弘前医療福祉大学紀要　2(1), 1 － 14, 2011

〔Original〕

The occurrence range of proper lesions (neurofibrillary tangles and senile plaques) to Alzheimer's disease: patho-anatomical study of a familial Alzheimer patient with the onset at age 38 and a 25-year clinical course

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Abstract

AD is a rapidly increasing dementia whose measure for medical and social welfare has been a serious social problem in Japan. The brain lesions of AD are characterized by 3 main histological changes: NFT, SP, and loss of neurons. With the reexamination of an AD case with a 25 year-clinical course as an opportunity, the author revealed the maximal range of occurrence of NFT and SP in AD. The results showed that neurons were classi›ed into 3 types: neuron types with NFT-rich, NFT-rare, and NFT-free. As to the pathogenesis of AD brain lesions, it is known that Aβ deposition occurs first and the oligomers with the highest toxicity develop into proto›brils and ›brils and ›nally form neuritic plaques which contain degenerated neurites. In addition, Aβ oligomers generated in and around synapses and inside neurons are considered to induce cell death due to the toxicity to neurons and glial cells. On the other hand, it is believed that by GSK3β which is activated by the overproduction of Aβ inside neurons, hyperphosphorylation of tau proceeds and soluble oligomers of tau polymerize to be insoluble granular aggregates, and then become larger insoluble NFT. It is still unclear where tau oligomers or granules associate with Aβ oligomers or proto›brils to develop NFT and Aβ ›brils, respectively, and what mechanisms play roles to develop NFT in "NFT only tauopathies". Detailed analyses that reveal all of differences between NFT-rich and NFT-free neurons may open a road to pathogenetic mechanisms of NFT formation.

Key words: Alzheimer's disease (AD), neuro›brillary tangles (NFT), senile plaques (SP), tau, Aβ

Introduction

Today, the population of people aged 65 and over in Japan is 25,560,000. It is predicted that it will be over 32,270,000 in 2015 and 34,730,000 in 2025, respectively (The Ministry of Internal Affairs and Communications of Japan, 2005). Approximately 8% of these are estimated to be of the aged with dementia. Forty per cent of the aged with dementia will be patients with Alzheimer's disease (AD) and 30% with cerebrovascular dementia. The remaining 30% will consist of patients with other types of dementia which include dementia with Lewy bodies (DLB), frontotemporal dementia (FTD) and so on. The aged with dementia who have shortages of pension and welfare funds have been increasing and are becoming a serious social problem in Japan. The number of patients with cerebrovascular dementia has been decreasing by taking measures to lifestyle-related diseases, whereas patients with AD have rapidly been increasing because there is no radical treatment for the disease so far.

To find radical treatments it is necessary to know mechanisms of the disease in detail. Patients with AD clinically present a steady decline in cognitive ability beginning with the loss of short-term memory and progressing through stages of increasing dementia. The severity of the symptoms varies dramatically among individuals and the time of progression through these stages may take from months to years (Shoji et al., 2005). These symptoms are related with histopathology of AD, whose hallmarks are intracellular neurofibrillary tangles (NFT) composed of paired helical filaments

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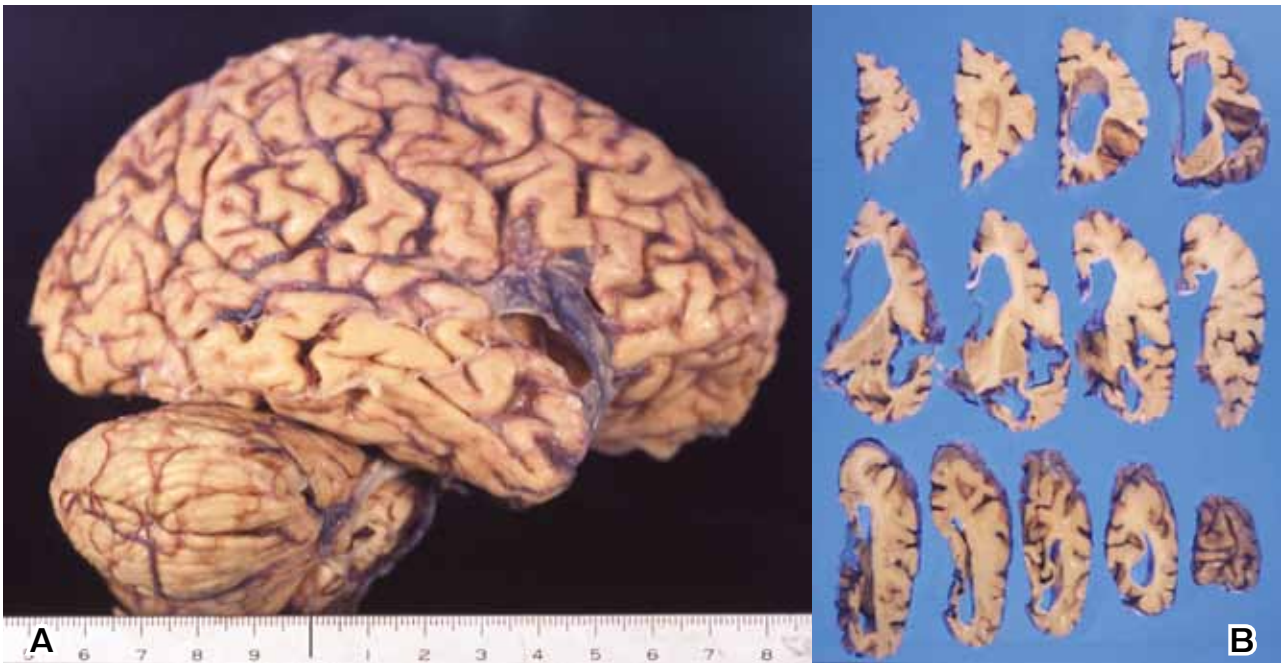

