

## Original Article

## Neurodegenerative changes in patients with clinical history of bipolar disorders

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**Neurodegeneration in bipolar disorder (BPD) is poorly understood. Therefore, the current study was designed to assess the immunohistochemical changes in neurodegenerative markers in patients with BPD. Eleven consecutive autopsy cases diagnosed with BPD were analyzed. Sections were obtained from archival paraffin blocks of representative areas and stained using conventional methods, as well as immunostained with several antibodies to screen for neurodegenerative diseases. Age- and non-argyrophilic grains (AGs) degeneration matched controls were selected for each case. Clinical information was retrospectively collected from medical charts. All patients were men, and the average age of death was 70 years. Neuropathological diagnoses included dementia with grains (2), argyrophilic grain disease (2), corticobasal degeneration (CBD, 1), Lewy body disease (1), hypoxic encephalopathy (1) and cerebral infarction (1). All cases showed AGs to various degrees. Three patients died in their 50s; one demonstrated dementia with Lewy bodies, while the other two showed abundant AGs in the thalamus and amygdala. Of the three patients who died in their 60s, one showed AGs preferentially in the thalamus and amygdala, while the others demonstrated limbic predominance. The**

**patients who died in/after their 70s demonstrated AGs similar to controls, except for the patient with CBD. Our data provides potentiality that neurodegenerative diseases may be an underlying pathology in certain cases of BPD.**

**Key words:** argyrophilic grain, chronic traumatic encephalopathy, lithium carbonate, mood disorder, tau.

## INTRODUCTION

Bipolar disorder (BPD) is an endogenous psychiatric disease that involves the repetition of manic and depressive states,<sup>1</sup> and has a lifetime prevalence of 0.8–2.6%.<sup>2</sup> BPD is treated with various medications, including lithium carbonate, which has been shown to be an effective mood stabilizer. Over the past half century, lithium carbonate has been used as a prophylactic treatment with both antimanic and antidepressant effects,<sup>3</sup> most likely due to its multiple biochemical and biological effects. Several mechanisms of action have been proposed for lithium carbonate, including inhibition of glycogen synthase kinase-3 beta (GSK-3 $\beta$ ),<sup>4</sup> 5-HT<sub>1B</sub> serotonin receptor binding,<sup>5</sup> modulation of glutamate uptake and release,<sup>6</sup> and induction of Bcl-2, a neuroprotective protein.<sup>7</sup> Among these, GSK-3 $\beta$  is a tau protein kinase.<sup>8</sup> Several lines of evidence indicate that BPD could be a circadian rhythm disorder mediated by a GSK-3 $\beta$  abnormality. For example, transgenic mice overexpressing GSK-3 $\beta$  exhibit hyperactivity.<sup>9</sup> In addition, *Drosophila* overexpressing GSK-3 $\beta$  demonstrate a shortened circadian cycle that can be extended by lithium.<sup>10</sup> Lastly, the symptoms of BPD are thought to be associated with circadian rhythm disruptions. Cell culture studies have also shown that the action of GSK-3 $\beta$  is suppressed by lithium. Lithium inhibits the phosphorylation of tau, promotes the binding of tau with microtubules, and eventually promotes microtubule aggregation.<sup>11</sup> This would suggest

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that pathological tau metabolism may have a role in the etiology of BPD.

Diseases with neuropsychiatric symptoms caused by the accumulation of abnormally phosphorylated tau are generally called tauopathies. One of these, dementia with grains (DG), was recognized as an independent disease relatively recently, thanks to the development of methods such as Gallyas-Braak staining. DG was first reported by Braak *et al.* in 1987.<sup>12</sup> It is characterized by the appearance of argyrophilic grains (AGs) in the neuropil of the limbic system gray matter and in oligodendroglia-derived coiled bodies in the white matter. The pathological significance of these structures has since been elucidated by the discovery that they are composed of phosphorylated tau<sup>13</sup> and deposits of 4-repeat tau, which can bind four microtubules.<sup>14</sup> At present, cases tend to be labeled as DG when dementia is caused solely by AGs, while cases are labeled argyrophilic grain disease (AGD) if pathological AGs are observed. However, with the latter, no clear connection to dementia has been established. The clinical symptoms of AGD are characterized by comparatively well preserved cognitive functions, but prominent psychiatric symptoms.<sup>15</sup> In addition, another tauopathy, chronic traumatic encephalopathy (CTE), a disease that is caused by repeated brain trauma and has received attention in recent years, shows psychiatric symptoms such as irritability, impulsiveness, depressive states and memory disorders, which are thought to appear 8–10 years after the actual trauma.<sup>16</sup> Neuropathological findings of CTE include atrophy of the cerebral cortex, medial temporal lobe, diencephalon, and mammillary body, as well as deposits of phosphorylated tau and phosphorylated transactive response DNA binding protein 43 kDa (TDP-43) over a wide area. In particular, phosphorylated tau is found throughout the frontotemporal lobe, limbic system and brainstem. These findings suggest a connection between diseases with prominent psychiatric symptoms and pathological tau metabolism.

