A case of concomitant dementia with Lewy bodies and argyrophilic grain disease with prominent psychiatric symptoms

Short running title ：A case of concomitant AGD and DLB

Fields of the journal：BPSD and Non-pharmacological Therapy

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Keywords

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Demented people frequently show behavioral and psychiatric symptoms, including agitation, aggression, depression, anxiety, irritability, disinhibition, hallucination and delusion, which are collectively referred to as behavioral and psychological symptoms of dementia (BPSD). The cases must sometimes be admitted to a psychiatric hospital due to the appearance or exacerbation of BPSD. Furthermore, even after admission, the BPSD affects their quality of life. It is therefore important to clarify the pathophysiology of BPSD and develop an effective treatment. Although the causes of BPSD are considered to be multiple, including biological, psychological and environmental variables, the involvement of pathological changes in the diseased brains is still not clear. Here we report a demented case of concomitant argyrophilic grain disease (AGD) and dementia with Lewy bodies (DLB), who needed admission to the psychiatric hospital because of severe anxiety, agitation and depression, and discuss the association between the distribution of pathological changes and the appearance of such psychiatric symptoms.

An 81-year-old woman complained of chest discomfort, a pounding heart, the feeling of being smothered and anxiety without any physical findings. She was referred to a psychiatrist at the age of 83 and diagnosed as panic disorder. Paroxetine was prescribed but her symptoms remained. She often got agitated and complained of

suicidal thoughts. Since the cognitive decline progressed gradually, she was referred to another psychiatrist in the same year. At first visit, she complained of agitation, palpitation and dyspnea, but denied having hallucinations or delusions. Physical examinations found no neurological symptoms, such as pyramidal signs, extrapyramidal symptoms or autonomic signs. The Mini-Mental State Examination score was 15/30. Brain magnetic resonance imaging showed atrophy of the anterior medial temporal lobe, especially, the right ambient gyrus (Figure 1). Although sertraline 50mg/day and alprazolam 0.8mg/day decreased her anxiety symptoms, her family members still had to watch her all the time, so she was admitted to a psychiatric ward. Her appetite decreased gradually, and she passed away at the age of 85.

Her brain weight was 1200g. Macroscopically, atrophy of bilateral frontal convexity, opercular part of the left frontal lobe, and right dominant anterior medial temporal lobe was observed.

The brain was fixed in 10% formalin. Brain slices were embedded in paraffin, cut into 10-μm-thick sections, and stained with Hematoxylin and Eosin, and by the Klüver-Barrera, methenamine-silver and modified Gallyas-Braak methods. Microscopically, neuronal loss with gliosis was observed in the dorsal nucleus of the vagus nerve, locus coeruleus, substantia nigra, amygdala, basal nucleus of Meynert,

caudate nucleus, putamen, globus pallidus, hippocampus and parahippocampal cortex (Figure 2A). État lacunaire was seen in the caudate nucleus, putamen and globus pallidus, and a small old infarction was observed in the globus pallidus. Lewy bodies were recognized by Hematoxylin and Eosin stain in the dorsal nucleus of the vagus nerve, locus coeruleus, substantia nigra, amygdala, basal nucleus of Meynert, temporal and insular cortex and hippocampal region (Figure 2B-E). The modified Gallyas-Braak stain showed argyrophilic grains, neuropil threads and neurofibrillary tangles in the subiculum, parahippocampal cortex and lateral occipitotemporal cortex (Figure 2F, G). The distribution of argyrophilic grains corresponded to Saito's Stage II, and that of neurofibrillary tangles to Braak stage III of primary age-related tauopathy.

For the immunohistochemical examination, the paraffin-embedded sections were immunostained using an anti-phosphorylated α–synuclein antibody (1175, Dr. Akiyama). The results showed many Lewy bodies and Lewy neurites in the brain stem, basal nucleus of Meynert, amygdala, temporal and insular cortices and hippocampal region (Figure 3H, I). Lewy body score corresponded to the limbic type of DLB. No amyloid plaques were observed by methenamine-silver staining. The pathological diagnosis was co-occurrence of AGD (Saito's stage II), DLB (limbic type), and primary age-related tauopathy.