Fig.1 A. Right lateral view of the brain showing striking atrophy of individual gyri, accentuated in the frontal, temporal and parietal lobes.
B. Serial coronal sections of the right hemisphere of the brain showing marked atrophy of all gyri, basal ganglia, centrum semiovale, and hippocampus, and revealing marked dilatation of the lateral ventricle and Sylvian fissure.

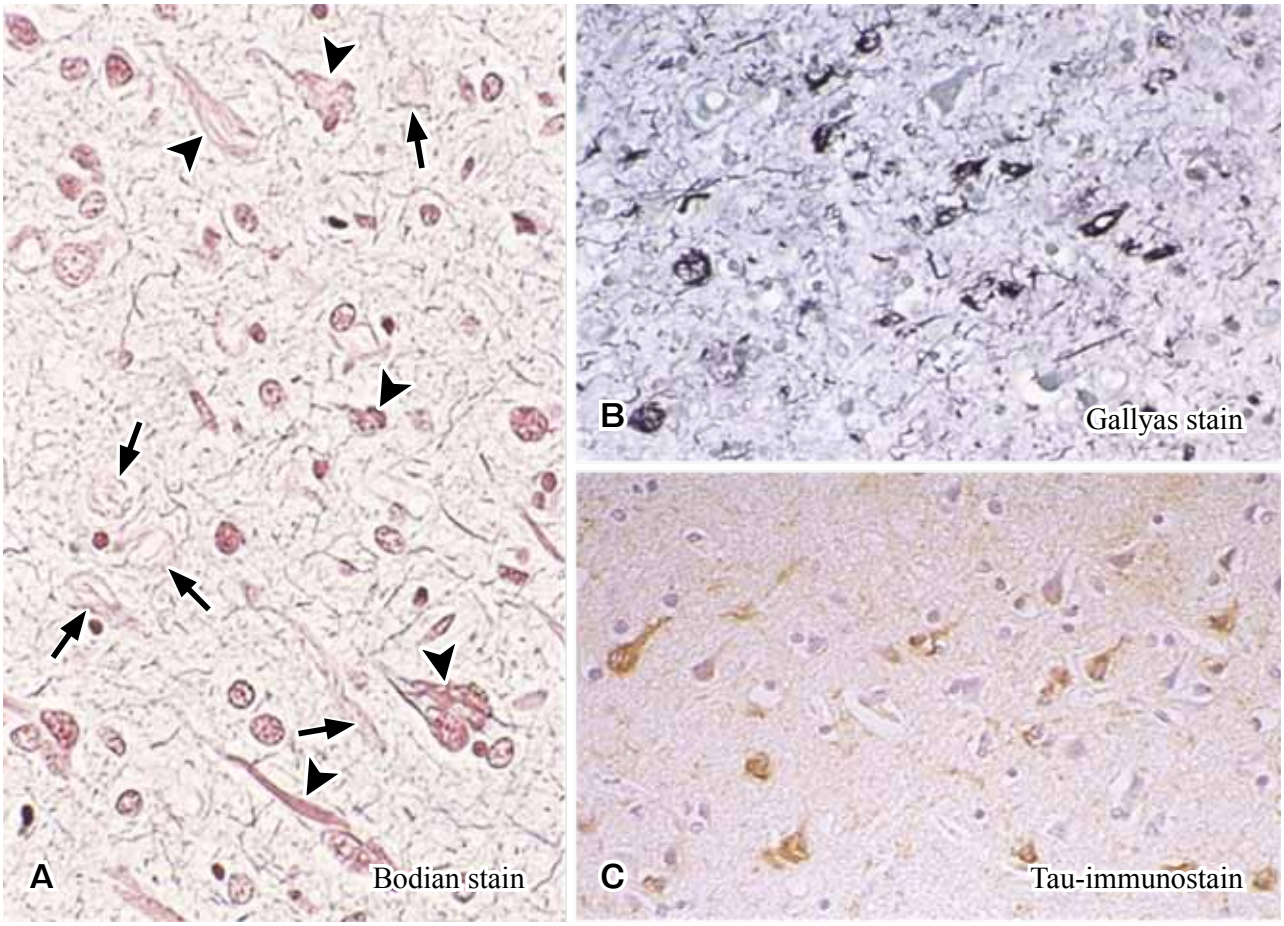

Fig.2 A. Parahippocampal cortex showing several neurofibrillary tangles (arrowheads), some of which are so-called ghost tangles (arrows). Bodian stain x 520
B. Frontal cortex showing surviving neurons bare tangles and neuropil threads. Gallyas stain x 260
C. Parietal cortex showing that many of surviving neurons have NFT. Tau-immunostain x 260

(PHF) of microtubule-associated protein, tau, and extracellular amyloid plaques (senile plaques; SP), composed principally of the amyloid β peptide (Aβ). For years, the amyloid cascade hypothesis proposed a central role for Aβ amyloid in the pathogenesis of AD (Hardy& Higgins, 1992; Hardy & Selkoe, 2002). However, the link between Aβ generation and NFT formation is not known yet (Lowe et al., 2008).

