior progressed.

Although a detailed medical history was not available, interviews with the family indicated that the mother of the two cases developed dementia in her 40s and died in her late 70s.

2.2 | Pathological and genetic investigation

The methods of neuropathological and genetic investigations are shown in the Supplemental methods and Table S1. Written consent was obtained from the next kin for genetic investigation. All procedures in studies involving human participants were performed in accordance with the ethical standards of the University of Toyama (R2020192) and/or national research committee and with the guidelines stipulated in the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

3 | RESULTS

3.1 | Pathological findings

The summary of the pathological findings of these two cases are shown in Table 1. The *post mortem* intervals for Cases 1 and 2 were 2 days and 0.5 days, respectively. Brain fixation periods were 2 weeks in both cases.

In Case 1, the brain weight was 1520 g. Mild atrophy of the hippocampus was found but neuronal loss was not evident in the whole brain (Figure 1A). In Case 2, the brain weight was 1494 g. Moderate atrophy of the medial temporal lobe, dilatation of the lateral ventricle, severe atrophy of the hippocampus, and mild depigmentation of substantia nigra were found on macroscopic examination (Figure 1B, C).

Microscopically, in Case 1, the abundant amyloid plaque, including the neuritic plaque, was noted in the whole brain. Moderate amounts of NFTs was found in the Pre-α and Pre-β layers in the entorhinal cortex, and a small amount of NFTs was found in the CA1 sector These findings were consistent with CERAD score C, Thal phase 5, and Braak NFT stage 2, and the level of AD neuropathologic change was "Low." Lewy body disease and TDP-43 pathologies were not found in the brain of this patient (Figure 2A-F).

In Case 2, severe neuronal loss with gliosis was found in the limbic system, especially in the entorhinal cortex and hippocampus. The amount of amyloid and neuritic plaques were slightly higher in this case than in Case 1, although the distribution of both gray and white matter was almost identical with that of Case 1. Amyloid angiopathy was occasionally found, and cotton wool plaque was not evident. Moderate amounts of NFTs were found in the brain stem and neocortex other than the temporal lobe, in addition to a large amount of NFTs including ghost tangles in the limbic and prelimbic systems, orbitofrontal cortex, and temporal lobe Figure 2G-L). These findings were consistent with CERAD score C, Thal phase 5, and Braak NFT stage 5, and the level of AD neuropathologic change was high. Astrocytosis in the limbic system and cerebral cortex was evident in Case 2 in comparison with Case 1 and the control case (60-year-old male without AD pathology). An increased number of Iba1-positive microglia was also found in the whole cerebrum of Case 2 (Figure S1). Lewy and TDP-43 pathologies were not found in the brain.

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TABLE 1 Distribution and the amount of Alzheimer's disease related pathology.

	Neuronal loss		Amyloid-β				Tau			
			Neuritic plaque		Amyloid angiopathy		Neurofibrillary tangle		Neuronal thread	
	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2
Superior frontal gyrus	–	–	++	+	++	+	–	++	–	++
Primary motor cortex	–	–	+	+	++	+	–	++	–	++
Middle temporal gyrus	–	+	++	++	++	+	–	+++	–	++
Striate cortex	–	–	+	+	+	+	–	+	–	++
Calcarine cortex	–	–	++	++	++	+	–	+	–	+
Caudata nucleus	–	–	–	–	+	–	–	+	–	+
Putamen	–	+	+	+	+	–	–	+	–	+
Globus pallidus	–	–	–	–	+	–	–	+	–	+
Amygdaloid body	–	++	++	++	+	+	+	+	++	+++
Entorhinal cortex	–	++	+	+	+	+	+	+	++	++
Hipoocampus	–	++	++	++	+	+	+	+	+	+++
Cerebellar cortex	–	–	+	+	–	–	–	–	–	+
Cerebellar dentate nucleus	–	–	+	+	+	–	–	–	–	–
Substantia nigra	–	–	–	–	–	–	+	++	–	+
Inferior olivary nucleus	–	–	+	+	–	–	–	+	–	+