Clinical features of this case were late onset, gradual progression, prominent psychiatric features, and asymmetrical atrophy in the anterior medial temporal lobe, which meet those of AGD previously reported ‘1’. Clinical diagnosis of DLB may be difficult because of lack of characteristic features such as parkinsonism, visual hallucination and rapid eye movement sleep behavior disorder. Pathologically verified concomitance of AGD and DLB in this case may accelerate the degeneration of the limbic regions including amygdala, since these regions are primarily affected in both diseases. Indeed, severe neuronal loss and massive argyrophilic grains and Lewy bodies were observed in the amygdala (Fig. 2). Since the amygdala plays a key role in regulating emotion, severe degeneration of it caused by concomitant AGD and DLB may exacerbate psychiatric symptoms in this case.

Patients with late-onset dementia tend to have mixed brain pathologies compared to those with early-onset dementia ‘2’. Mixed pathology is more frequent in AGD and Lewy bodies disease, compared to Alzheimer’s disease ‘2’. Based on the pathological study, the frequency of DLB is known to be about 20%, which is second only to Alzheimer’s disease. Although clinical diagnostic criteria of AGD has not yet been established, its frequency is said to be 8.5% ‘1’. Considering this, we should always keep in mind the possibility of the co-occurrence of DLB and AGD when making a

diagnosis of senile dementia cases with severe psychiatric symptoms. In such cases, atrophy and hypoperfusion of the ambient gyrus revealed by neuroimaging might be useful for clinical diagnosis of AGD.

Moreover, we should keep in mind that TAR-DNA binding protein 43 (TDP-43) pathology frequently occurs concomitantly with DLB or AGD. For instance, TDP-43 pathology was reported to appear in 16-22% of Lewy body disease ‘3’ or 53-60% of DLB in which about 20–30% showed neocortical TDP-43 pathology resembling the frontotemporal lobar degeneration with TDP-43 inclusions ‘4’. In AGD, 60% of cases show TDP-43 pathology mainly in the limbic regions and lateral occipitotemporal cortex ‘5’. Cases of AGD with TDP-43 pathology are assigned to higher AGD stages than those without TDP-43 pathology, and TDP-43 pathology tends to be prominent in cases with severe grain pathology.

The results of the present study and these previous findings suggest that major proteins to cause neurodegeneration, especially tau, α-synuclein and TDP-43, tend to concomitantly accumulate in brains of older adults and modify the clinical presentations of diseases. The limitation of this study is lack of analysis of TDP-43 pathology since it is sometimes combined with Lewy body pathology or grain pathology. Although it is difficult to know the existence or non-existence and the degree of the concomitance of

accumulation of these proteins clinically, prominent psychiatric symptoms in dementia cases may be one of the factors to remind us of such concomitant pathology especially in the limbic regions. Development of positron emission tomography imaging targeting these proteins may help make diagnoses of these cases in the near future.

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Disclosure statement

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References

1. Togo T, Isojima D, Akatsu H, *et al.* Clinical features of argyrophilic grain disease: a retrospective survey of cases with neuropsychiatric symptoms. *Am J Geriatr Psychiatry* 2005;**13**: 1083–1091.

2. Kovacs GG, Alafuzoff I, Al-Sarraj S, *et al*. Mixed brain pathologies in dementia: the BrainNet Europe consortium experience. *Dement Geriatr Cogn Disord* 2008; **26**: 343–350.

3. Robinson J, Lee E, Xie S, *et al.* Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. *Brain* 2018; **141**: 2181–2193.

