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Correlation in Lewy pathology between the claustrum and visual areas in brains of dementia with Lewy bodies

Ryoko Yamamoto [a,b], Eizo Iseki [a,*], Norio Murayama [a], Michiko Minegishi [a], Wami Marui [a], Takashi Togo [c], Omi Katsuse [c], Kenji Kosaka [c], Masanori Kato [d], Takeshi Iwatsubo [e], Heii Arai [b]

[a] *Department of Psychiatry, Juntendo Tokyo Koto Geriatric Medical Center, Juntendo University School of Medicine, 3-3-20 Shinsuna, Koto-ku, Tokyo 136-0075, Japan*
[b] *Department of Psychiatry, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan*
[c] *Department of Psychiatry, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan*
[d] *Soga Hospital, 148 Sogagishi, Odawara 250-0203, Japan*
[e] *Department of Neuropathology and Neuroscience, Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

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Abstract

We investigated Lewy pathologies in the claustrum and the related cerebral cortices and subcortical nuclei of dementia with Lewy bodies (DLB) brains using α-synuclein-immunohistochemistry to clarify the relationship between Lewy pathology in the claustrum and visual misidentification of DLB patients. The claustrum is known to have strong reciprocal connections with the visual areas. Consequently, the claustrum demonstrated many Lewy bodies (LB) and LB-related neurites. The insular and inferior temporal cortices, amygdala, BA 18, 19, transentohrinal and cingulate cortices showed stronger or similar Lewy pathology as compared with the claustrum, while BA 17, precentral, postcentral and transverse temporal cortices showed weaker Lewy pathology. Comparing the correlation coefficient of Lewy pathology between the clausturm and other regions, BA 18 and 19 as well as the insular and transentorhinal cortices demonstrated a higher correlation coefficient. These findings suggest that Lewy pathology in the claustrum is more closely associated with that in visual areas than in auditory, somatosensory or motor areas, and that dysfunction of the visuo-claustral pathway participates in visual misidentification in addition to the visuo-amygdaloid pathway. The paralimbic cortices including the insular and transentorhinal cortices may connect visual areas with limbic areas by relay of the visuo-claustral or visuo-amygdaloid pathway.

Keywords: Dementia with Lewy bodies; Claustrum; Visual area; Visual hallucination; Lewy pathology; α-Synuclein-immunohistochemistry

Dementia with Lewy bodies (DLB) is the second most frequent neurodegenerative dementing disorder after Alzheimer's disease (AD). DLB is clinically characterized by progressive dementia, which is frequently accompanied by parkinsonism and psychiatric symptoms, and is pathologically characterized by the occurrence of Lewy bodies (LB) in the brain [14].

The psychiatric symptoms of DLB patients are mainly composed of visual misidentification symptoms including visual hallucinations [9,14]. These symptoms are considered to be associated with hypoperfusion or glucose hypometabolism in the occipital lobe using the SPECT or PET examination [7,19]; however, the pathomechanism of their occurrence is not yet understood.

The visual pathway is usually considered to consist of not only the geniculo-striate visual pathway (primary visual pathway), but also the extrastriate visual pathway (secondary visual pathway) [1,3]. The primary visual pathway goes from the retina through the lateral geniculate body to Brodmann's area (BA) 17 (primary visual cortex). On the other hand, the secondary visual pathway goes from the retina through the pulvinar to BA 18 and 19 (visual association cortex), and connects to the inferior temporal cortex (visual related cortex) [1,3,18]. This pathway participates in the recognition of objects (shape and color) [16]. In addition, the amygdala has reciprocal connections by relay of the visual related cortex with the primary visual and visual association cortices, and is consid-

* Corresponding author. Tel.: +81 3 5632 3111; fax: +81 3 5632 3728.
E-mail address: iseki@juntendo.gmc.ac.jp (E. Iseki).

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ered to modulate visual processing according to cognition and emotion [16].

The claustrum has fiber connections with the entire neocortex [18,20], especially the visual, auditory, somatosensory and motor areas [15,17,20], as well as subcortical nuclei such as the putamen and thalamus [15,20]. Some cat studies demonstrated the existence of claustro-cortical connections, especially the close connection between the claustrum and visual areas [17,22]. On the other hand, the claustrum is known to be a favorable site of LB in DLB brains [11].

Recently, α-synuclein was recognized as a major component of LB [23], and α-synuclein-immunohistochemistry sensitively demonstrated Lewy pathology including LB and LB-related neurites in DLB brains [2,13]. We have shown using α-synuclein-immunohistochemistry that degeneration of the nigro-amygdaloid dopaminergic pathway may be related to the psychiatric symptoms of DLB patients [8], and that Lewy pathologies in the secondary visual pathway and amygdala may cause dysfunction of the visuo-amygdaloid pathway and participate in visual misidentification of DLB patients [25].

In this study, we investigated Lewy pathologies in the claustrum and the related cerebral cortices and subcortical nuclei of DLB brains using α-synuclein-immunohistochemistry to clarify the relationship between Lewy pathology in the claustrum and visual misidentification of DLB patients.

