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〔博士論文概要〕

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（肺炎合併に伴う認知症患者の予後についての検討）

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Prognosis of patients with dementia complicated with pneumonia

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Purposes:

Dementia is increasingly becoming a major healthcare challenge as the population ages. Dementia occurs when the brain is affected by certain diseases or conditions. Currently, many different types of dementia were determined. Among them, Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and Vascular dementia (VaD) encompass approximately 90% of the total population of dementia in Japan. Persons with dementia tend to die at an earlier age compared persons without dementia. Several studies reported that pneumonia increased the risk of death on dementia. However, the disease prognosis of dementia with pneumonia has not been fully understood as well as the risk factors relating to the survival-time on dementia complicated with pneumonia.

The aim of the present study was to elucidate the effects of pneumonia for the disease prognosis and prognostic factors on neuropathologically confirmed patients with AD, DLB, and VaD.

The purposes on each sub-study were: (Study 1) to determine the cause of death; (Study 2) to evaluate the time from dementia onset to death (survival-time) and to assess the influence of pneumonia complication and prognostic factors on patients with AD, DLB, and VaD; (Study 3) to examine the survival-time and prognostic factors on patients with DLB.

Subjects and Methods:

The retrospective observational studies were conducted. The subjects of study were hospitalized and deceased patients between January 2005 and December 2014 in Fukushima Hospital, Toyohashi, Japan. All patients were underwent brain autopsies in the study site. Data relating to the general and clinical backgrounds of the patients, clinical time courses, and clinical conditions on patients during the hospitalization including swallowing dysfunction, nosocomial infections, percutaneous endoscopic gastrostomy (PEG), medications, and results of neuropathological examinations were collected. The cause of death (Study 1), the survival-time and the risk factors for the survival-time (Study 2) were analyzed for all 157 eligible patients, and compared among patients with AD, DLB, and VaD, and between patients with and without pneumonia. The risk factors on the survival-time on DLB complicated with pneumonia

were examined on 42 patients with DLB (Study 3).

In the statistical analysis, the Mann-Whitney U test and the Kruskal–Wallis tests were used for continuous variables, and the Chi-squared and Fisher’s exact tests were used for categorical variables. Survival curves of the number of years on survival-times of dementia in groups of AD, DLB, and VaD with or without pneumonia were analyzed by the Kaplan–Meier method and comparisons were made using the log-rank test. To evaluate independent factors for the survival time of dementia, a step-wise method was used for a Cox proportional hazard analysis.

The study was approved by the Institutional Review Boards of the University of Tsukuba and Fukushima Hospital. Written informed consent was obtained from patients’ relatives.

Results:

Among 230 cases who underwent autopsy during the observational period in the study site, 157 patients with AD (63), DLB (42), and VaD (52) were eligible to the study.

Study 1

The patients with all three major subtype of dementia complicated with pneumonia with high incidence. Especially, over 90% of patients with DLB had pneumonia complication during the hospitalization.

Cerebral infarction and hypertension were more common comorbidity in VaD than those in AD and DLB. In the patient with DLB, the main underlying cause of death was heart failure, but the main immediate cause of death was pneumonia.

Study 2

Patients with all three major subtype of dementia complicated with pneumonia with high incidence. The medians of total survival-time of dementia onset were 8 years in AD and DLB, and 5 years in VaD. The factors associating with shorter time of survival time of dementia were gender-male, pneumonia complication, diabetes mellitus, older age at onset (≥ 75 yr.), and VaD.

Study 3

The prognostic factors identified in autopsy-confirmed DLB patients with pneumonia were pathologically-confirmed cerebral infarction, muscle weakness of the lower extremities, gender-male, and older age at onset (≥ 78 years).

Discussion:

The present study intended to elucidate the disease prognosis and prognostic factors on neuropathologically confirmed patients with three major subtypes (AD, DLB, and VaD) of dementia in the relation of the pneumonia complication. The study revealed

that the survival-time of patients with AD and DLB was 8 years and those with VaD was 5 years. The survival-time of patients with DLB but without pneumonia complication was 5 years longer than those with pneumonia. The prognostic factors on survival-time of three major subtypes of dementia were gender-male, pneumonia complication, diabetes mellitus, older age at onset (≥ 75 yr.), and VaD. The prognostic factors identified in DLB complicated with pneumonia were pathologically-confirmed cerebral infarction, muscle weakness of the lower extremities, a male sex, and older age at onset (≥ 78 years).

The reported survival-time on patients with dementia was various, 8 - 12 years in AD and 1.8 - 9.5 years in DLB. These wide range may be caused by the heterogeneity among these studies including the cause of death (underlying or immediate), the methods of diagnosis (neuropathological or clinical) and the subtypes and severity of dementia. Therefore, in the present study, the patients of dementia who were neuropathologically diagnosed on dementia were examined. In the survival-time of patients with AD and DLB were 8 years and 5 years in patients with VaD. This difference among types of dementia may cause the different pathogenesis of each types of dementia. VaD is a progressive disease and may associate with some types of cerebral events. In addition, VaD has systemic vascular damages, and it is reasonable to suppose that these damages, in part, contributing shortening the survival-time. As the result, cerebral infarction was a more common comorbidity in VaD than those in AD and DLB. AD and DLB are neurodegenerative diseases, and they may have slower progression than those of VaD. In this study of DLB, cerebral infarction was one of the independent factors that associated the shortness of survival-time (Study 3). The result indicated the possibility of the long-term influence of cerebral infarction, including asymptomatic cerebral infarction and a history of small cerebral infarctions, on the progression of DLB.

The pneumonia complication was determined as the prognostic factor on patients with AD, DLB and VaD. Although the survival-time both on AD and DLB was same as 8 years, only survival-time of patients with DLB with- and without-pneumonia was significant. Although the number of DLB patients without pneumonia was small, the more effects of pneumonia were possibly existed in DLB than those in AD. Pneumonia results in further aggravation of cardiac and circulatory dysfunction in DLB. Once patients with DLB reach the terminal stage, pneumonia can lead to mortality, due to the decreasing ventilator response to hypercapnia.

In the study on DLB, muscle weakness of the lower extremities tended to effect to shorter survival-time on patients with DLB (Study 3). The previous studies

indicated an association between muscle strength of the extremities and the risk of death in older adults. Similar to these observations, the results of the present study suggest that weakness of the extremities in DLB patients may be associated with a low respiratory function and thus aggravate the poor prognosis for patients with pneumonia. These may suggested that the deterioration of lung function would risk being dementia and the risk to shortness of life expectancy once dementia is occurred.

Conclusions:

The careful management on pneumonia are crucial for maximizing the patients' life expectancy, especially for patients who developed dementia in older age. Cerebral infarction and diabetes mellitus are also import for clinical management on older adults with dementia. The study warrants further prospective cohort studies with alternative and larger populations for generalizing the results of present study.