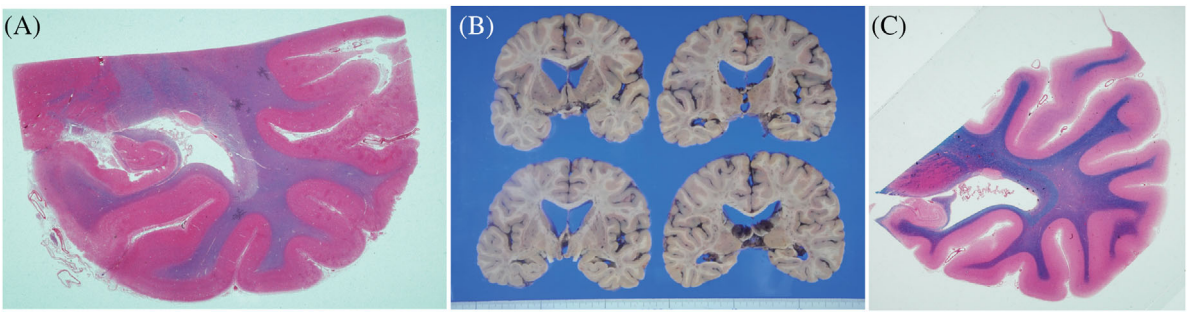

FIGURE 1 (A) Low-magnification view of a pathological specimen of the temporal lobe, including the hippocampus, in Case 1. (B) Gross appearance of the cerebrum in Case 2. (C) Low-magnification view of a pathological specimen of the temporal lobe, including the hippocampus, in Case 2.

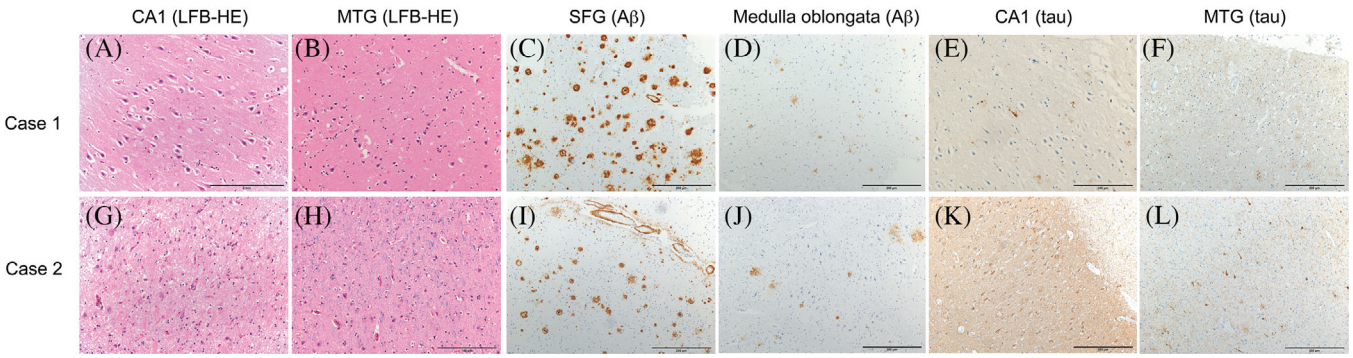

FIGURE 2 Neuropathological appearance of Case 1 (A–F) and Case 2 (G–L). Neuronal loss of nervous tissue was not evident in the CA1 region (A) of the hippocampus or middle temporal gyrus (MTG) (B) in Case 1, but was severe in Case 2 (G, H). The amount of amyloid β (Aβ)-positive plaques in the superior frontal gyrus (SFG) and medulla oblongata was almost identical between Cases 1 (C, D) and 2 (H–J). In contrast, the amount of tau-positive neurofibrillary tangles in the CA1 region and MTG was less in Case 1 (E, F) than Case 2 (K, L). Scale bar = 200 μm (C–F, I–L), 100 μm (A, B, G, H).