Recently, we reexamined an autopsied Alzheimer patient with the onset at age 38 and a 25-year clinical course. Since the clinical course is very long, it is important to know which nuclei (neurons) are affected by the lesions peculiar to AD and which are not, when we consider the pathogenesis of NFT and/or SP. The purpose of the present study is to clarify the occurrence range of NFT (and SP), in order to obtain some clue to the pathogenesis of NFT.

Subjects and Methods

The patient was a 65-year-old house-wife when she died. At the age of 38, she initially developed progressive dementia. From the age of 46, myoclonic jerks which occasionally developed into general convulsions, polyphagia, dysphagia and aspiration pneumonia appeared subsequently. The patient became bed-ridden with contractured extremities. The gene analysis performed with her family's consent revealed a point mutation in the presenilin-1 gene (Tanahashi et al.,1995; Tabira, 1997). She died of aspiration pneumonia at the age of 65. Out of 7 siblings, 4 showed the same disease (Watanabe et al., 1982).

The brain and spinal cord were fixed in a 10% buffered neutral formalin fixative for 7 days. The brain, weighing 630g, showed severe atrophy with narrowing of gyri and widening of sulci in almost all lobes (Fig.1A).

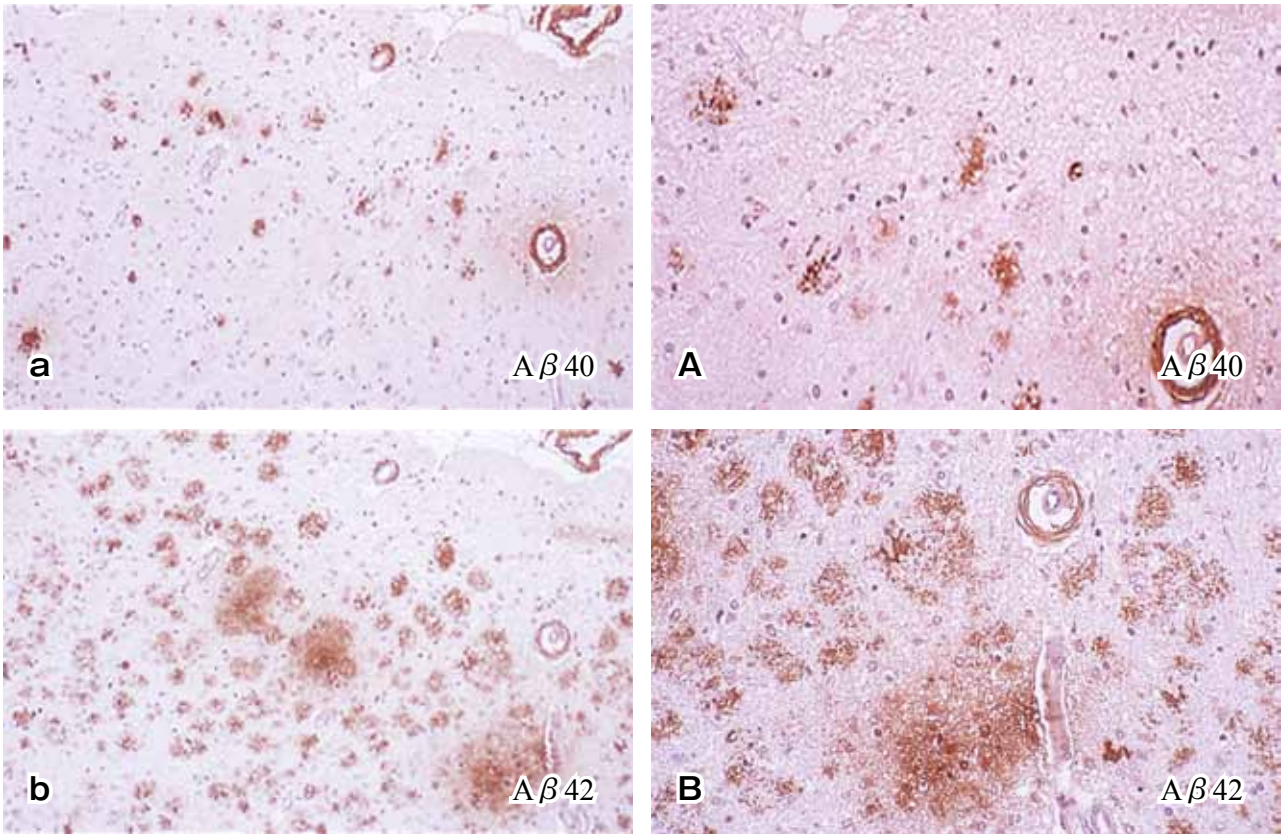

Fig.3 a. Middle frontal gyral cortex showing many plaques of amyloid deposition demonstrated by an antibody against Aβ_{40}. Aβ_{40}- immunostain x 130
A. Higher magnification of Fig.3a. Aβ_{40}- immunostain x 260
b. The same area as Fig.3a. exhibiting innumerable plaques of amyloid deposition demonstrated by an antibody against Aβ_{42}. Aβ_{42}- immunostain x 130
B. Higher magnification of Fig.3b. Aβ_{42}- immunostain x 260