In the current study, an immunohistological examination was performed on archival tissue specimens of patients who had previously been clinically diagnosed with BPD in order to clarify the relationship between BPD and neurodegenerative diseases, particularly AGD.

## MATERIALS AND METHODS

### Tissue source

From the cases registered at our brain bank networks (the Brain Bank for Aging Research (BBAR) and Research Resource Network (RRN)), we selected 11 consecutive autopsy cases that had been diagnosed with BPD. The controls included 1240 consecutive cases (ages 48–104

(mean  $\pm$  SD, 80.6  $\pm$  8.9) years; men : women, 662:578) registered to the BBAR and 164 consecutive autopsy cases under the age of 65 (ages 0–64 (45.0  $\pm$  20.2 years); men : women, 101:63) from the Yokohama Rosai Hospital, a community-based hospital in the BBAR network.<sup>17</sup> The study was approved by the Institutional Review Board of the National Center of Neurology and Psychiatry (NCNP).

### Clinical information

Clinical diagnosis of BPD followed the “Diagnostic and Statistical Manual, 4th Edition-Text Revision” (DSM-IV-TR) with retrospective analysis of each medical chart. Eight cases were classified to have had Bipolar I Disorder (cases 1, 2, 3, 4, 5, 6, 8 and 9) and the other three case were unclassifiable (cases 7, 10 and 11). The history of medication and cognitive function was also studied, and the Mini-Mental State Examination (MMSE)<sup>18</sup> was used as an index of cognitive function.

### Neuropathology

The brains of cases 4, 5, 7, 9, 10 and 11 and all of the control cases from the BBAR were prepared with the BBAR protocol as previously reported.<sup>19</sup> Briefly, one side of each brain was frozen for biochemical and molecular biological studies, while the other side was used for pathological studies. At the time of autopsy, 7-mm coronal sections of one side of the cerebrum were obtained for freezing. In addition, 5-mm axial slices were obtained from the brainstem and 5-mm sagittal slices were obtained from the cerebellum. Representative areas from the frozen side, including the amygdala, hippocampus, midbrain, motor cortex, frontal cortex, temporal pole, parietal lobe and occipital pole, were then fixed for 48 h in 4% paraformaldehyde and subsequently embedded in paraffin. The other side of the brain was fixed in 20% neutral formalin for 7–13 days and sliced in the same manner as the opposite side. The representative areas were then embedded in paraffin. For Case 1, parts of one side of the brain (frontal, temporal and occipital lobes) were freeze-fixed, and the remaining tissue was post-fixed for approximately 1 year in acidic formalin. For cases 2, 3 and 6, the entire brain was fixed in acidic formalin for approximately 4 months, 20 days and 50 days, respectively. For case 8, the entire brain was fixed for approximately 11 days in neutral formalin. After fixation, the brains were sliced as described above and the representative areas embedded in paraffin. The control brains from the community-based hospital followed the BBAR protocol, skipping the recovery of frozen tissue. For this study, the following regions were intensively analyzed: the medulla oblongata, pons, midbrain, cerebellum, amygdala, hippocampus, thalamus, basal nucleus of Meynert and cerebral neocortex (frontal, temporal, parietal and occipital

lobes). Slices were cut at a thickness of 6  $\mu\text{m}$  and stained with HE or KB stain, or were silver-impregnated using the Gallyas-Braak method on all of the sections.

### Immunohistochemistry

Immunostaining was performed with an automated immunostainer (Ventana XT DISCOVERY; Ventana, Tucson, AZ, USA). As described in detail previously,<sup>20</sup> the antibodies used included anti-phosphorylated tau (ptau; AT8, monoclonal; Innogenetics, Temse, Belgium), 3-repeat/4-repeat tau-specific (RD3/RD4, Upstate, Lake Placid, NY, USA), anti-phosphorylated  $\alpha$ -synuclein (psyn; monoclonal; Psyn#64, WAKO, Osaka, Japan), anti-amyloid- $\beta$  ( $A\beta$ ) (12B2, monoclonal; IBL, Maebashi, Japan), and anti-phosphorylated TDP-43 antibodies (pS409/410-2, polyclonal; COSMO BIO CO., LTD, Tokyo, Japan). Anti-phosphorylated tau immunostaining was performed on all areas. For the other forms of immunostaining, the BBAR protocols<sup>17</sup> were followed.

