学 位 論 文 の 要 旨

氏名　　田原　大資

学 位 論 文 名　Clinical Characteristics of Japanese Patients With Corticobasal Degeneration

発 表 雑 誌 名（巻，初頁～終頁，年）　Journal of the Neurological Sciences (466, 123212, 2024)

著 者 名　Daisuke Tahara, Nao Tahara, Akio Akagi, Yuichi Riku, Jun Sone, Hiroaki Miyahara, Atsushi Nagai, Mari Yoshida, Yasushi Iwasaki

論 文 内 容 の 要 旨

INTRODUCTION

Corticobasal degeneration (CBD) is a rare neurodegenerative disorder classified as four-repeat tauopathy. Classically, patients with CBD had been thought to present with corticobasal syndrome (CBS): conditions with asymmetric extrapyramidal and cortical signs. However, various phenotypes other than CBS have been reported. The clinical diagnosis of CBD is quite challenging due to its heterogeneity; thus, pathological investigations are essential for definitive diagnosis.

The clinical characteristics of patients with CBD have been reported; however, most of patients included in previous studied are Western populations. It is necessary to investigate them in patients of multiple ethnicities for elucidating the general clinical characteristics of CBD.

We examined the clinical characteristics of Japanese patients with pathologically proven CBD.

MATERIALS AND METHODS

We investigated Japanese patients with pathologically confirmed CBD who underwent consecutive autopsies at our institute. Patients with insufficient clinical data were excluded.

The pathological diagnosis of CBD was based on the presence of Gallyas/tau-positive lesions in the cerebral cortex and basal ganglia, including astrocytic plaques and pretangles (*J Neuropathol Exp Neurol*. 61 (2002) 935–946.).

Clinical data were obtained from medical records and clinicopathological conferences. We retrospectively examined the information regarding sex, age at onset, age at death, disease

duration, initial symptoms, cause of death, final clinical diagnosis, clinical phenotype, the implementation of tube feeding (TF) or tracheostomy, and the presence of dysphagia and central respiratory disturbance. We also examined the latency to the implementation of TF or tracheostomy, dysphagia, and central respiratory disturbance. We adopted the four clinical phenotypes proposed by Armstrong *et al.* (*Neurology*. 80 (2013) 496–503.): possible or probable CBS, frontal behavioral-spatial syndrome, nonfluent/agrammatic variant of primary progressive aphasia, and progressive supranuclear palsy syndrome (PSPS). We determined one clinical phenotype per patient. We treated missing data as nonexistent.

Data are expressed as mean ± standard deviation (range) or median (range). The Holm method, Mann–Whitney U-test, Steel–Dwass tests, and Pearson's correlation coefficients were used for the statistical analyzes. Statistical significance was set at $P < 0.05$.

RESULTS AND DISCUSSION

Of the included 31 patients, 16 were men and 15 were women. The mean ages at onset and death were 63.3 ± 6.7 (51–79) years and 69.1 ± 6.9 (54–86), respectively. The median disease duration was 6.0 (2.5–12) years. Initial symptoms were as follows: parkinsonism (n = 10, 32.3%), gait impairment (n = 8, 25.8%), apraxia (n = 3, 9.7%), dystonia (n =1, 3.2%), and language impairment (n = 1, 3.2%). Causes of death included pneumonia (n = 19, 61.3%), choking (n = 5, 16.1%), and urinary tract infections (n = 2, 6.5%). Final clinical diagnoses were as follows: progressive supranuclear palsy (n = 11, 35.5%), CBD or CBS (n = 10, 32.3%), Parkinson's disease or dementia with Lewy bodies (n = 5, 16.1%), frontotemporal lobar degeneration or frontotemporal dementia (n = 3, 9.7%), Alzheimer's disease (n = 1, 3.2%), and multiple system atrophy (n = 1, 3.2%). The clinical phenotypes were as follows: PSPS (n = 20, 64.5%), probable or possible CBS (n = 6, 19.4%), frontal behavioral-spatial syndrome (n = 4, 12.9%), nonfluent/agrammatic variant of primary progressive aphasia (n = 1, 3.2%). Twenty-two (71.0%) and three (9.7%) patients had been received TF and tracheostomy, respectively. Patients who received TF survived longer than those who did not ($P = 0.013$). Twenty-eight (90.3%) patients exhibited dysphagia with a median latency of 3.5 (1.0–10.0) years. The latency to dysphagia significantly correlated with the disease duration (Pearson's correlation coefficient 0.596, 95% CI 0.279–0.796, $P = 0.001$). Two (6.5%) patients had central respiratory disturbances. The latency to central respiratory disturbance was unknown in both two patients.

One of the characteristics of this cohort was the high prevalence of PSPS (64.5%). Armstrong *et al.* (*Neurology*. 80 (2013) 496–503.) proposed four clinical phenotypes based on the final clinical diagnosis of patients with pathologically proven CBD: including PSPS (23.3%). Other western studies which adopted the four clinical phenotypes proposed by Armstrong *et al.* have reported a low prevalence of PSPS, where as a Japanese study has reported a high

prevalence of that (*J Neurol Neurosurg Psychiatry*. 85 (2014) 925–929.) (*Brain Commun*. 5 (2023) fcad296.). The enumeration method was not consistent with studies, and the background of this cohort was in movement disorders. These may have influenced the results; however, we believe that the high prevalence of PSPS is a clinical characteristic of Japanese patients with CBD. In addition, we think that the high prevalence of PSPS influenced the result about initial symptom: the proportion of patients with gait impairment as an initial symptom was higher compared to the Western study. Another Japanese study also reported the high prevalence of PSPS and the gait impairment as an initial symptom (*Brain Commun*. 5 (2023) fcad296.).

In this study, four patients with PSPS were clinically diagnosed as CBD. We think that asymmetricity is an important indicator of CBD. In addition, five patients have been diagnosed as PD or DLB in the present study. However, it is difficult to consider the presence of PD/DLB phenotype in patients with CBD from the present study. The basis of the clinical diagnosis was ambiguous, and patients diagnosed as PD or DLB had an atypical clinical course as those conditions.

Another characteristic of this cohort was showing the possibility of the effectiveness of TF. Reports on TF in patients with CBD are limited; no studies have reported on the proportion of Western patients with CBD receiving TF. We speculated that the proportion of patients receiving TF in the present study was high. The Japanese healthcare system, social environment, and traditional ethical values may encourage patients with advanced neurological disorders to receive life-sustaining treatments (*Prion*. 11 (2017) 186–194.). In the present study, the total disease duration was significantly longer in tube-fed patients than in non-tube-fed patients. Thus, TF may contribute to prolonged survival in patients with CBD. However, disease duration of this study did not differ from that previously reported. In the present study, dysphagia occurred in many patients with early latency. Dysphagia in many patients with early latency may shorten the disease duration despite the high proportion of patients receiving TF.

Compared to previous Western studies, it was challenging to reveal characteristics specific to Japanese patients in the sex distribution, mean ages at disease onset and death, mean disease duration, and the cause of death. No previous studies investigated the tracheostomy or central respiratory disturbances in patients with CBD. We consider it difficult to determine the effect of tracheostomy on the disease course. Central respiratory disturbances would be rare in patients with CBD and may not influence the disease duration.

CONCLUSION

A high prevalence of PSPS may be a characteristic of Japanese patients with CBD. In this cohort, dysphagia occurred more often with early latency, which might be correlated with shorter survival. TF contributed the prolonged survival of patients with CBD.