Serial coronal sections revealed a great reduction in the volume of the centrum semiovale and marked dilatation of the lateral ventricles (Fig.1B). The brainstem and cerebellum also showed considerable atrophy. Routine histological examinations disclosed that there were a great number of NFT and SP in all cerebral cortices and subcortical gray matter in addition to a great reduction of their neurons (Fig.2A-C, Fig.3a, A, b, B). Further findings were reported elsewhere (Yoshimura, 2005). After performing routine neuropathological examinations, immunostained slides for phosphorylated tau (*p*tau) and Aβ, in addition to Bodian slides which were made extensively, were prepared and all were observed.

Results

The results of histological examinations focused on the occurrence of NFT and SP in the brain, spinal cord, peripheral nerves and ganglia, and the adrenal medulla are summarized in Tables 1-5.

All telencephalic neocortices had NFT of more than 100 per gyrus and SP of more than 10 per gyrus, except for the calcarine cortex which had NFT of at least 126 and SP of more than 10 per gyrus, respectively. The distribution of these NFT and SP in the neocortex of the brain is shown in Table 1.

Almost all limbic and paralimbic cortices and nuclei had NFT of more than 100 and SP of more than 10. Although there were no SP, various numbers of NFT were observed in the following structures: claustrum 91/78, caudate 8/11/8, putamen 7/8/13, globus pallidus 6/7/5, hypothalamus 6/38, tuber cinereum 7, nucleus basalis of Meynert 4, diagonal band of Broca 40, thalamus 98/49, pulvinar 11, and mammillary body 13. (The numbers divided by a slash indicate values obtained from 2-3 different parts.) The distribution of NFT and SP in the limbic-paralimbic system, basal ganglia and diencephalon is summarized in Table 2.

In the cerebral cortex, especially in the bottoms of sulci of frontal and temporal cortices, there were innumerable numbers of SP most of which were demonstrated to be diffuse plaques by Aβ_{42} immunostaining, whereas SP

Table l. Distribution of neurofibrillary tangles and senile plaques; Neocortex

Neuron/Structure	NFT	SP
Telencephalon		
F_1	>100	>50
F_2	>100	>50
F_3	>100	>50
T_1	>100	>50
T_2	>100	>50
T_3	>100	>50
Premotor cortex	>100	>50
Motor cortex	>100	>50
Sensory cortex	>100	>50
Superior parietal lobule cortex	>100	>50
Angular gyrus cortex	>100	>50
Supramarginal gyrus cortex	>100	>50
Occipital cortex	>100	>50
Calcarine cortex	126	>50

The data were obtained by observing Bodian slides. NFT, neurofibrillary tangles; SP, senile plaques;
F1, F2, F3; superior, middle, inferior frontal gyrus cortex, respectively
T1, T2, T3; superior, middle, inferior temporal gyrus cortex, respectively

Table 2. Distribution of neurofibrillary tangles and senile plaques; Limbic-Paralimbic System, Basal Ganglia and Diencephalon

Neuron/Structure	NFT	SP
Cingulate cortex, mid./post.	268/316	>50
Orbital gyrus cortex	>100	>50
Rectal gyrus cortex	>100	>50
Olfactory bulb	42	0
Nucl. accumbens septi	262	8
Uncus	>100	>50
Amygdaloid nucleus	>100	>50
Hippocampus	>100	>50
Parahippocampus	>100	>50
Occipitotemporal gyrus cortex, lat.	>100	>50
med.	>100	>50
Insular cortex	>100	>50
Claustrum, ant./post.	91/78	0
Caudate, ant./mid./post.	8/11/8	0/1/0
Putamen, ant./mid./post.	7/8/13	0/2/1
Glob.pallidus, ant./mid./post.	6/7/5	0/0/0
Diencephalon		
Preoptic area	n. e.	n. e.
Hypothalamus, medial/lateral	6/38	0/0
Tuber cinereum	7	0
Nucleus basalis of Meynert	4	0
Diagonal band of Broca	40	0
Thalamus, ant.nucl./other nucl.	98/49	0/0
Pulvinar	11	0
Subthalamic nucleus	n. e.	n. e.
Mammillary body	13	0

The data were obtained by observing Bodian slides. NFT, neurofibrillary tangles; SP, senile plaques ant./mid./post., anterior/middle/posterior; nucl., nucleus; lat., lateral; med., medial; n.e, not examined

demonstrated by Aβ_{40} immunostaining were mostly cored and much less in number at the same part of the cortex (Figs.3 a, A, b, and B).