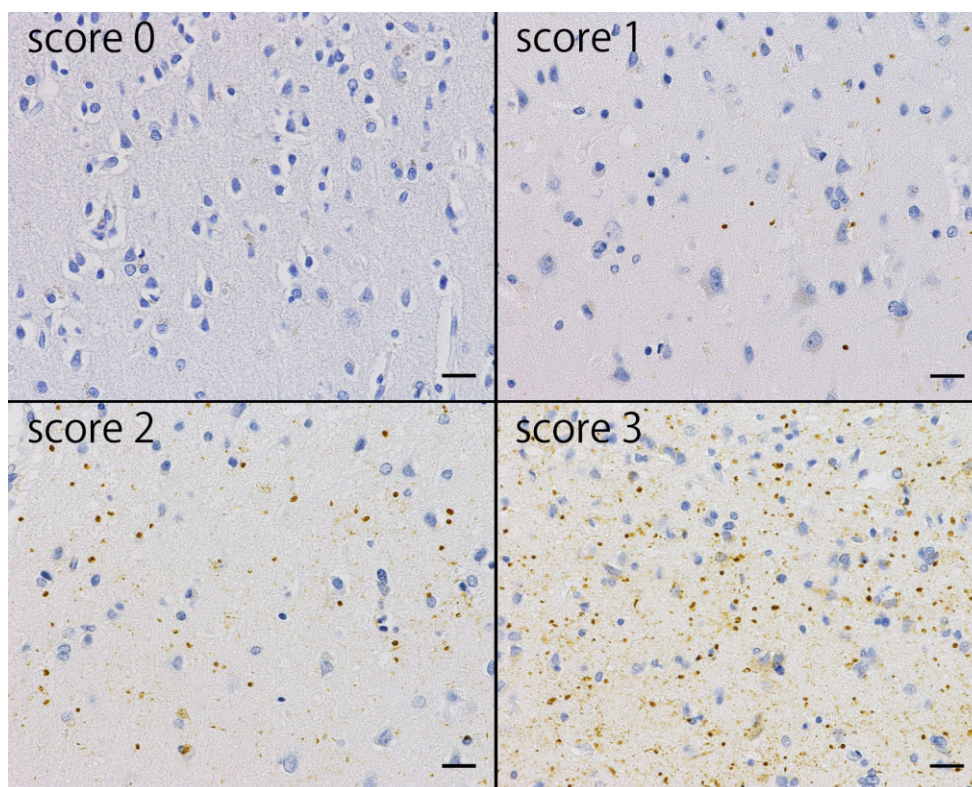
### Neuropathological diagnosis

AGs were classified into four stages based on Saito's staging.<sup>17</sup> Neurofibrillary tangles (NFTs) were classified

into seven stages (0–6), and senile plaques into four stages (0 and A–C), based on Braak's staging.<sup>21</sup> Lewy body pathology was diagnosed based on the dementia with Lewy bodies (DLB) consensus guideline – revised (DLBCG-R).<sup>22</sup> Amyloid angiopathy was diagnosed based on BBAR (<http://www.mci.gr.jp/BrainBank/index.cgi>) staging.<sup>23</sup> The original stages (none, A, B and C) were converted to 0, 1, 2 and 3 for quantitative analysis. Diagnosis of corticobasal degeneration was based on National Institutes of Health criteria.<sup>24</sup>

### Argyrophilic grain examination

The AG density for all BPD cases was semi-quantified. Specifically, the representative areas were immunostained with anti-phosphorylated tau and the field of view (FOV) with the greatest number of AGs at 200 $\times$  magnification was semi-quantified (score 0 = no AGs; 1 = 1–30 AGs/200 $\times$  FOV; 2 = 31–60 AGs/200 $\times$  FOV; 3  $\geq$  61 AGs/200 $\times$  FOV) (Fig. 1). Cases were extracted from the control group that largely matched these cases in age and non-AG senile degeneration (NFTs, senile plaques, Lewy body pathology and amyloid angiopathy). The AG density of these cases was also semi-quantified as described above.



