Neuropathologic Features of Suicide Victims Who Presented With Acute Poststroke Depression: Significance of Association With Neurodegenerative Disorders

Naoki Nishida, MD, PhD, Yukiko Hata, PhD, Koji Yoshida, MD, and Koshi Kinoshita, PhD

Abstract
To investigate the neuropathologic characteristics of poststroke depression (PSD) leading to suicide, we retrospectively selected deceased subjects who had been diagnosed as having early PSD. Cases were divided into subjects who had committed suicide and those who had not. Neuropathologic examinations, including immunohistochemistry, were conducted. Twenty-four subjects fulfilled criteria for early PSD; 11 of these had committed suicide, and the other 13 had not. Lesion type, size of stroke, and location of stroke were variable but did not differ significantly between the groups. Alzheimer disease–related pathology stages also did not differ between the groups. Argyrophilic grain disease was found in both the suicide group (6 of 11) and the nonsuicide group (2 of 13); there were 2 highly possible cases of early progressive supranuclear palsy in the suicide group. Together, argyrophilic grain disease and progressive supranuclear palsy were found significantly more frequently in suicide cases than in nonsuicide cases (p = 0.01). These data suggest that overlapping 4-repeat tauopathies, which include argyrophilic grain disease and progressive supranuclear palsy, might be an important aggravating factor of PSD that could lead to suicide. The presence of other neurodegenerative diseases does not preclude PSD because the prevalence of these diseases in older persons suggests that they might often occur concomitantly.

Key Words: Argyrophilic grain disease, Neurodegenerative disease, Poststroke depression, Progressive supranuclear palsy, Suicide.

INTRODUCTION
Psychiatric disorders such as depression are important risk factors for late-life suicide (1). Poststroke depression (PSD) is a special condition that may serve as a hallmark of late-life mood disorders (2). Poststroke depression is classified as “early phase” when depression occurs within 3 months of the stroke and as “late phase” when symptoms appear more than 3 months after the stroke (3). Fuller-Thomson et al (4) showed that stroke survivors had twice the odds of depression and suicidal ideation than persons without stroke, and Santos et al (5) reported that 15% of patients with acute stroke present with suicidal thoughts. Risk factors for suicidal thoughts and suicide attempts after stroke have been variously reported to be younger age, alcohol abuse, anterior lesion, poor social support, and sensory or cognitive deficits (6), as well as previous mood disorder, lower education level, and depressive symptoms (5). Although organic lesions relevant to stroke might affect the occurrence of PSD and related suicide (7), no autopsy study of such cases has been conducted thus far.

Patients with various neurodegenerative diseases other than vascular disorders, such as Alzheimer disease (AD) (8), Lewy body–related disease (LBD) (9), progressive supranuclear palsy (PSP) (10), corticobasal degeneration (CBD) (11), argyrophilic grain disease (AGD) (12), and TAR DNA-binding protein 43 (TDP-43) proteinopathy (13), also present with depression and other psychiatric symptoms. Few neuropathologic examinations have focused on the correlation between PSD and neurodegenerative diseases, but understanding this correlation may be useful for preventing suicide caused by late-onset depression.

To identify risk factors for PSD-related suicide, we retrospectively reviewed forensic autopsies on the brains of patients who had committed suicide after an antemortem diagnosis of early PSD. We compared the findings with those from autopsies of subjects with PSD who had not died of suicide. The findings included vascular and neurodegenerative lesions in both patient groups.

MATERIALS AND METHODS
Case Selection
We reviewed the archives of 1,042 serial medicolegal autopsies performed in our department between 2006 and 2013. The clinical histories of all of the subjects were obtained from the families and records of police examinations, and all available medical records were provided by primary physicians. We identified subjects as having had early PSD if: 1) the onset of stroke and the onset of depression were recorded by a neurologist or psychologist, and a diagnosis of depression was made following International Classification of Diseases, Tenth Revision (14) or Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (15) criteria; 2) the first episode of
depression occurred within 3 months of the stroke; and 3) there was no history of dementia, psychologic disorder, or suicide attempt before the stroke. The final judgment of suicide was made by reference to police reports that included information gathered from family and medical records in the hospital, in addition to autopsy findings. Control subjects fulfilled the criteria for PSD but died of causes other than suicide. In all cases, age, sex, onset of depression after onset of stroke, and presence or absence of hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, and atrial fibrillation were noted. Severity of depression was divided into 3 categories (i.e. mild, moderate, and severe) based on both medical records