In the brainstem, NFT were present in the substantia nigra 6, superior colliculus 3, inferior colliculus 7, central gray of midbrain and pons 5/4, locus coeruleus 3, dorsal tegmental nucleus 1, superior central nucleus11/12, reticulotegmental nucleus 5/6, pontine nuclei 9/43/22, nucleus of IV nerve 2, nucleus of VIII nerve 1, nucleus dorsalis nervi vagi l, nucleus of XII nerve 1, and inferior olivary nucleus 2 (Table 3).

In the cerebellum, no NFT were detectable in any Purkinje cells, although a few Golgi cells and one nucleus fastigius cell that bore NFT were observed

Table 3. Distribution of neurofibrillary tangles and senile plaques; Brainstem

Neuron/Structure	NFT	SP
Brainstem		
Red nucleus	0	0
Substantia nigra	6	0
Superior colliculus	3	0
Inferior colliculus	7	0
Central gray, midbrain/pons/pons	14/11/10	0/0/0
Reticular formation, midbrain/pons	5/4	0/0
Nucl. tractus mesencephalicus n. V	0	0
Oculomotor nucleus	1	0
Trochlear nucleus	0	0
Locus coeruleus	6	0
Dorsal raphe nucleus	3	0
Dorsal tegmental nucleus	1	0
Superior central nucleus	11/12	0
Reticulotegmental nucleus	5/6	0
Pontine nuclei, upper/middle/lower	9/43/22	0
Nucleus sensorius principalis n. V	0	0
Nucleus spinalis n. V	0	0
Nucleus of VI nerve	0	0
Nucleus of VII nerve	2	0
Nucleus of VIII nerve	1	0
Nucleus solitarius	0	0
Nucleus dorsalis n.vagi	1	0
Nucleus ambiguus	0	0
Nucleus of XII nerve	1	0
Olivary nucleus, superior/inferior	0/2	0
Gracile nucleus	0	0
Cuneate nucleus	0	0

The data were obtained by observing Bodian slides. NFT, neurofibrillary tangles; SP, senile plaques. The numbers divided by a slash indicate values obtained from 2-3 different parts.

(Table 4). In the spinal cord, a few anterior horn cells bearing NFT were observed, but none were detectable in any ganglion cells of either posterior root ganglia or the Gasserian ganglion examined (Table 4). Although NFT formation in adrenal medullary cells has been expected to occur, there is no report on the issue so far, except for a report on occurrence of NFT in pheochromocytoma cells of the adrenal medulla (Izumiyama et al., 1990). In the present case, 3 medullary cells that bore NFT were found by Bodian staining as well as by phosphorylated tau immunnohistochemistry. Two of them which were demonstrated in Bodian slides

Table 4. Distribution of neurofibrillary tangles and senile plaques in the nervous system; Cerebellum, Spinal Cord, and Peripheral Nerve

Neuron/Structure		NFT	SP
Cerebellum			
Cortex,	Molec. layer	0/0/0	11/15/10
	Purkinje cell	0/0/0	—
	layer	—	7/5/6
	Golgi cell	1/2/0	—
	Granule cell	0/0/0	—
	layer	—	6/3/4
Nucleus dentatus/emboliformis/		0/0/	0/0/
	globosus/fastigius	0/1	0/0
Spinal cord			
Anterior horn, C/Th/L/S		3/0/1/0	0/0/0/0
Posterior horn, C/Th/L/S		0/0/0/0	0/0/0/0
Intermediolateral horn		0	0
Clarke's column		0	0
Onuf's nucleus		0	0
Peripheral neurons			
Gasserian ganglion		0	0
Posterior root ganglion		0	0
Sympathetic trunk		0	0
Ganglion solare		0	0
Auerbach's plexus, E/S/SI/LI		0/0/0/0	0/0/0/0
Meissner's plexus, E/S/SI/LI		0/0/0/0	0/0/0/0
Pelvic nerve plexus		0	0
Adrenal medulla		3	0

The data were obtained by observing Bodian slides. NFT, neurofibrillary tangles; SP, senile plaques C/Th/L/S, cervical/thoracic/lumbar/sacral; E/S/SI/LI, esophagus/stomach/small intestine/large intestine
The numbers divided by a slash indicate values obtained from 2-3 different parts.

had melanin granules (Fig.4 A, B).

In the olfactory bulb (Table 5), NFT occurred in the mitral cells, tufted cells and granule cells. Main transmitters of these cells are mitral cells (Glu/Asp, NAAG), tufted cells (Glu/Asp, DA, S-P), granule cells (GABA, Enk), and anterior olfactory nucleus cells (Asp, Enk, SOM, calbindin, and parvalbumin).