**Fig. 1** Semi-quantification of argyrophilic grains (AGs). AT8 staining and high-power fields (HPF; generally 200 $\times$ ) were used to measure AG density. Score 0 is the absence of AGs. Score 1 is 1–30 AGs/HPF, score 2 is 31–60 AGs/HPF, and score 3 is  $\geq$  61 AGs/HPF. Bar = 20  $\mu\text{m}$ .

## RESULTS

### Clinical information

Table 1 provides the detailed clinical information of the 11 BPD patients. The age of onset of BPD ranged from 22–56 years (mean  $\pm$  SD =  $41.8 \pm 12.6$  years), age at death from 52–90 years ( $70.3 \pm 12.9$  years) and disease duration from 13–34 years ( $27.2 \pm 7.1$  years). All of the patients were male. Three cases (cases 2, 5, 6) had violent behavior episodes in their manic phase, and three cases (cases 3, 8, 10) had hallucinations and delusional episodes. Regarding other diseases, case 2 was diagnosed with diabetes mellitus, case 3 with and convulsive seizures, cases 4 and 9 with malignant lymphoma, case 5 with alcoholic liver cirrhosis and alcohol dependency, case 6 with bronchial ectasia, case 8 with corticobasal syndrome, and case 11 with atrioventricular blockage. Cognitive impairment, including mild forms, was observed in four cases (cases 1, 5, 8 and 11) (36.4%). Five cases (cases 2, 4, 5, 7 and 8) had taken lithium carbonate for BPD, five had taken antipsychotic drugs (cases 2, 3, 4, 5 and 8), and five had taken antidepressant drugs (cases 2, 3, 4, 5 and 9). Three of the cases which had parkinsonism (cases 3, 7 and 10) and one case, which received diagnosis of corticobasal syndrome (case 8), had taken levodopa and other antiparkinsonian drugs.

### Neuropathology

Table 2 summarizes the neuropathological findings. Four cases presented Stage III AG, two of whom had a history of cognitive decline (DG) and two without a description of dementia (AGD). One case each fulfilled the diagnostic criteria of Lewy body disease (corresponding to the limbic form in the DLB consensus guidelines),<sup>22</sup> corticobasal degeneration, hypoxic encephalopathy and cerebral infarction. Three cases did not fulfill any diagnostic criteria, including one case with incidental Lewy body disease (Figs 2 and 3). Except for the case of hypoxic encephalopathy (652 g brain weight), brain weights ranged from 1160–1470 g. Alzheimer changes were relatively mild: Braak's NFT<sup>21</sup> Stage being I–II (mean  $\pm$  SD =  $1.5 \pm 0.5$ ) and senile plaque (SP) stage 0–A ( $0.5 \pm 0.5$ ). The pathology of corticobasal degeneration was indistinguishable from the pathology of patients without a history of BPD.

### Argyrophilic grains

AGs were observed in all 11 cases, with a mean stage<sup>17</sup> of 2.1 (Stage 0.5: two cases (18.2%); Stage I: one case (9.1%); Stage II: three cases (27.3%); and Stage III: five cases (45.5%)). In the control group, 68.2% (958 individuals)

**Table 1** Clinical profile of each case with bipolar disorder (BPD)

Case	Age at death (years)	Age at onset (years)	Sex	Mental manifestation	Comorbidity other than bipolar disorder	Cognitive impairment	MMSE	Lithium carbonate treatment duration	Antipsychotic or antidepressant treatment	
									Antipsychotic	Antidepressant
1	52	22	M	Manic, depressive	Hypoxic encephalopathy, after suffocation	Yes	ND	ND	ND	ND
2	52	34	M	Manic, depressive, violent	Diabetes mellitus	ND	ND	Over 7 years	(+)	(+)
3	58	28	M	Manic, depressive, hallucination	Parkinsonism, seizure	ND	ND	ND	(+)	(+)
4	67	33	M	Manic, depressive	Malignant lymphoma, diabetes mellitus	ND	ND	Over 1 year	(+)	(+)
5	68	45	M	Manic, depressive, violent	Alcohol abuse, alcoholic liver cirrhosis	Yes	22 points (63 years)	5 years	(+)	(+)
6	69	56	M	Manic, depressive, violent	Bronchial ectasia	ND	ND	ND	ND	ND
7	71	38	M	Manic, depressive	Heavy use of alcohol, parkinsonism	ND	ND	Over 1 year	ND	ND
8	79	50	M	Manic, depressive, hallucination	Corticobasal syndrome	Yes	24 points (76 years)	2 years	(+)	ND
9	83	Young age	M	Depressive main	Malignant lymphoma	ND	ND	ND	ND	(+)
10	84	56	M	Manic, depressive, delusion	Parkinsonism	ND	ND	ND	ND	ND
11	90	56	M	Depressive main	AV block	Yes	12 points (87 years)	ND	ND	ND

AV, atrioventricular; M, male; ND, not described; MMSE, Mini-Mental State Examination.