4. Arai T, Mackenzie I, Hasegawa M, *et al.* Phosphorylated TDP-43 in Alzheimer's disease and dementia with Lewy bodies. *Acta Neuropathologica* 2009; **117**: 125-136

5. Fujishiro H, Uchikado H, Arai T, *et al.* Accumulation of phosphorylated TDP-43 in brains of patients with argyrophilic grain disease. *Acta Neuropathologica* 2009; **117**: 151-158

Figure Legends

Figure 1

Brain magnetic resonance image showed atrophy of the anterior medial temporal lobe, especially of the right ambient gyrus (arrow).

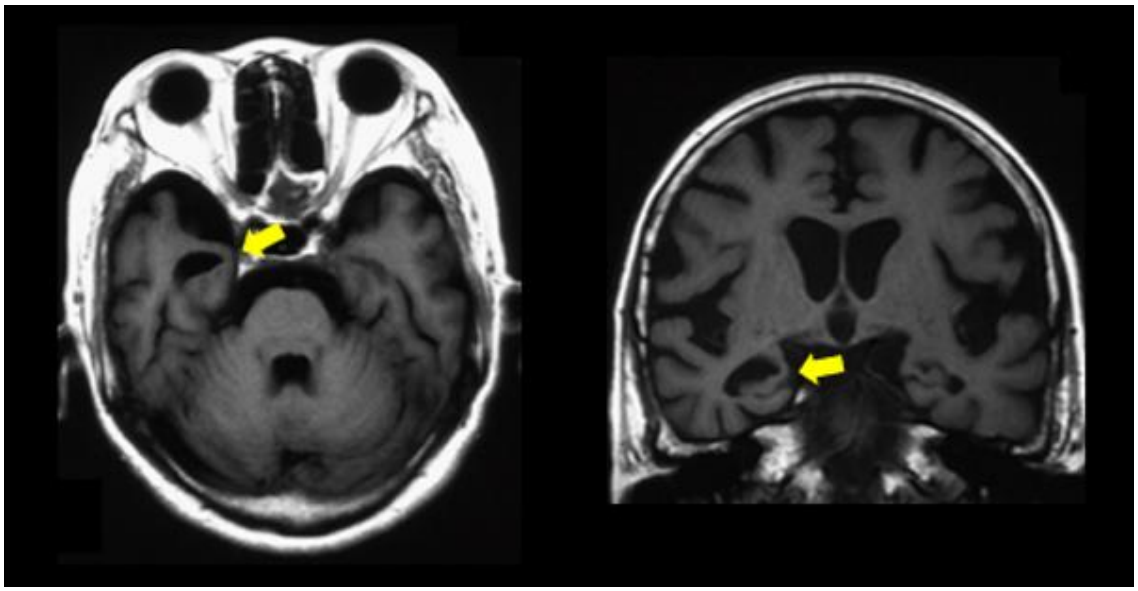


Figure 2

Neuropathological findings.