Discussion

The amyloid cascade hypothesis proposes a central role for Aβ amyloid in the pathogenesis of AD. Namely, accumulation of Aβ in the brain is the primary influence driving AD pathogenesis. The rest of the disease process, including formation of NFT containing tau protein, is proposed to result from an imbalance

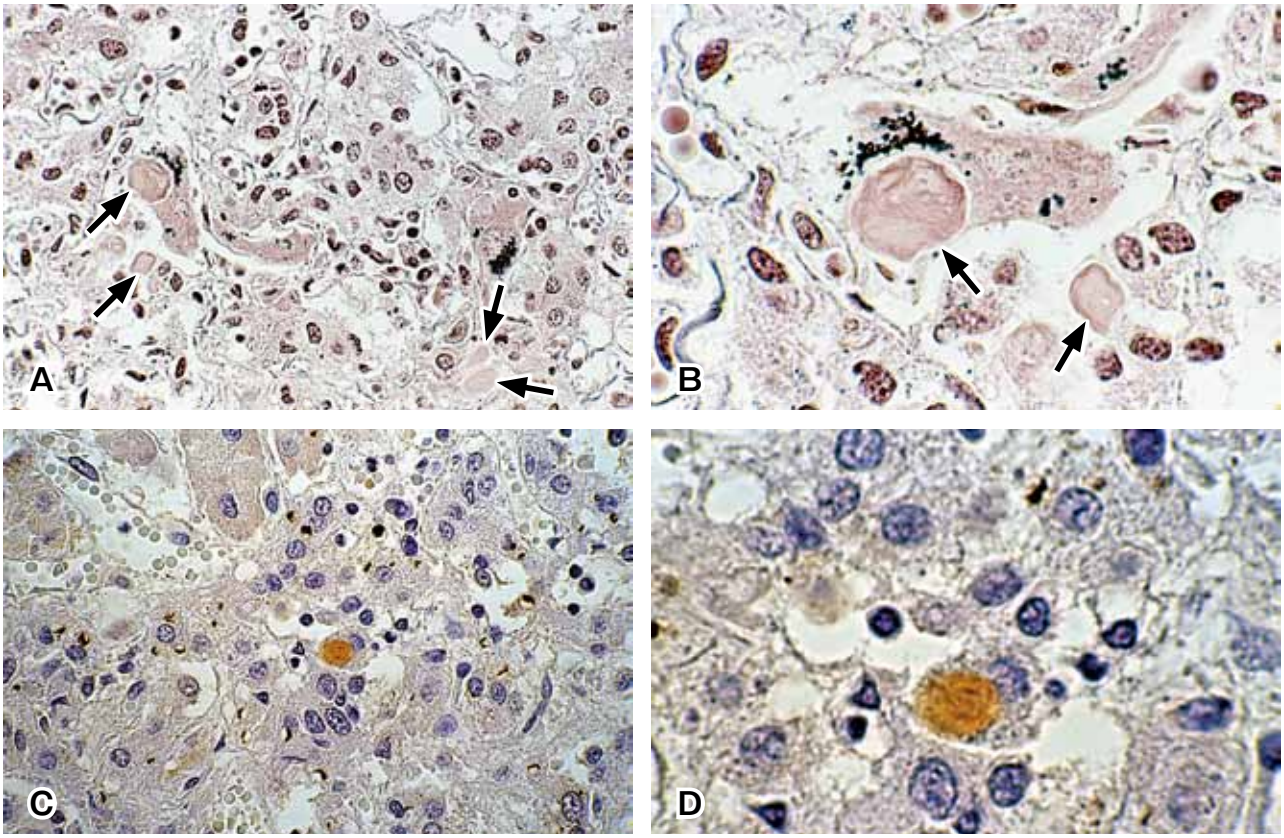

Fig. 4
A. NFT bearing medullary cells (arrows). Adrenal medulla Bodian stain x 260
B. Higher magnification of Fig.4A. Bodian stain x 520
C. NFT bearing medullary cells revealed by *p*tau immunostain Adrenal medulla *p*tau immunostain x 260
D. Higher magnification of Fig.4C. *p*tau immunostain x 520

Table 5. Distribution pattern of NFT-bearing cell bodies in the nervous system ; Olfactory bulb

	Lamination of the bulb	NFT-bearing cell	
		Count	Cell type
I.	outer fibrous layer	0	
II.	glomerular layer	0	
III.	outer granular layer	3	granule cell
IV.	outer plexiform layer	14	tufted cell
V.	mitral cell layer	4	mitral cell
VI.	inner plexiform layer	4	tufted cell
VII.	inner granular layer	1	granule cell
VIII.	white layer	0	
·	anterior olfactory nucleus	16	anterior olfactory nucleus cell

The data were obtained by observing Bodian slides. NFT, neurofibrillary tangles

between Aβ production and Aβ clearance (Hardy & Higgins, 1992; Hardy & Selkoe, 2002).

At a morphological level, Aβ- and tau-associated changes are linked so inextricably, e.g. in neuritic plaques, both proteins are intermingled, that it is difficult to assign primacy to one over the other. Namely, the link between Aβ generation and NFT formation is not known (Lowe et al, 2008). Several lines of evidence point to a primary role for Aβ amyloid in the pathogenesis of AD. First, diffuse plaques are detectable in the brain of patients with Down's syndrome, before the development of neuritic plaques and NFT (Mann & Esiri, 1988; Lowe et al., 2008). Second, although mutations in the gene for tau (*MAPT*) protein have not been found to be associated with familial AD, mutations in *MAPT* are associated with frontotemporal dementia and parkinsonism (FTDP-17), with extensive tau pathology in neurons and glia, but no amyloid deposits. Third, diverse neurological disorders which are different in origin are well known to develop NFT (tauopathies) with no amyloid deposits (Tolnay & Probst, 2003; Hirano & Tomiyasu, 2003; Lowe et al., 2008; Murayama, 2009).