**Table 2** Summary of neuropathological findings

Case	Age at death (left)/duration of disease (right) (years)	Neuropathologic diagnosis	Brain weight (g)	Argyrophilic grain stage <sup>17</sup>	NFT stage <sup>21</sup>	Lewy body stage <sup>22</sup>	Senile plaque stage <sup>21</sup>	Amyloid angiopathy stage <sup>23</sup>
1	52 / 30	Hypoxia	652	II	I	None	None	None
2	52 / 18	Argyrophilic grain disease	1,430	III	I	None	A	None
3	58 / 30	Lewy body disease	1,470	0.5	I	Limbic	None	1A
4	67 / 34	Unremarkable	1,325	II	II	None	None	None
5	68 / 23	Dementia with grains	1,116	III	I	None	A	None
6	69 / 13	Unremarkable	ND	II	II	None	None	None
7	71 / 33	Unremarkable	1,360	0.5	I	Incidental	A	1C
8	79 / 29	Corticobasal degeneration, argyrophilic grain disease	1,266	III	II	None	None	None
9	83 / -	Acute cerebral infarction	1,458	I	I	None	None	1A
10	84 / 28	Argyrophilic grain disease	1,300	III	II	None	A	1A
11	90 / 34	Dementia with grains	1,160	III	II	None	A	None

ND, not described.

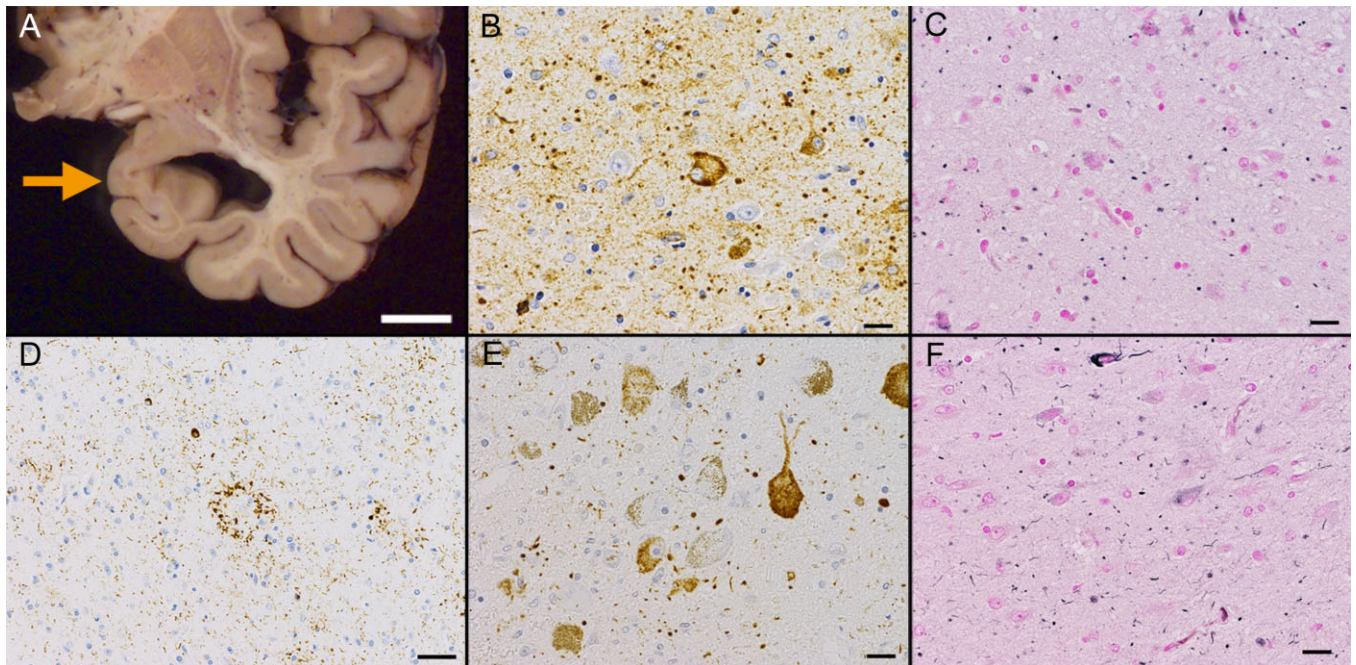
belonged to Stage 0, 0.1% (two individuals) to Stage 0.5, 16.4% (230 individuals) to Stage I, 8.1% (114 individuals) to Stage II and 7.1% (100 individuals) to Stage III in both genders. Among the male gender, 72.1% (550 individuals) belonged to Stage 0, 15.3% (117 individuals) to Stage I, 6.0% (46 individuals) to Stage II, and 6.6% (50 individuals) to stage III. The incidence and extent of AG appeared to be more severe in the BPD group than in the control group, although the number of cases in the BPD was too small for statistical analysis. The youngest case in the BPD group was 52 years old (at the time of death) with an AG of Stage III, which was definitely more severe than the Stage I of the youngest brain with AGs at 56 years of age in the control group. We selected 4–7 cases of each decade with similar NFT and SP stage and semi-quantified for AGs using the method described in the “Materials and Methods” section (Fig. 1). The detail of the control cases were as follows: five cases for 50 control cases (death age  $56.0 \pm 1.9$  years old), seven cases (death age  $66.7 \pm 2.9$  years old) for 60 control cases, and four case (death age  $84.3 \pm 1.0$  years old) for more than 70 control cases. The patients who died in their 50s (cases 1 and 2) and had BPD onset in their 20s and 30s, respectively, tended to have higher AG density than the control group. Case 2, in particular, showed a prominent presence of AGs in the limbic system, including the hippocampus proper, subiculum, amygdala and anterior thalamic nucleus, as well as the locus coeruleus. Among the patients who died in their 60s (cases 4, 5 and 6), case 5 presented the similar unique distribution of AGs, while cases 4 and 6 followed the usual distribution, but had more dense AG deposition compared with the control group. The patients who died above the age of 70 also presented the latter pattern. There was no apparent difference between cases that were administered lithium and those that were not (Fig. 4).

