P-3-C5

Power Neuropathology of Aging Brain

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Abstract

(Background) Aging process involves human brain in continuous fashion from "physiological", "intermediate" to "pathological" state. ***(Method)*** We extracted 17 representative sections to be applicable to a general hospital and sampled at brain cutting from all cases. Four anatomical sites, including medulla oblongata, amygdala, anterior hippocampus and occipital lobe are initially screened with immunohistochemical method. The antibodies employed consist of anti- A beta, phosphorylated tau, phosphorylated alpha- synuclein and ubiquitin antibodies. When pathological aging process is suspected, further diagnostic investigation will be persecuted. The abbreviated protocol has been employed in the general hospital since July 2007. ***(Result)*** Ten cases have been studied with this protocol. We detected one case of Alzheimer disease (AD), AD with amygdala Lewy bodies, plaque dominant senile change, two cases of Lewy body disease stage 0.5, and one case of Parkinson disease (PD) with dementia (PDD). ***(Discussion)*** Since AD and PD affects 10% and 1% of aged population respectively, easily- applicable protocols for morphological studies of dementia should be essential. This abbreviated protocol may be useful for cooperative morphological approach to human degenerative aging process.

Background

The Brain Bank for Aging Research (BBAR) ; for prevention and cure of age-related motor and cognitive decline, and evaluated the consecutive autopsy cases of Tokyo Metropolitan Geriatric Hospital (TMGH) ;a dignified community-based general geriatric hospital. The BBAR Project consists of prospective clinical studies of Alzheimer, Parkinson and their related disorders, and pathological studies with internationally standardized protocols. The BBAR protocol for neuropathological studies covers all representative diagnostic criteria based on the international consensus guidelines for AD, PD, DLB, PSP, AGD, NFTD, and FTD-U.

To the demands of the routine diagnostic laboratory, we also extracted the essential 17 blocks which are appropriate to the ability of management of each general hospital, and established the Parkinson disease brain resources network (PdBrn). As an advance of PdBrn, we started construction of brain resources network for aging research and investigation of routinely autopsied material of International Medical Center Japan (IMCJ) by immunohistochemical technique.

PdBrn resource 2007

	Autopsy	Brain	PdBrn*
Tokyo Metropolitan Geriatric Hospital	95	60	2/1/0/1/0
University of Tokyo Hospital	78	25	0/0/0/0/0
Yokohama Rosai Hospital **	28	9	2/0/0/0/0
International Medical Center of Japan	114	41	1/0/0/0/1
NHO Tokyo Hospital	25	7	2/0/0/0/0
Shizuoka National Epilepsy Center**	0	0	0/0/0/0/0
Shimoshizu National Hospital**	4	4	0/0/0/0/0
Kameda Medical Center**	43	11	1/0/0/0/0
		153	8/1/0/1/1

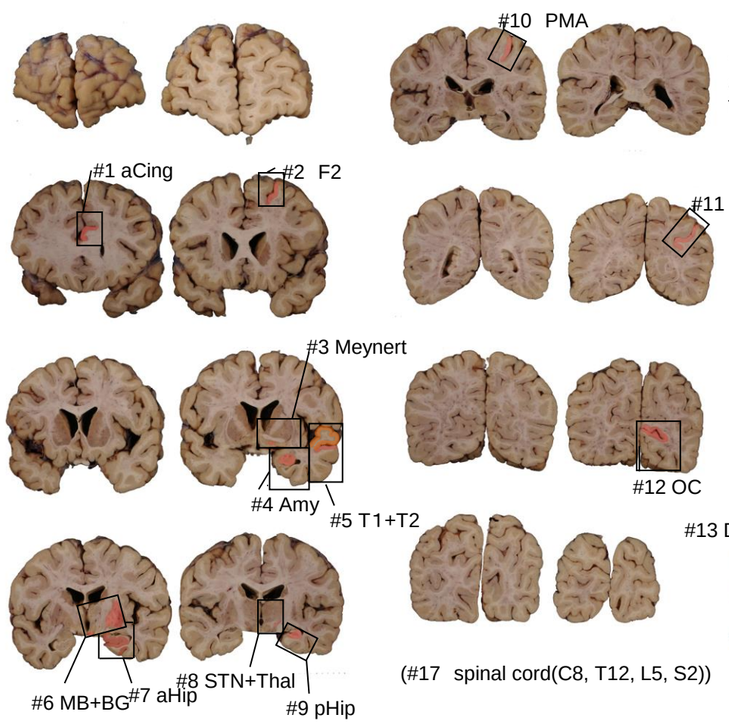
*PdBrn：PD・PDD・DLB/ PSP/ CBD/ MSA/NPH

**BBAR protocl

underline：Frozen brains were separately stocked.