TABLE 1. Case Profiles and Autopsy Findings for Suicide Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Type of Stroke</th>
<th>Int St-D (days)</th>
<th>Int St-Sc</th>
<th>MCI</th>
<th>Other Neuropathology</th>
<th>Other Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>F</td>
<td>Rt MCA (M1) infarct</td>
<td>36</td>
<td>2 years</td>
<td>−</td>
<td>Aβ 2, CERAD B, Braak 3</td>
<td>HT, DM, Afib</td>
</tr>
<tr>
<td>2</td>
<td>93</td>
<td>F</td>
<td>Rt temporal WM hemorrhage</td>
<td>16</td>
<td>6 months</td>
<td>−</td>
<td>Aβ 2, CERAD C, Braak 2, AGD grade 3</td>
<td>HT</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>F</td>
<td>MLTI (Rt putamen, Lt thalamus and caudate)</td>
<td>28</td>
<td>7 years</td>
<td>+</td>
<td>AGD grade 2</td>
<td>HT</td>
</tr>
<tr>
<td>4</td>
<td>94</td>
<td>M</td>
<td>MLTI (both thalami and Rt putamen)</td>
<td>62</td>
<td>3 months</td>
<td>+</td>
<td>Aβ 1, CERAD B</td>
<td>HT</td>
</tr>
<tr>
<td>5</td>
<td>86</td>
<td>M</td>
<td>Rt posterior WM hemorrhage</td>
<td>15</td>
<td>4 months</td>
<td>−</td>
<td>Aβ 1, CERAD A, Braak 3, AGD grade 2</td>
<td>HT</td>
</tr>
<tr>
<td>6</td>
<td>86</td>
<td>F</td>
<td>MLTI (cerebral cortex, Lt caudate, Lt putamen), stenosis of carotid artery</td>
<td>7</td>
<td>2 months</td>
<td>+</td>
<td>Aβ 2, CERAD B, Braak 2, AGD grade 3</td>
<td>HT, HL, CAD</td>
</tr>
<tr>
<td>7</td>
<td>88</td>
<td>M</td>
<td>Rt MCA (M2) infarct</td>
<td>42</td>
<td>3 years</td>
<td>+</td>
<td>Braak 2</td>
<td>HL, Afib</td>
</tr>
<tr>
<td>8</td>
<td>84</td>
<td>F</td>
<td>Lt MCA (M2) infarct</td>
<td>21</td>
<td>3 years</td>
<td>+</td>
<td>PSP, AGD grade 2</td>
<td>HT</td>
</tr>
<tr>
<td>9</td>
<td>75</td>
<td>F</td>
<td>MLTI (pons, Rt frontal white matter, Lt caudate)</td>
<td>78</td>
<td>2 years</td>
<td>−</td>
<td>Aβ 1, CERAD A, PSP</td>
<td>HT, DM</td>
</tr>
<tr>
<td>10</td>
<td>74</td>
<td>M</td>
<td>Lt putaminal hemorrhage</td>
<td>78</td>
<td>1 month</td>
<td>+</td>
<td>LBD (limbic), Aβ 2, CERAD B, Braak 3, AGD grade 2</td>
<td>HT, DM</td>
</tr>
<tr>
<td>11</td>
<td>65</td>
<td>M</td>
<td>Rt/Lt putaminal and Rt thalamic hemorrhage</td>
<td>10</td>
<td>1 month</td>
<td>−</td>
<td>None</td>
<td>HT</td>
</tr>
</tbody>
</table>

(−) Absent; (+) present; Afib, atrial fibrillation; Braak, Braak stage of NFT pathology; CAD, coronary artery disease; DM, diabetes mellitus; F, female; HL, hyperlipidemia; HT, hypertension; Int St-D, interval between onset of stroke and depression; Int St-Sc, interval between onset of stroke and suicide; Lt, left; M, male; MCA, middle cerebral artery; MLI, multiple lacunar infarcts; Rt, right; WM, white matter.