### Corticobasal degeneration (CBD)

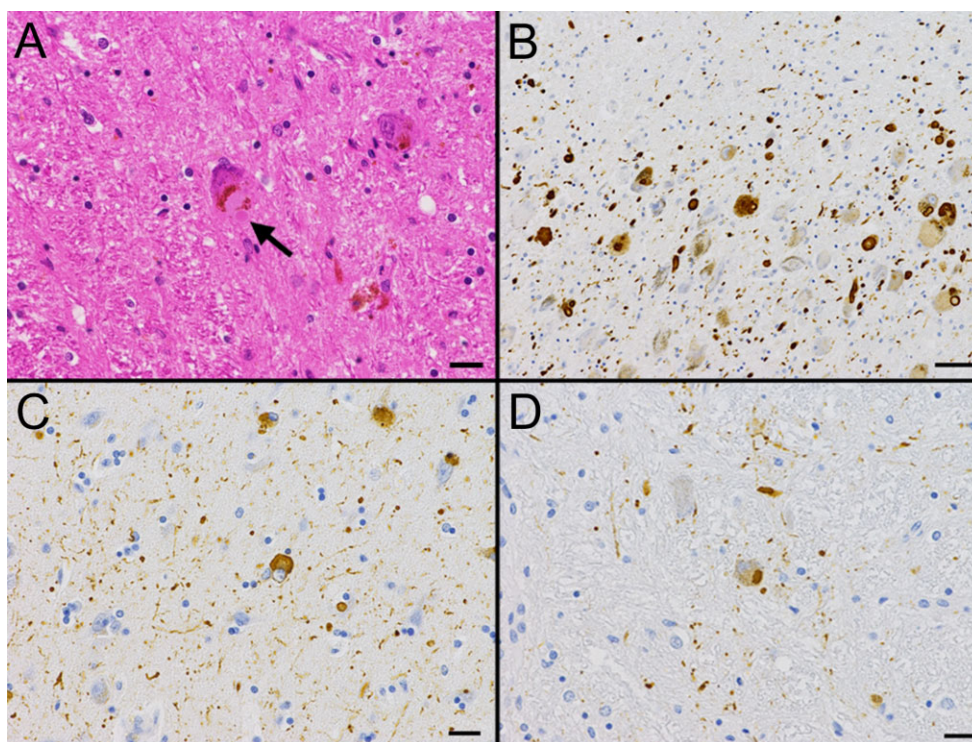
Neuropathological diagnosis of CBD was reached in a manner blind to this research project. Distribution of tauopathy is typical for CBD and could not point out any unique features.