Method

Scheme of 17 blocks for abbreviated protocol

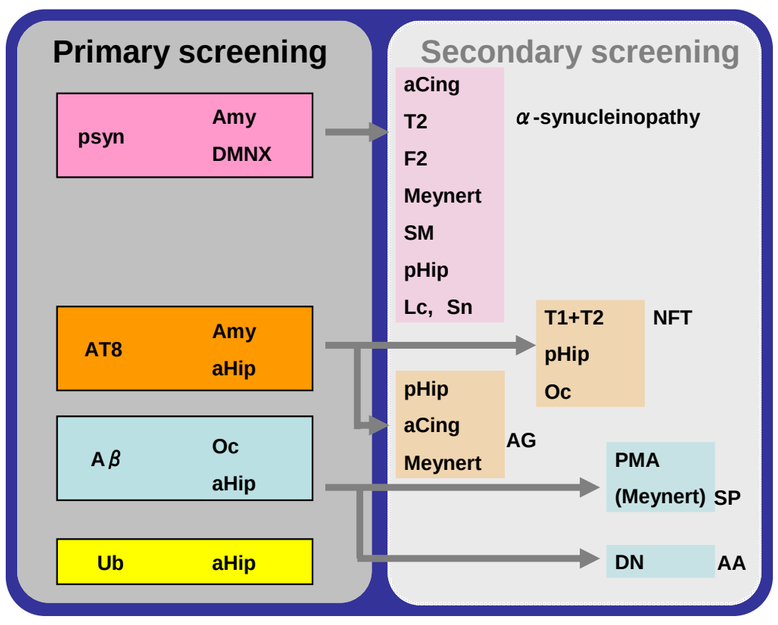


•17 representative sections are sampled at brain cutting from all cases.

#1 aCing: anterior cingulate
#2 F2
#3 Meynert: nucleus basalis of Meynert and basal ganglia
#4 Amy: amygdala
#5 T1+T2
#6 MB+BG: mamilary body and basal ganglia
#7 aHip: anterior hippocampus
#8 STN+Thal: subthalamic nucleus and thalamus
#9 pHip: posterior hippocampus
#10 PMA: primary motor area
#11 SM: supramarginal gyrus
#12 OC: occipital lobe (including striate and peristriate area)
#13 DMNX: medulla (including dorsal motor nucleus of vagus）
#14 Lc: pons (including locus ceruleus)
#15 Sn: mid brain (including substantia nigra)
#16 DN: cerebellum (including dentate nucleus)
#17 spinal cord: C8, T12, L5, S2

Stainings

•Routine staining with hematoxyline & eosin and Klüver-Barrera.

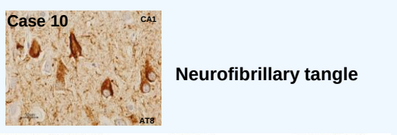


Targets	Antibody	Dilution	Pretreatments
Neurofibrillary tangles(NFT) **Argyrophilic grain**(AG) **Astrocytic tangles**(AT)	Phosphorylated tau (AT8: Inogenetics)	x 1000	none
Senile plaques(SP) **Amyloid angiopathy**(AA)	Amyloid beta(Aβ) (12B2: IBL)	x 50	99%FA 5 minutes
Lewy bodies(LB)	Phosphorylated alpha synuclein (Psyn#64: WAKO)	x 20000	99%FA 5 minutes
Ubiquitinated inclusions	Ubiquitin(Ub) (DAKO)	x 1000	Microwave 30 minutes

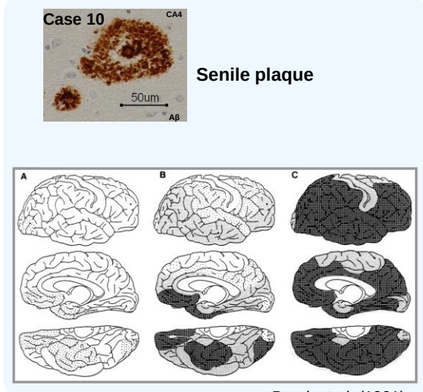
•Using a Ventana NX20 (Ventana, Tucson, AZ) autoimmunostainer

Semiquantative evaluation of senile changes

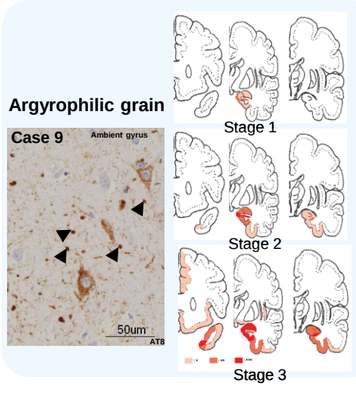
A/S:	Age/ Sex	
PMI:	postmortem interval	
NFT:	Neurofibrillary tangle, Braak Stage	0-VI
SP:	Senile plaque, Braak Stage	0-C
Grain:	Argyrophilic grain BBAR Stage (Saito Y, JNEN 2004)	0-3
AA:	Amyloid angiopathy, BBAR Stage	0-3
Lewy:	Lewy body BBAR stage (Saito Y, JNEN 2003, 2004,2006)	0-5
AT:	Astrocytic tangle BBAR Stage	0-3
UD:	Ubiquitinated dots, BBAR Stage	0-3
NPD:	neuropathological diagnosis	