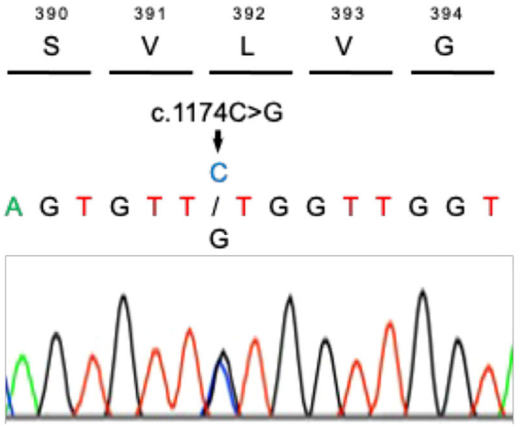

FIGURE 3 Electropherogram of PSEN1 (NM_002739.5) c.1174C > G, p.L392V.

3.2 | Genetic findings

Genetic investigation revealed PSEN1_p. L392V in both Cases 1 and 2. This variant has already been reported to cause AD (Figure 3).[5] The apolipoprotein E (APOE) genotype was ε3/ε3 in both cases.

4 | DISCUSSION

The neuropathological findings of patients with *PSEN1*_L329V mutations include cortical atrophy in the frontal and temporal cortex with abundant senile plaques and NFTs throughout the neocortex and hippocampus, without comorbid pathology.[4] These findings are consistent with those observed in Case 2. In contrast because of the less objective neuropsychiatric investigation before death, we cannot conclude that Case 1 was a definitive "preclinical case." Nonetheless, Case 1 was a very rare autopsy case of preclinical or very early clinical AD with a *PSEN1* mutation that did not affect his ability to perform his activities of daily living.

The boundaries between symptomatic and preclinical AD, which is defined as the span from the first neuropathological brain lesions to the onset of the first clinical symptoms of AD, are challenging. The preclinical phase should be integral to the symptomatic AD process, and without it, both Aβ and tau pathologies that characterize the AD cannot progress to or beyond the threshold, eventually leading to the symptomatic phase.[6,7] The pathophysiology of Aβ accumulation may differ in sporadic and familial AD cases, with familial AD cases showing overproduction of Aβ42 and sporadic AD cases demonstrating reduced clearance of Aβ42; however, the final outcomes including neuropathologic and clinical presentation of sporadic and familial AD seem to be similar.[7] Therefore, the investigation of two familial AD cases who died at different disease stages may be useful for understanding the boundaries between preclinical and symptomatic AD caused by a *PSEN1* mutation.

The most striking difference between Cases 1 and 2 was the incidence of neuronal loss and the amount and extension of the tau pathology, especially those in the neocortex. These results may be consistent with those of a previous report, which showed that the severity of cognitive impairment correlates best with the burden of neocortical NFTs rather than that of the Aβ plaques, and that the involvement of the temporal lobe, which is consistent with Braak stage IV, may be key to the development of overt dementia rather than the Aβ pathology, in AD.[8] Contrarily, autopsy reports of preclinical *PSEN1* mutation carrier are very scarce, and only one case reported by Gliebus et al. was found in our literature review. The pathological findings of the case were sparce neuritic Aβ plaques but with abundant diffuse form plaque, and the Braak tau stage was II.[3] Cases 1 and 2 showed that the significance of neuronal loss and/or extension to the cerebral neocortex of NFTs may be essential for the occurrence of overt dementia in PSEN1 carriers. Contrarily, in addition to both genetic and phenotypic heterogeneities in PSEN-associated AD, pathological diversity has also been reported, including frontotemporal neuronal loss, cotton wool plaque with mutations in exons 8 and 9, and a range of biochemical changes in white matter.[9,10]

