ISMRM Educational course

Role of neuroimaging in the treatment strategy for dementia

-Significance of a clinico-radio-pathological relationship-

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In this unprecedented aging society, appropriate medical interventions are crucial for the diagnosis of dementia, the disease course of which extends over several decades, and there is now an urgent need for countermeasures.

Recent advances in neuroimaging for dementia have moved the field past ruling out possible pathological causes towards clarifying specific pathophysiological processes. High-resolution volumetric MRI has increased the capacity to facilitate diagnoses, even in the very early or pre-symptomatic phases of the degenerative forms of dementia.

As proposed in the international diagnostic criteria for Alzheimer's diseases in 2011, the use of several objective biomarkers is essential for the development of and clinical trials on fundamental therapeutic agents.

In this lecture, I will discuss what neuroradiologists need to consider in a routine diagnosis of dementia, what information is appropriate to give to clinicians (attending physicians) in order to be truly useful for individual patients, and provide image

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information directly connected to treatment, care, and nursing in accordance with the wishes of the patient's family, in addition to information on the most advanced diagnostic techniques.

Background pathology needs to be accurately identified in order to utilize an imaging diagnosis at clinical sites. The images presented here were selected based on a retrospective study collated with the images of 1,212 serial autopsy cases between August 1999 and May 2012 in the Brain Bank Tokyo Metropolitan Medical Center of Gerontology, as well as an analysis of the imaging diagnosis of dementia involving 7,800 patients who were prospectively followed between 2005 and 2014.

Figures 1 and 2 show the background pathology of serial biopsy specimens from 1,212 patients with degenerative dementia. While the prevalence of Alzheimer’s disease (AD) was high when the concomitant pathologies of dementia with grains (DG), neurofibrillary tangle disease (NFTD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) were included, it reached 33% in the group with CDR>0.1 and 57% in the group with CDR=0.5. These were degenerative disease groups in which the abnormal deposition of tau protein was more prominent than that of amyloid β, and was collectively termed senile tauopathy.

Neuroimaging is now being employed as both a diagnostic biomarker and efficacy–surrogate marker in the early diagnosis of AD and development of fundamental therapeutic agents, and differentiating between AD and DG in the mild cognitive impairment (MCI) stage is of importance. I here reviewed the significance of a clinical imaging diagnosis of DG as a new disease concept in consideration of its differentiation from AD.

AD is the most prevalent degenerative dementia, and its diagnosis is important. In 2011,

the National Institute on Aging-Alzheimer's Association (NIA-AA) revised the diagnostic criteria for AD, in which the pathology of steps earlier than that previously used to diagnose AD was investigated to elucidate the developmental mechanism of AD and make an early diagnosis. It was classified into 3 steps based on the stage: the preclinical stages of AD, MCI due to AD, and dementia due to AD, and criteria and concrete diagnostic techniques are presented for each step. These diagnostic criteria are expected to perform more accurate in early clinical trials, clearly setting the target at the development and verification of fundamental therapeutic agents for AD.

The diagnosis of MCI due to AD is already required at routine clinical sites. In early AD, a significant degree of local atrophy is observed in the hippocampus, parahippocampal gyrus, and entorhinal cortex, and that based on statistical MRI image processing is described as a feature showing the pathophysiological process of AD in the diagnostic criteria.

DG was pathologically identified by Braak et al. in 1987, and its relationship with dementia as a pathology stage involved in cognitive dysfunction in the elderly was reported by Saito et al. in 2004. Argyrophilic grain deposition starts from the ambient gyrus and amygdaloid nucleus (Stage I), and spreads backward and forward in the medial side of the temporal lobe (Stage II). Although cognitive dysfunction does not frequently manifest in these stages, it occurs at a high rate when deposition spreads to the frontal lobe and cingulate gyrus (Stage III).

Regarding localization and the spread of pathological changes, differentiation from the MCI stage of AD is always problematic because it is close to the pathology of AD and the initial symptom with forgetfulness as a premonitory sign develops. Its clinical characteristics include elderly onset, a slow progression, and symptoms similar to those

of FTLD (character change, irritability, and poor personal contact). The morphological characteristics of MRI images are atrophies in the region near the ambient gyrus and ventral side of the temporal lobe with laterality. Statistical image processing is an essential investigation item; however, differentiating from AD is not necessarily easy because the ambient gyrus, which atrophies in the early stage, is very close to the entorhinal cortex, in which the early features of AD are observed, and the laterality of atrophy may be present in AD. Therefore, the accumulation and investigation of cases in which the background pathology is confirmed is required, and clinical diagnostic criteria need to be established.

Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB) are as important as AD and senile tauopathy disease in the elderly with dementia. PDD and DLB belong to the disease spectrum termed Lewy Body Dementia, in which pathological changes develop in an extended area and the clinical phenotypes are diverse. PD mainly manifests when the substantia nigra and corpus striatum are impaired, dementia manifests when impairments to the neocortical limbic system is severe, and autonomic failure, such as Shy-Drager syndrome, develops when the peripheral autonomic nervous system is severely impaired. The differentiation between AD and DG is important because internal medical problems that influence a vital prognosis develop at a high rate in PDD/DLB. Patients easily fall and develop dysphagia and aspiration pneumonia, and, thus, rapidly become bed-ridden. In this lecture, I will introduce neuromelanin imaging as a new technique expected for clinical application, in addition to dopamine transporter imaging, 123I-MIBG myocardial scintigraphy, MRI, and SPECT (cerebral perfusion), with regards to the positioning of imaging diagnoses. I would also like to highlight the significance of identifying various

internal medical problems that develop due to the presence of dementia in the background pathology, i.e., the clinical significance of pulmonary aspiration in dementia patients and autonomic neuropathy-associated ileus in PDD patients.