### Lewy body-related $\alpha$ -synucleinopathy

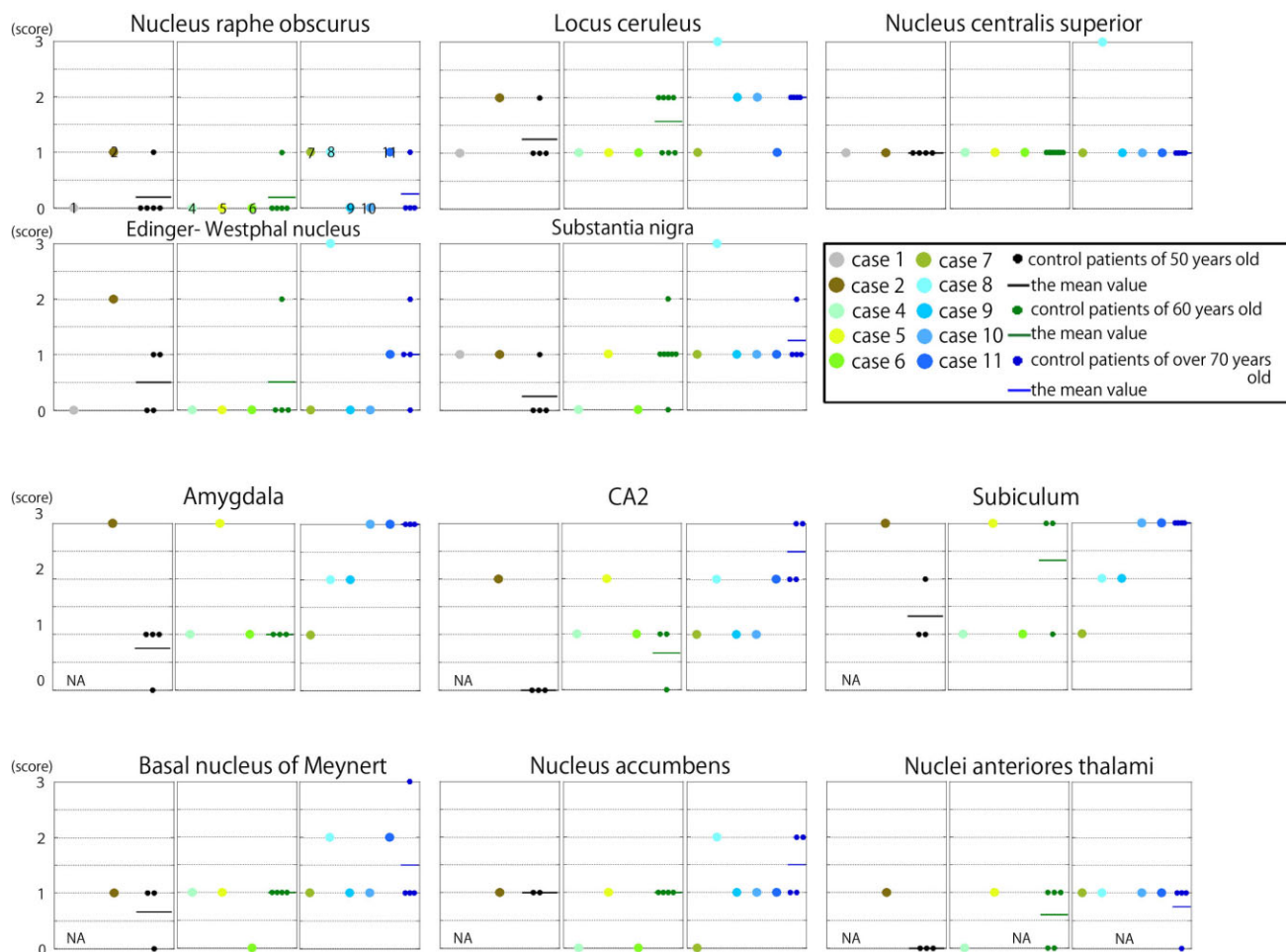
Case 3 exhibited limbic-type Lewy body pathology according to Dementia with Lewy Bodies Consensus Guidelines – Revised (DLBCG-R).<sup>22</sup> Lewy bodies and Lewy neurites were scattered in the brainstem, including the dorsal motor nucleus of the vagus nerve, locus coeruleus and substantia nigra. There was a heavy burden of phosphorylated  $\alpha$ -synuclein-immunoreactive structures in the amygdala, corpus striatum and hypothalamus. In the neocortex and hippocampus, Lewy body pathology was minimal.