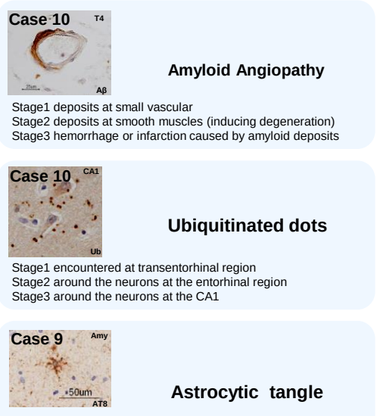
Braak et al. (1991)

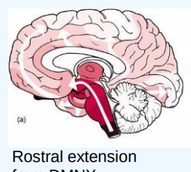


Braak et al. (1991)

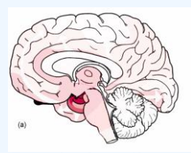


Saito Y et al: J Neuropath Exp Neurol (2004)

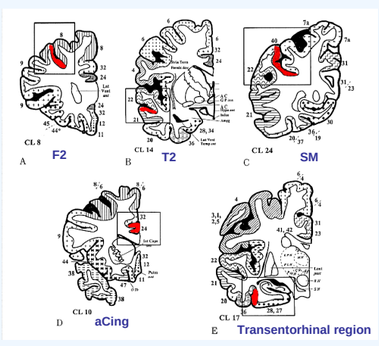




Rostral extension from DMNX



Extension from olfractory bulb and amygdala system influenced by AD and tauopathy
Braak et al. (2003) modified



Lewy body score
Total number of LB
0: score 0
1-5: score 1
6≦:score 2

The sum of the score
0-2: Brainstem predominant（B）
3-6: Limbic (transitional)（T）
7-10：Neocortical（N）

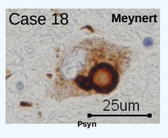
1996 Consensus Guidelines for Dementia With Lewy Bodies

BBAR Lewy body Stage

Stage	SN+LC Loss of pigment	LB ANS (preG)	LB SN/ Stri	LB Limb./ NeoCx.	LB Score**	Dement	PA	
0	-	-	-	-	0			
0.5	-	+/-*	+/-*	+/-*	0			Incidental
I	-	+/-	+/-	+/-	0-10			
II	+	+/-	+	+/-	0-10	-	-	Presymptom
III	+	+	+	+	0-2(10)	-	+	PD
IV	+	+	+	+	3-6	+	+/-	PDD/DLBT
V	+	+	+	+	7-10	+	+/-	PDD/DLBN

PA parkinsonism
* Only Lewy neurites and dots without Lewy bodies
** Following the 1996 Consensus Guidelines for Dementia With Lewy Bodies

Saito Y et al: J Neuropath Exp Neurol (2003, 2004, 2006)