It is also known that cognitively normal individuals can have a large number of neocortical plaques, although predominantly of diffuse type, and only sparse NFT. Furthermore, the correlation between plaque density and the severity of dementia is weak. However, the correlation between the severity of tau pathology (i.e. neuritic plaques and NFT) and the clinical severity of the disease is known to be best in studies that correlate severity of pathological features with the clinical severity of the disease (Lowe et al., 2008). There are several key questions that remain to be solved. First, what are the steps that lead from amyloid production to tau pathology? Why does AD pathology occur or progress in some brain regions and not others? Why are some neurons vulnerable to neurofibrillary tangle formations and others largely spared? These questions are essential for understanding AD pathogenesis and may also be critical for therapeutic strategies (Lowe et al., 2008).

To summarize the results obtained from the present study, the brain in AD (Braak stage VI) with a PS1mutation (H163R) showed numerous $A\beta_{42}$-positive SP together with a relative small number of $A\beta_{40}$-positive SP in the cerebral cortices (Figs. 3 a, A, b, B). This can be interpreted that $A\beta_{42}$-positive SP keep increasing in number until the patient dies, because $A\beta_{42}$ is known to be an initially deposited species of Aβ to form mature (cored) SP (Iwatsubo et al., 1994).

As to NFT, neurons were classified into 3 types; NFT-rich, NFT-rare and NFT-free types (Table 6). The cells of the cerebral cortex, hippocampus, parahippocampus, neostriatum and so on belong to NFT-rich type. The cell of the inferior olivary nucleus, anterior horn of the spinal cord and adrenal medulla belong to the NFT-rare group and Purkinje cells and Gasserian ganglion cells are the only cells that belong to the NFT-free group (Table 6). Inferior olivary nucleus cells, posterior root ganglion cells, paravertebral sympathetic ganglion cells, celiac ganglion cells and cells of the adrenal medulla have been known to belong to the NFT-rare group (Urasaki et al., 2000; Nishimura et al., 1993; Hirano & Tomiyasu, 2003; Izumiyama et al.,1990; Kawasaki et al., 1987). The neuron types with easy, rare, and no NFT formations were summarized in Table 6 with their designations and main transmitters (Tohyama, 2004). The neurons with easily formed NFT tend to have glutamate, GABA, Ach or monoamine. It may be necessary to clarify whether the neurons with no NFT formation have something to do with calcitonin gene-related peptide.

The present study has shown the nearly maximal range of NFT occurrence in the whole body. It has also shown that there are 3 neuron types; neuron types with easily formed NFT (NFT-rich), with rarely formed NFT, and with no NFT formations (NFT-free). NFT are known to be mainly composed of hyperphosphorylated tau protein and are the hallmark of tauopathy which includes, other than AD, diverse neurological disorders of a different etiology (Tolnay & Probst,2003; Lowe et al., 2008).

In the brain, Aβ exists extracellularly and inside neurons. It has now become evident that in AD accumulation of Aβ inside neurons definitely occurs, largely by way of internalization by clathrin-independent, and dynamin-dependent endocytosis (Mohamed & de Chaves, 2011). The soluble Aβ oligomers are known to be so toxic that cell death of neurons and glia can be induced (Chui et al., 2001; Ahmed et al., 2010; Fantini & Yahi, 2010; Mohamed & de Chaves, 2011). The soluble oligomers develop and

Table 6. Neuron types with easy, rare, and no NFT formations and their designations with main transmitters

Neuron Types	Designations Neurons/Nucleus	Main Transmitters*
Neuron with easily formed NFT	Pyramidal cells in hippocampus	Glu, GABA
	Meynert/Broca nuclei	Ach
	Cerebral cortical cells	Ach, Glu, GABA, VIP, SOM, NPY, S-P, CRF, NT
	Neostriatum	GABA, Ach, S-P, SOM, NPY Enk, CCK, NADPH-DP, Dyn
	Sunstantia nigra	DP
	Locus ceruleus	NorAD,
	Dorsal raphe nucleus	5-HT
Neurons with rarely formed NFT	Inferior olivary nucleus	Asp, Enk
	Anterior horn cells	Ach, CGRP
	Paravertebral sympathetic ganglia	AD, NorAD
	Prevertebral ganglia	AD, NorAD, Ach
	Adrenal medulla	AD, NorAD
Neuron with no NFT formation	Purkinje cells	GABA, CGRP
	Posterior root ganglion cells	SOM, S-P, /CGRP
	Gasserian ganglion cells	SOM, S-P, /CGRP

Ach, acetylcholine; AD, adrenaline; Asp, aspartate; CCK, cholecystokinin; CGRP, calcitonin gene-related peptide; CRF, corticotrophin releasing factor; Dyn, dynorphin; Enk, enkephalin; DA, dopamine; GABA, γ-aminobutylic acid; Glu, glutamate; NPY, neuropeptide Y; NT, neurotensin; 5-HT, serotonin; SOM, somatostatin; S-P, substance P; VIP, vasoactive intestinal polypeptide.
* Tohyama M (2004)

become protofibrils, then fibrils and finally form neuritic plaques which contain degenerated neurites (Ahmed et al., 2010; Fantini& Yahi, 2010).