The differential diagnosis of potentially treatable dementia is the most important role of MRI in clinical practice.

Some cases of dementia are curable by appropriate treatments. We can remember "Vascular, Infections, Toxic-Metabolic, Autoimmune, Metastasis/neoplasia, Iatrogenic/inborn errors of metabolism, Neurodegenerative, and Systemic/seizures" as VITAMINS for a differential imaging diagnosis. Although the lecture time given to me today is only 30 minutes, I will review pathologies in which an imaging diagnosis made at an appropriate time directly led to treatments by linking the background pathology with images. Amyloid angiopathy (AA) shows not only subcortical hemorrhage, but also diverse pathological conditions, such as subarachnoid hemorrhage and reversible inflammation in the white matter (leukoencephalopathy). In this lecture, I will present images and the pathologies of AA in order to deepen understanding on pathological conditions.

In addition, I would like to introduce images and the pathology of the newly reported neuronal intranuclear inclusion disease (NIID), in which neuroimaging characteristics lead directly to a diagnosis.

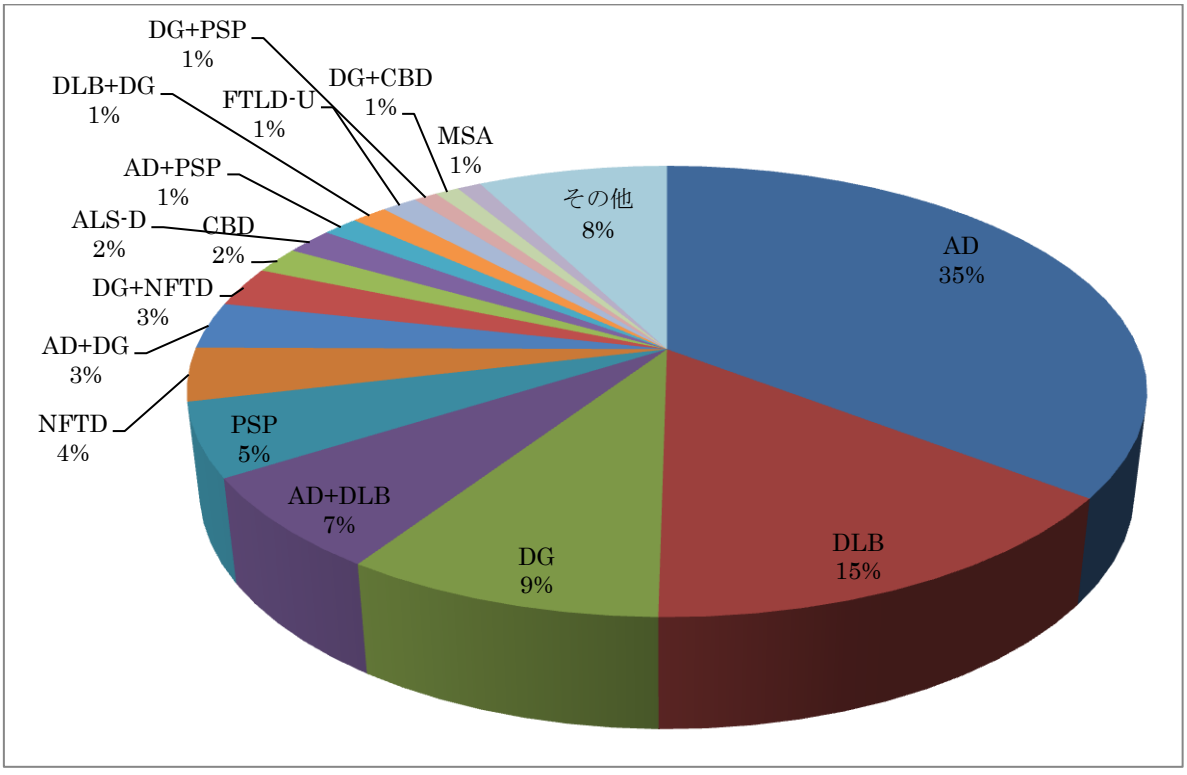
Vascular disorders are the background pathology in 1/4 of dementia cases. Vascular dementia is the collective name used for dementia that develops in association with cerebrovascular disorders, and there are diverse causes and pathological conditions. The regions involved in strategic infarct dementia that must not be missed on neuroimaging include the angular gyrus, basal forebrain, cingulate gyrus, fornix, caudate nucleus,

thalamus, corpus callous, and hippocampus. Impairments to the Papez circuit are also associated with the development of dementia.

The relationship between micro infarcts with a 0.05-0.4-mm diameter that are microscopically observed in the cortex and cognitive function has recently been reported. I will briefly discuss the possibility of the visualization of lesions using double inversion recovery (DIR).

We have to make use of an advantage of each modality and advance to the future desired.

Figure1: CDR 1 ≦ background pathology of degenerative form of dementia



AD: Alzheimer disease　DLB: diffuse Lewy body disease　DG: demential with grain

PSP: progressive supranuclear palsy

NFTD: neurofibrillay tangle disease　ALS-D:amyotrophic lateral sclerosis with

dementia FTLD-U: frontotemporal lobar degeneration-U

CBD: corticobasal degeneration

Figure2: CDR =0.5 Background pathology of degenerative dementia