TABLE 2. Demographic Variables of Suicide and Nonsuicide Cases

<table>
<thead>
<tr>
<th></th>
<th>Suicide (n = 11)</th>
<th>Nonsuicide (n = 13)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>5/6</td>
<td>9/4</td>
<td>0.68</td>
</tr>
<tr>
<td>Age, mean ± SD, years</td>
<td>81.2 ± 9.3</td>
<td>76.2 ± 12.0</td>
<td>0.26</td>
</tr>
<tr>
<td>Onset of depression, mean ± SD, days</td>
<td>30.0 ± 23.4</td>
<td>47.5 ± 18.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>10 (91.0)</td>
<td>10 (77.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>3 (27.2)</td>
<td>2 (15.4)</td>
<td>0.63</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>2 (18.2)</td>
<td>3 (23.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>1 (9.1)</td>
<td>2 (15.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>2 (18.2)</td>
<td>2 (15.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Degree of PSD (mild/moderate/severe)</td>
<td>2/45</td>
<td>9/3/1</td>
<td>0.03*</td>
</tr>
<tr>
<td>Clinical Dementia Rating Scale grade (0/0.5/1/2/3)</td>
<td>5/5/1/0/0</td>
<td>9/4/0/0/0</td>
<td>0.49</td>
</tr>
<tr>
<td>Brain weight, mean ± SD, g</td>
<td>1,257.3 ± 150.2</td>
<td>1,255 ± 108.0</td>
<td>0.98</td>
</tr>
<tr>
<td>Thal Aβ score (0/1/2/3)</td>
<td>4/3/4/0</td>
<td>4/3/4/2</td>
<td>0.61</td>
</tr>
<tr>
<td>CERAD (0/a/b/c)</td>
<td>4/4/2/1</td>
<td>7/3/2/1</td>
<td>0.85</td>
</tr>
<tr>
<td>Braak (0-II/III-IV-V-VI)</td>
<td>8/3/0</td>
<td>10/2/1</td>
<td>0.70</td>
</tr>
<tr>
<td>NIA-AA criteria (not/low/intermediate/high)</td>
<td>3/6/2/0</td>
<td>2/4/6/1</td>
<td>0.47</td>
</tr>
<tr>
<td>AGD, n (%)</td>
<td>6 (54.5)</td>
<td>2 (15.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>PSP, n (%)</td>
<td>2 (18.2)</td>
<td>0</td>
<td>0.20</td>
</tr>
<tr>
<td>AGD + PSP, n (%)</td>
<td>8 (63.6)</td>
<td>2 (15.4)</td>
<td>0.01†</td>
</tr>
<tr>
<td>LBD, n (%)</td>
<td>1 (9.1)</td>
<td>0</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*p ≤ 0.05, †p ≤ 0.01

Braak, Braak stage of NFT pathology.
and interview with the attending psychologist for confirmation (14, 15). Cognitive status during the time from stroke to death was evaluated using the Clinical Dementia Rating Scale (16).

This study was approved by the ethical committee of Toyama University and was conducted in accordance with ethical standards established in the 1964 Declaration of Helsinki.

Neuropathologic Examination

Brains were fixed in 20% buffered formalin for at least 2 weeks before sectioning. Frontal, parietal, temporal, and occipital neocortices; amygdala; hippocampus; basal ganglia; hypothalamus; thalamus; midbrain;pons; medulla; cerebellar cortex; and dentate nucleus were sampled. All sections were cut (5 μm thick) and stained with Luxol fast blue/hematoxylin and eosin, Elastica-Masson, Gallyas-Braak, and thioflavin S stains.

Immunohistochemistry was performed on the frontal and temporal lobes, basal ganglia, and midbrain of all cases using antibodies to phosphorylated tau (clone AT8, 1:1000; Endogen, Woburn, MA), phosphorylated α-synuclein (clone LB508, 1:500; Zymed, San Francisco, CA), TDP-43 (1:5000; Protein Tech Group, Chicago, IL), glial fibrillary acidic protein (clone ZCG 29; Nichirei, Tokyo, Japan), β-amyloid (Aβ; clone 6 F/3D, 1:50; Novocastra, Leica, Tokyo, Japan), and αβ-crystallin (Santa Cruz Biotechnology Inc, Dallas, TX). Sections were pretreated with hydrated autoclaving (121°C, 15 minutes) to enhance α-synuclein and with 88% formic acid (5 minutes) to enhance Aβ detection. Antibody binding was detected using a biotin-streptavidin detection system (Nichirei), with 3,3'-diaminobendizine as chromogen substrate. When findings were positive in these preliminary immunohistochemistry analyses, staining with the same antibody was performed on additional sections. Staining for 3-repeat tau and 4-repeat tau was also performed in additional sections. Staining for 3-repeat tau and 4-repeat tau (RD4) (Merck-Millipore, Billerica, MA) was also performed in cases positive for AT8.