Although the suicide rate in Japan is currently on a slight downward trend because of preventive measures taken by the government, it remains among the highest in the world. According to the latest statistics from the World Health Organization, Japan is ranked 48th of 183 countries in terms of suicide rates.[11] This high suicide rate is influenced by many cultural factors, including the tradition of honorable suicide and the relatively permissive attitudes toward suicide that remain in modern times.[12] Ng et al. reported that suicidal ideation is common among cognitively intact at-risk patients with autosomal dominant AD. While such individuals have greater depressive symptoms, an awareness of their mutation status, which may be a strong risk factor for suicidal ideation, was not associated with suicidal ideation in this study.[13] Ringman et al. showed that behavior changes, including apathy, disinhibition, irritability, sleep changes, depression, and agitation, are more common in mildly affected familial AD mutation carrier than in non-carriers.[14] However, neuropathological investigations targeting the AD pathology among patients who died of suicide are scarce and had a common limitation, which is the lack of standard neuropathological investigations and evaluations of the AD pathology.[15] In forensic autopsies, immunostaining appears to be rarely performed on suicide autopsy cases without a history of dementia or movement disorders. It is therefore possible that patients with early familial dementia are overlooked even when forensic autopsies are performed. Furthermore, family history is often not adequately communicated before and after autopsy. The findings from the present study and our previous studies indicate the need for immunostaining-based neuropathological examinations in autopsy cases of suicide in which neuropsychiatric disease history is unclear.[15–17]

Yasuno et al. showed that emotional dysregulation because of the Aβ pathology in the precuneus/posterior cingulate cortex may be related to depression symptoms,[18] and they additionally showed tau aggregation in the transentorhinal region by using positron emission tomography (PET), which was correlated with more severe neuropsychiatric symptoms, especially affective symptoms.[19] We previously reported that argyrophilic grain disease (AGD), whose pathological

features include the presence of punctate or filiform structures in the neuropil of limbic regions and the temporal lobe, may be a significant risk factor for suicide attempts in older adults with a clinical history of acute post-stroke depression[16] or incipient progressive supranuclear palsy lesions.[17] Furthermore, we recently showed that AGD may contribute to the progression of functional impairment of the limbic system, leading to psychiatric disorders and suicide attempts.[15] In the study, the progression of AD-related tau pathology decreased the risk of suicide. We speculate that the ability to attempt and/or complete suicide is diminished as cognitive impairment progresses owing to the deterioration of the AD pathology.[15] Adversely, mild or moderate AD pathology might be associated with suicide attempts in younger patients. Together, the aforementioned findings suggest that the risk of suicide might be increased over a specific period during the progression of limbic Aβ and/or NFT lesions associated with familial AD, but before the onset of clear dementia. The advancement of PET imaging enables us to obtain a more detailed quantification of in vivo AD-related pathology. According to previous studies, tau PET binding was elevated in symptomatic mutation carrier, and a higher level of tau deposition was associated with worse performance on a cognitive function test.[20,21] Additional pathological investigation of mutation carrier similar to Case 1 may provide fundamental information for future bioimaging investigations targeting the association between Aβ and psychiatric disorder including suicide attempts, and might clarify relevant pathological changes in the brain.

Recent studies showed that the homozygous *APOE3* status may delay the age of onset of cognitive symptoms in *PSEN1* mutation carriers.[22,23] The association between the *APOE* genotype in PSEN1-mutated AD patients and suicidal behavior may also be of relevance to future cases so should be carefully investigated.

In conclusion, our data showed the possible boundaries of neuropathological appearance between symptomatic and preclinical AD cases with pathogenic *PSEN1* mutation. Moreover, neuropathological investigation targeting the AD pathology and genetic investigation as necessary may be significant in young and middle-aged forensic autopsy cases to determine the more detailed clinicopathological features of familial AD-related mutation carrier and to explore the association between preclinical/early clinical familial AD and suicide.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Written consent was obtained from the next of kin for the genetic investigation and for the publication of anonymized data obtained through the clinical characterization and the scientific research carried out.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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