**Fig. 2** Case 11 (argyrophilic grain disease: AGD) and case 8 (corticobasal degeneration and AGD). A, B, C. Case 11 (AGD). A. Macroscopic observation confirmed prominent atrophy of the ambient gyrus and amygdala (arrow) (bar = 10 mm). B. Histopathology of the amygdala showing many AGs, accompanied by ballooned neurons and pre-tangles (AT8 immunostaining, bar = 20  $\mu$ m). C. The medial temporal lobe contained many AGs (Gallyas-Braak (GB) staining, bar = 20  $\mu$ m). D, E, F. Case 8 (corticobasal degeneration and DG). D. The precentral gyrus had an astrocytic plaque (AT8 immunostaining, bar = 50  $\mu$ m). E. The locus coeruleus had abundant AGs with pre-tangles and neurofibrillary tangles (NFTs) (AT8 immunostaining, bar = 20  $\mu$ m). F. Amygdala had many AGs (GB staining, bar = 20  $\mu$ m).



**Fig. 3** Case 3 (Lewy body disease). A. Substantia nigra: a brainstem-type Lewy body (arrow) accompanied by melanophages and free melanin (HE staining, bar = 20  $\mu$ m). B. Locus coeruleus. C. Amygdala. D. Nucleus raphe obscurus: Lewy bodies and dots were present (pSyn#64 immunostaining, Bar = 50  $\mu$ m (B), bar = 20  $\mu$ m (C, D)).



**Fig. 4** A comparison of the semi-quantified density of argyrophilic grains (AG) in cases of bipolar disorder (BPD) and age-matched controls with similar Alzheimer pathology. Case 1 had superimposed hypoxic encephalopathy and only the brainstem was evaluated. Compared to the controls, patients who died in their 50s exhibited higher AG density in the amygdala, hippocampus proper, subiculum, Edinger-Westphal nucleus, locus ceruleus and anterior thalamic nucleus. Of the cases with death in their 60s, case 5 exhibited AG density and distribution similar to that of patients who died in 50s, while cases 4 and 6 showed distribution patterns similar to that of age-matched controls, as did the cases with death in their 70s. NA: not available.

### DISCUSSION

This study is the first to demonstrate the neurodegenerative outcome of some cases in bipolar disorder, including argyrophilic grain-type tauopathy and Lewy body-related alpha-synucleinopathy.

AG was present in all our cases. The distribution of AG in the younger group was unique. In the older group except case 8 with a diagnosis of CBD and AGD, AG distribution was similar to that observed in the control group, but the staging was higher. Our observation may be consistent with those of Nagao *et al.*<sup>25</sup> who reported an association of AG with late-onset schizophrenia and delusional disorders (LOSD).

A group of patients with BPD who died in their 50s and 60s exhibited a heavy burden of AGs in the amygdala, thalamus and locus coeruleus, which did not follow Saito’s

extension paradigm.<sup>17</sup> In this group, we could not find patterns of chronic traumatic encephalopathy (CTE) associated with neocortical NFTs, which does not follow Braak’s extension paradigm. Instead, our observation of a unique distribution of AG-type tauopathy (as observed in patients with BPD who died at a younger age) could suggest that these anatomical sites are involved in AG formation during aging. Alternatively, the mere presence of AGs may contribute to the psychiatric symptoms.

It is also worthy to comment that one case who received diagnosis of BPD later developed into CBD. It is difficult to deny the possibility of coincidence, but further accumulation of cases may be indicative.

In the current study, Lewy body pathology was observed in two cases in the BPD group, with one case corresponding to the DLBCG-R<sup>22</sup> limbic stage. Although depression is regarded as one of the prodromal symptoms of Lewy body

dementia,<sup>26</sup> the very small number of neuropathological reports of patients with BPD<sup>25,27</sup> prevent any definitive conclusions.

We could not determine the effect of lithium carbonate on the neurodegenerative outcome, partly due to the small number of cases as well as the retrospective manner of our study design. Studies that are currently in progress include positron emission tomography imaging for amyloid and tau as well as alpha-synuclein imaging. Although the CSF biomarkers utilized in the diagnosis of Alzheimer's disease may be difficult to apply to BPD, our study indicates that BPD could be a potential target for these imaging studies.

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