Distribution and severity of histologic findings were examined using the following standard methods: Pathologic staging of neurofibrillary tangles (NFTs) was evaluated according to modified Braak stages of NFT burden (17), using AT8 immunohistochemistry. Density of neuritic plaques was evaluated in accordance with Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) criteria (18), using thioflavin S staining. Extent of senile plaques in the brain was evaluated using Aβ immunohistochemistry, following the criteria of Thal et al (19). Based on these results, level of AD neuropathologic change was divided into 4 categories (i.e. not, low, intermediate, and high), following criteria of National Institute on Aging–Alzheimer’s Association (NIA-AA) guidelines (20). Lewy body–related pathology was assessed according to the Third Consensus Guidelines for dementia with Lewy bodies, using α-synuclein immunohistochemistry (21). Distribution of argyrophilic grains was evaluated with AT8 and RD4 immunohistochemistry and Gallyas-Braak staining. Pathologic staging was assessed following the system proposed by Saito et al (22). Diagnoses of CBD (23), PSP (24), and TDP-43 proteinopathy (25) were made following currently established criteria.

Statistical Analysis

Data were analyzed using SPSS (version 22.0) statistical package. The demographic and pathologic variables of subjects who died by suicide were compared with those of control subjects using nonparametric Mann-Whitney U test for skewed data (e.g. age). Chi-square test or Fisher exact test (2-tailed) for dichotomous variables was used for other group comparisons that did not involve skewed data. Significance level was set to p < 0.05.

RESULTS

General Clinical Characteristics of Subjects

Twenty-four cases fulfilled our criteria for PSD. Of these, 11 subjects had died by suicide, and the other 13 had died of other causes. Detailed clinical and pathologic findings for those who died by suicide are listed in Table 1, and a comparison of the demographic and pathologic characteristics of those who had and those who had not committed suicide is shown in Table 2. The methods of suicide were as follows: drowning in a river (11 cases), drowning at sea (6 cases), falling from a height (2 cases), hanging (2 cases), and self-immolation (1 case).

The distribution of age, sex, and prevalence of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and atrial fibrillation was not statistically different between the groups (Mann-Whitney U test and Fisher exact test; Table 2). Hypertension and hyperlipidemia were treated medically in all patients with these conditions in both groups after the stroke. Two of 3 subjects with diabetes mellitus in the suicide group and both subjects with diabetes mellitus in the nonsuicide group were treated with oral antidiabetic drugs; the remaining subject with diabetes in the suicide group was treated with insulin. All cases of atrial fibrillation in both groups were treated with warfarin. Although the interval between the stroke and onset of depression was shorter in the suicide group than in the nonsuicide group, the difference was not significant (p = 0.06, Mann-Whitney U test). However, the severity of depression was significantly higher in the suicide group than in the nonsuicide group (p = 0.03, chi-square test). Six of 11 subjects who committed suicide were initially diagnosed as having mild cognitive impairment (MCI) after the stroke, whereas 4 of 13 subjects in the nonsuicide group were diagnosed as having MCI, a difference that was not significant (p = 0.49). Except for 1 subject in the suicide group, the Clinical Dementia Rating Scale grade of the subjects was less than 1 point. The interval from onset of depression to suicide completion varied from 1 month to 7 years (Table 1).

Neuropathologic Findings

Brain weights did not differ between the groups. Neuropathologic findings for subjects in the suicide group are shown in Table 1. Large cerebral infarcts were found in 3 cases (Case 1 [Fig. 1A], Case 7, and Case 8). Two cases showed white matter hemorrhage: Case 2 had hemorrhage in the right temporal white matter (Fig. 1B), and Case 5 had hemorrhage in the right posterior white matter. The cause of hemorrhage in both cases was hypertensive arteriosclerosis; no amyloid angiopathy was found in either brain. Multiple lacunar strokes were found in 4 cases (Cases 3 and 4 [Fig. 1C], Case 6 [Fig. 1D], and Case 9 [Fig. 1F]). Cases 6 and 9 also showed severe atherosclerotic narrowing of the bifurcation of the left carotid ar-
tery and basilar artery, respectively (Figs. 1E, G). Two cases showed hemorrhage in subcortical nuclei (Cases 10 and 11; Fig. 1H). Stroke lesions in the 13 subjects who had not committed suicide are listed in Table 3.