A. Mild neuronal loss in the substantia nigra. Klüver-Barrera staining.

B. Severe neuronal loss with gliosis and Lewy bodies (arrows) in the amygdala. Hematoxylin and Eosin (HE) staining.

C. Lewy body in the locus coeruleus. HE staining.

D. Lewy body in the dorsal nucleus of the vagus nerve. HE staining.

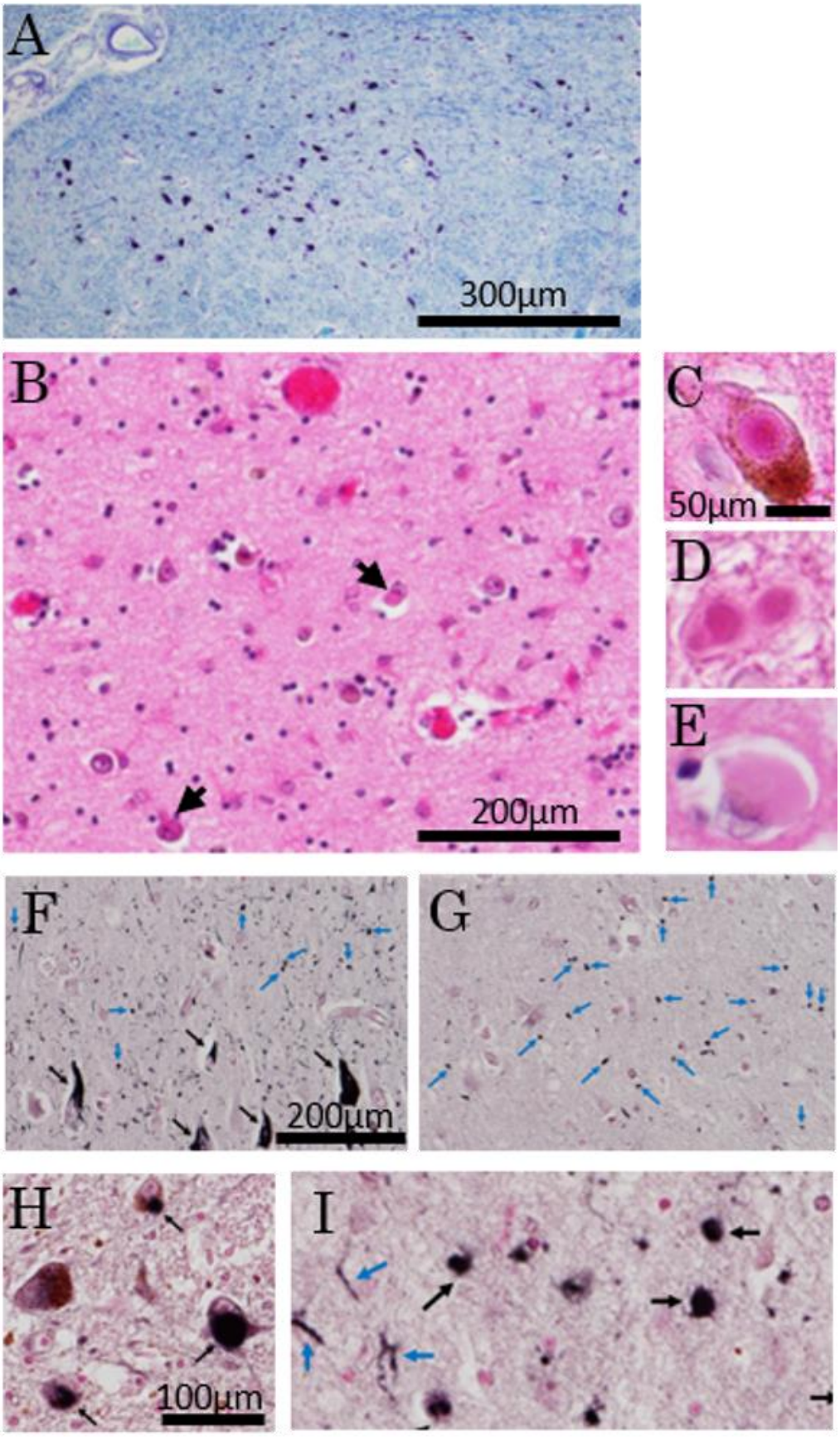
E. Lewy body in the insular cortex. HE staining.

F. Massive argyrophilic grains (blue arrows) and some neurofibrillary tangles (black arrows) in the subiculum. Modified Gallyas-Braak staining.

G. Argyrophilic grains (arrows) in lateral occipitotemporal cortex. Modified Gallyas-Braak staining.

H. Lewy bodies (black arrows) and Lewy neurites (blue arrows) in the substantia nigra. Phosphorylated α-synuclein immunohistochemistry.

I. Lewy bodies in the basal nucleus of Meynert (black arrow). Phosphorylated α-synuclein immunohistochemistry.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