On the other hand, soluble oligomers of hyperphosphorylated tau, which are toxic for synapses to disintegrate, occur. And then they become insoluble aggregates of granular tau polymers inside neurons, which are so highly toxic that neuronal death can be induced. Finally many of those aggregates of tau polymers are conjugated to one another to form tau fibrils, i.e., neurofibrillary tangles (PHF) which are believed to have no toxicity (Santacruz et al., 2005; Maeda et al., 2007; De Felice et al., 2008; Takashima, 2010).

It has become evident that hyperphosphorylation of tau protein is induced by activation of glycogen synthase kinase3β (GSK3β) which is normally inhibited by insulin or insulin-like growth factor (IGF). In AD, activation of GSK3β is induced by inhibition of insulin or IGF which is brought about by overproduced Aβ protein (Hong & Lee, 1997; Rankin et al., 2007).

In addition, it has also become clear that both in familial and sporadic AD age-dependent high-density clustering of GM1 ganglioside at presynaptic terminals promotes Aβ protein fibrillogenesis (Hayashi et al., 2004), and such a favorable milieu is provided by accumulation of sphingomyelin (Hayashi et al., 2004; Yuyama & Yanagisawa, 2010; Fantini & Yahi, 2010).

However, it is still unclear why in non-Alzheimer (i.e. NFT only) tauopathy tau is also hyperphosphorylated and forms PHF, although the implication of kinases (GSK3β and cdk5) and/or reduced activities of phosphatases (PP2a etc.) has been discussed so far (Clodfelder-Miller et al., 2006; Sontag et al., 2007; Sontag et al., 2008; Mc Caddon & Hudson, 2010).

An emerging concept that was learned from Alzheimer's Aβ-peptide has been proposed (Haass & Selkoe, 2007). Namely, a series of brain proteins in misfolded diseases whose soluble oligomers can gain an adverse bioactivity in the aggregation process and affect synaptic structure and plasticity, leading to neural cell death (neurodegeneration). Although the mechanisms by which soluble protein oligomers kill neural cells are not fully understood, a common feature is said to be the concentration of unstructured monomers on bidimensional membrane lattices. Membrane-bound monomers undergo a series of lipid-dependent conformational changes, leading to the formation of oligomers of varying toxicity rich in β-sheet structures or in α-helix structures (Fantini & Tahi, 2010). Condensed membrane microdomains formed by sphingolipids and cholesterol are privileged sites for binding and oligomerisation of proteins. By controlling the balance between unstructured monomers and α or β conformers, shingolipids can either inhibit or stimulate the oligomerisation of proteins (Fantini & Tahi , 2010; Matsuzaki et al., 2010).

Molecular analyses that reveal all of qualitative and quantitative differences between NFT-rich and NFT-free neuron types, e.g. by using laser microdissection and proteome, transmitters and phospholipids (especially sphingolipids) analyses, may be a way to obtain some clue to the pathogenesis of NFT formation. The clarification of NFT pathogenesis will surely open a road to preventions and inhibitions of not only AD but also many of other tauopathies.

Acknowledgements

The author expresses his gratitude to those who gave him support and offered their kindness.

（受理日　平成 23 年 2 月 9 日）

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アルツハイマー病の固有病変（神経原線塊と老人斑）の発現範囲 ―38歳で発症し25年の経過をとった家族性アルツハイマー病例の病理・解剖学的研究―

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要　　旨

アルツハイマー病（AD）は近年急増しつつある認知症で、その医療・福祉対策は大きな社会問題であり、根治療法の開発がまたれる。ADの脳病変は３つの組織細胞病変－神経原線維塊、Aβ沈着（老人斑）、細胞脱落－で特徴づけられる。本研究では25年経過のAD剖検例検索を契機にその固有病変の発現範囲を明らかにした。その結果NFTが形成されやすいニューロン群と稀にしか形成されない群と 全く形成されない群に分類された。 ADの脳病変形成については、Aβカスケード仮説によれば、まず最初にAβの沈着がおこり、その際Aβのオリゴマーが最も細胞毒性があり、プロトフィブリル、フィブリルへと発展してやがてneuritic plaqueとなる。また、神経細胞内やシナプス部にAβオリゴマーが生じて神経細胞やグリア細胞に毒性に作用して細胞死を誘導すると考えられている。他方、神経細胞内ではAβの産生過剰によりGSK3βが賦活されるなどにより、タウの過剰リン酸化が進み可溶性オリゴマーが重合して不溶性のタウ顆粒状凝集体となり、さらに大きな不溶性の神経原線維塊になると考えられている。しかし、Aβオリゴマーやプロトフィブリルと、タウオリゴマーや顆粒状凝集体がどこで会合して互いを発達させるのか、またNFTのみのタウオパシーのタウリン酸化機序等も十分には明らかではない。NFTが形成されやすい細胞群とされない細胞群の相違の詳細な検討から、NFT形成機序に通じる手掛かりが得られる可能性がある。

キーワード：アルツハイマー病、神経原線維塊、老人斑、タウ蛋白質、アミロイドβ（Aβ）