Lacunar infarcts or severe atherosclerosis of the cerebral arteries was confirmed microscopically (Figs. 2A, B). The extent of pathologic Aβ plaques determined with the Thal method, CERAD score, and modified Braak staging of NFT was not significantly different between the groups, nor was the level of AD neuropathologic change as determined with NIA-AA criteria. Typical pathologic findings of AGD included AT8-positive and Gallyas-Braak Y-positive argyrophilic grains (Fig. 3A; compare with the age-matched negative control in Fig. 3B), achromatic ballooned neurons positive for AT8 and/or β-crystallin (23, 26) (Fig. 3C), and bush-like astrocytes showing glial fibrillary acidic protein immunoreactivity and abundant AT8-immunoreactive hair-like branching processes sprouting from cell bodies rather than cell processes in the amygdala and other limbic areas (27) (Fig. 3D). Typical AGD pathology was found in 6 of 11 suicide cases (54.5%) and in 2 of 13 nonsuicide cases (13.5%); this difference was not significant (p = 0.08, Fisher exact test). The pathologic staging of AGD in the 6 suicide cases was as follows: Grade 1, 1 case; Grade 2, 1 case; Grade 3, 4 cases. The AGD pathology in the 2 nonsuicide cases was Stage 1 in 1 subject and Stage 2 in the other.

Two patients (Cases 8 and 9) showed pathologic findings fulfilling criteria for PSP. Neither of these patients had a family history of the condition or any clinical history of PSP before the onset of stroke. In Case 8, dysarthria, depression, and MCI were the symptoms of the stroke. Patient 9 had a gait disorder and falls that were attributed to lacunar infarcts in the brainstem; these symptoms were subsequently followed by depression and dysphagia, which were also considered to be symptoms of the stroke. Moderate neuronal loss was evident in the substantia nigra in both Cases 8 and 9 (Fig. 3E) versus the age-matched control (Fig. 3F). However, neuronal loss was not obvious in other regions commonly affected in PSP, such as the globus pallidus, subthalamic nucleus, cerebellar dentate nucleus, and cerebral cortex. In both cases, moderate numbers of AT8-positive and RD4-positive NFT were found in the globus pallidus, subthalamic nucleus, mesencephalic tectum, substantia nigra, cerebellar dentate nucleus, pontine nucleus, and limbic system, including the amygdala, entorhinal cortex, and CA1 of Ammon horn (Fig. 3G). Four-repeat tau–positive tufted astrocytes showing a concentric arrangement of conglomerated fine processes that branched in a tree-shaped pattern without collaterals (28) (Fig. 3H) and oligodendroglial coiled bodies were found in many brain regions. The incidence

<table>
<thead>
<tr>
<th>Stroke Lesion</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left putaminal hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Middle cerebral artery infarction</td>
<td>3 (1/2)</td>
</tr>
<tr>
<td>Left cerebellar hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Multiple lacuna</td>
<td>6</td>
</tr>
<tr>
<td>White matter hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Right caudate hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
</tr>
</tbody>
</table>

FIGURE 1. Gross appearance of the brains of subjects with PSD who committed suicide. (A) Right middle cerebral artery infarct in Case 1. (B) Right temporal white matter hemorrhage in Case 2. (C) Bilateral lacunar infarcts (arrows) of the thalamus in Case 4. (D) Small cortical infarct (arrow) of the right posterior lobe in Case 6. (E) Serial sections of carotid artery in Case 6. Severe stenosis of the bifurcated region can be seen. (F) Lacunar infarct of the pons in Case 9. (G) Severe atherosclerotic lesion of the basilar artery in Case 9. (H) Old bilateral hemorrhages of the putamen in Case 11.

FIGURE 2. Microscopic vascular pathology of the brains of subjects with PSD who committed suicide. (A) Lacunar infarct of the putamen in Case 3 (Luxol fast blue/hematoxylin and eosin). (B) Severe stenosis caused by atherosclerosis of the basilar artery in Case 9 (Elastica-Masson). Scale bar = 1 mm.
of RD4-positive cases (AGD + PSP) was significantly higher in the suicide group than in the control group (p = 0.01, Fisher exact test).