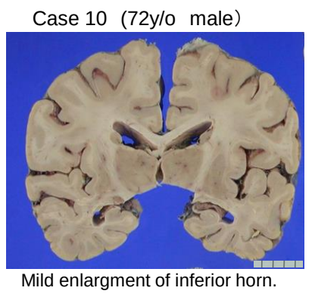


Result

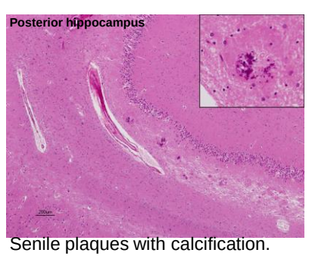
case	Age	gender	PMI	BW	Braak	SP	Lewy	Grain	AA	tastro	UbIRd	NPD
1	30	F	18:15	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	bacterial meningitis, respirator brain
2	52	M	13:45	1550	0	0	0.5	0	0	0	1	meningial carcinomatosis
3	52	F	2:14	1170	0	A	0	0	0	0	1	brain infarction
4	59	M	3:00	1300	1	0	0	0	0	0	2	cytomegalovirus encephalitis (AIDS)
5	60	M	21:00	1310	1	A	0	0	0	0	2	chronic subdural hematoma (AIDS)
6	61	M	18:16	1400	1	0	0	1	0	1	1	contusion
7	63	M	16:09	1500	N/A	N/A	N/A	N/A	N/A	N/A	N/A	intracerebral hemorrhage, brain abscess, respirator brain
8	69	M	6:35	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	AVM, respirator brain
9	71	F	2:00	1150	2	0	0	2	1	2	3	brain infarction
10	72	M	10:40	1350	5	C	1	1	1	0	3	AD (amygdala variant)
11	73	F	8:15	1220	2	C	0	2	0	2	3	brain infarction
12	74	M	23:11	1280	1	C	0	1	1	1	2	PSC
13	74	M	6:23	1190	2	0	0	0	0	1	3	meningitis (SLE)
14	74	M	16:00	1340	1	0	0	0	0	0	1	unremarkable
15	74	M	17:14	1350	1	0	0.5	0	0	0	1	meningitis, cranial nerve metastasis (myeloma)
16	80	M	7:12	1270	2	B	0	1	1	1	3	meningial leukemia (myeloma)
17	82	M	11:39	1330	3	A	0	1	1	2	3	hemorrhagic infarction
18	82	M	10:32	1320	2	B	4	1	0	0	3	PDD
19	85	F	2:05	1070	3	0	2	1	0	0	3	ventircular enlargement
20	85	M	6:16	1300	3	C	1	1	1	0	3	AD
21	86	M	3:35	1280	2	A	0	2	0	2	3	bacterial meningitis

dementia

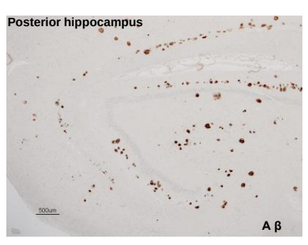
Case 10 (72y/o male）

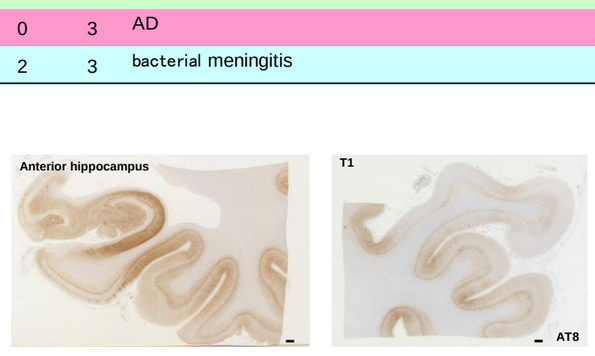


Mild enlargment of inferior horn.

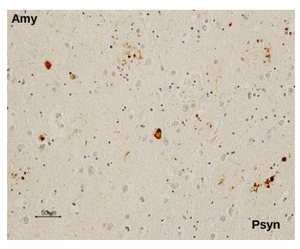


Senile plaques with calcification.





Immunopositive plexuses are recognized in transentorhinal region, hippocampus and the superior temporal gyrus.



Lewy bodies and Lewy neurites were observed in amygdala.

Braak	NFT stage 0	I	II	III	IV	V	VI
SP stage 0 / A	MSC minimal senile change			NFTC Neruofibrillary tangle change			
SP stage B / C	PSC plaque dominant senile change			AD Alzheimer disease change			

International Medical Center of Japan (IMCJ)

IMCJ is a general hospital at Sinjuku in Tokyo.
In Japan, separated permission for autopsy of the brain was required. The 32 permission (26.4%) for brain autopsy was granted from 121 cases with the consent for general autopsy in 2006.
This protocol was introduced since July 2007.
Forty one permissions for brain autopsy (36.0%) were granted from 114 cases with the consent for general autopsy.
From July 2007 to March 2008, the examination of twenty one brains was completed.

Age:30-86 (69.43±13.72), Gender: male 16、female 5
Three cases（Case1,7,8）presented "respirator brains" and were not appropriate for examination of the senile changes.
Except for these three cases, all five cases younger than 65 years of age were categorized into MSC. One case of BBAR Lewy body stage 0.5 (Case 2; 52y/o male) was also detected.
The following were the details of those cases older than age 65.
Two case of AD, with Lewy bodies in DMNX（Case 20; 85y/o male）and preferentially in amygdala (amygdala variant, Case10; 72y/o male ）
One case of PSC (Case12; 74y/o male ）
One case of PDD (Case 18; 82y/o male）
One case of BBAR Lewy body Stage 0.5（Case15; 74y/o male）

Discussion

Since AD and PD affects 10% and 1% of aged population respectively, easily- applicable protocols for morphological studies of dementia should be essential. This BBAR abbreviated protocols has been employed in the IMCJ for routine diagnostic laboratory with satisfactory results. This protocols may be useful for cooperative morphological approach to human degenerative aging process, finally culminating in dementia.

Conclusion

Power neuropathology (unbiased unanimous screening) by generally approved immnocytochemistry may build up core knowledge of biological aspects of human aging brain.