We examined 20 pathologically verified DLB cases (13 men and 7 women; mean age, 74.9 years; mean disease duration, 4.6 years, and mean brain weight, 1138 g) preserved in our laboratories. All 20 cases also fulfilled the clinical diagnostic criteria for probable DLB [14], because they showed parkinsonism and fluctuating cognition or visual hallucinations in addition to progressive dementia. Visual hallucinations were noted on the charts for 16 of the 20 cases.

The brains were fixed in 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). Three coronal slices of the cerebral hemispheres through the anterior end of the thalamus, the posterior end of the putamen and the tip of the posterior horn, and a horizontal slice of the midbrain through the red nucleus were embedded in paraffin. Six-micrometer thick sections were stained using hematoxylin–eosin (HE) and Klüver–Barrera (KB) methods for pathological examination. Serial sections were also immunostained with anti-α-synuclein (SyαC: polyclonal, rabbit, 1:200) [12] and anti-phosphorylated α-synuclein (PSer129: monoclonal, mouse, 1:20,000) [21], anti-PHF tau (AT8: monoclonal, mouse, 1:2000, Innogenetics, Belgium) and anti-Aβ (polyclonal, rabbit, 1:5000, donated by Dr. T. Ishii) antibodies. Immunolabeling was detected using the avidin–biotin–horseradish peroxidase complex (ABC) method (Elite Kit: Vector, USA) and visualized with diaminobenzidine (DAB: Wako, Japan). Before immunostaining, these sections were pretreated with 70% formic acid for 10 min for SyαC, PSer129 and anti-Aβ antibody.

Lewy pathology, including LB and LB-related neurites, was evaluated by SyαC- or PSer129-immunostaining, and Alzheimer pathology, including neurofibrillary tangles and amyloid deposits, was evaluated by AT8- and Aβ-immunostaining, respectively [13]. The number of SyαC-positive or PSer129-positive LB was counted using microscopic fields (field size: 0.1 mm^2) at ×200 magnification in the BA 17, 18, 19, inferior temporal cortex, amygdala (basal amygdaloid nucleus), claustrum, insular, precentral, postcentral, transverse temporal (Heschl), transentohrinal and cingulate cortices, thalamus (lateral posterior thalamic nucleus), and putamen. The claustrum was divided into dorsal and ventral parts. BA 17 was defined as the striate cortex, BA 18 as the cortex adjacent to BA 17, and BA 19 as the cortex adjacent to BA 18 in the section though the tip of the posterior horn. The average number of the largest three values of PSer129-positive LB obtained for each region was calculated and scored from (0) to (4): (0) absent; $1 > (1) > 0$; $3 > (2) > 1$; $9 > (3) > 3$; $(4) > 9$. In addition, the degree of Pser129-positive LB-related neurites in these regions was graded from (−) to (+++): (−) absent; (±) rare; (+) some; (++) many; (+++) numerous [13,25].

For statistical analyses, SPSS software (version 10.0) for Windows was employed. The *t*-test was performed for the mean values of LB scores of all cases between two regions, and for the mean values of LB scores between cases with and without visual hallucinations. *p* values under 1% were considered significant. In addition, the correlation coefficient was calculated for the mean values of LB scores for all cases between the claustrum and other regions.

The results of the regional evaluation of Lewy pathology using Pser129 are shown in Table 1. The claustrum showed many LB and LB-related neurites in both the ventral and dorsal parts (Fig. 1A and B). The average scores of LB in the ventral and dorsal claustrum were 2.5 and 2.7, respectively. Their average score was 2.6, and was used as the statistical LB score of the claustrum, because there was no significant difference between the LB scores of the two parts. The grades of LB-related neurites in the claustrum ranged from (+) to (+++) and were almost parallel to LB scores. The average LB scores in BA 17, 18 and 19 were 1.1, 2.1 and 2.5, respectively. The LB score was significantly higher in BA 18 and 19 than in BA 17 ($p < 0.01$) (Fig. 1C and D). BA 19 tended to show a higher LB score than BA 18 ($p < 0.05$). The grades of LB-related neurites in these regions ranged from (+) to (++). The average LB score in the inferior temporal cortex was 3.3 (Fig. 1E). The grade of LB-related neurites ranged from (+) to (+++). The degree of Lewy pathology varied in the subcortical nuclei. The average LB score in the basal amygdaloid nucleus was 3.6, and the grade of LB-related neurites ranged from (++) to (+++). The putamen and lateral posterior thalamic nucleus showed no LB but LB-related neurites. The grades of LB-related neurites in the putamen and lateral posterior thalamic nucleus ranged from (+) to (+++) and from (−) to (+), respectively. The degree of Lewy pathology in the paralimbic cortices was strong. The average LB scores in the insular, transentorhinal and cingulate cortices were 3.6, 3.0 and 2.0, respectively (Fig. 1F). The grades of LB-related neurites in the insular and transentorhinal cortices were ranged from (++) to (+++), while those in the cingulate cortex were from (±) to (+++). The average LB scores in the precentral, postcentral and transverse temporal cortices were 1.7, 1.1 and 0.5, respectively. The grades of LB-related neurites in these regions were ranged from (−) to (+++).