In Case 10, Lewy bodies and moderate AD pathology were present in the limbic system, including the entorhinal cortex, hippocampus, and amygdala. No positivity for TDP-43 was found in any of the patients in this study.

**DISCUSSION**

For many years, the location of a stroke has been hypothesized to be an important factor in the pathogenesis of PSD. The “left frontal region” (29), “frontal subcortical circuit” (30), and “limbic-cortical-striatal-pallidal-thalamic circuit” (31) have been proposed as possible regions associated with PSD. However, several studies (32–34) showed no association between PSD and lesion location. Krishnan et al (35) and Alexopoulos et al (36) proposed the alternative hypothesis of “vascular depression,” which emphasizes the role of cerebrovascular (particularly small-vessel) disease in the pathogenesis of late-life depression. In a study of patients with PSD that was conducted for an extended period, Brodaty et al (37) found that PSD was associated with accumulation of vascular brain pathology rather than the severity of a single stroke. Santos et al (38) also found that higher lacuna scores in the basal ganglia, thalamus, and deep white matter were significantly associated with increased risk of PSD. Many researchers have accepted the concept of vascular depression as a potential explanation for the pathogenesis of PSD (7, 38). In the present study, the pathologic findings of stroke varied within both the suicide group and the nonsuicide group, and we did not find any difference in the location, size, or type of stroke between the 2 groups.

Cognitive impairment may also contribute to PSD-related suicide. A positive correlation between PSD-related suicide and cognitive impairment was reported in 2 large clinical studies (5, 6); however, 2 other reports reached the opposite conclusion (i.e. that the incidence of dementia and other cognitive disorders was relatively low in a group of elderly subjects who committed suicide compared with control subjects) (1, 39). Neuropathologic studies focusing on the significance of neurodegenerative diseases for suicide have been rare, as have studies on PSD. We are aware of 2 studies that investigated AD pathology in victims of suicide, but they reached different conclusions. Rubio et al (40) examined autopsies of 28 people who had died of suicide and found a higher prevalence of AD pathology in this group than in those with minimal AD pathology alone; they concluded, therefore, that AGD may be associated with the occurrence of late-onset schizophrenia and delusional disorders. The present study does not address whether AGD is a potential independent risk factor for overall late-life suicide; however, AGD might be a possible aggravating factor for PSD-related suicide, even in the absence of obvious dementia. Considering the predominant distribution of tau protein in the limbic system in AGD, dysfunction of the limbic system may play a role in the psychiatric symptoms of AGD. Dysfunctions of the limbic system and brainstem nuclei have been associated with depression (57).

**FIGURE 3.** Microscopic degenerative lesions in the brains of subjects with PSD who did and did not commit suicide. (A) Argyrophilic grains in the amygdala of Case 5 (Gallyas-Braak). (B) An age-matched nonsuicide case free of argyrophilic grains (Gallyas-Braak; 80-year-old man). (C) Ballooned neuron in the amygdala of Case 5 (Luxol fast blue/hematoxylin and eosin). (D) Bush-like astrocytes in the amygdala of Case 5 (AT8). (E) Neuronal loss in the substantia nigra of Case 8 (Luxol fast blue/hematoxylin and eosin). (F) Substantia nigra of an age-matched nonsuicide case (Luxol fast blue/hematoxylin and eosin; 82-year-old man). (G) Tufted astrocytes in the subthalamic nuclei of Case 8 (Gallyas-Braak). Scale bars = (E, F) 200 μm; (A, B, H) 20 μm; (C, D, F, G) 50 μm.
Furthermore, psychosis tends to occur after the limbic region and temporal cortex are affected in various diseases, including cerebrovascular disease, traumatic brain injury, and epilepsy (58, 59). Selective limbic dysfunctions, such as amnesia and behavioral changes, have been reported to be caused by herpes simplex encephalitis and paraneoplastic syndrome (60, 61). Togo et al (12) also showed that amnesia and emotional disorders are frequently present in AGD, whereas other cognitive functions tend to be spared relative to the severity of amnesia. The amygdala has been considered to play a role in depression and other mood disorders and is thought to be a region that is commonly affected by AGD early in the disease process (22). Morphometric analyses of the amygdala using clinical imaging data in patients with depression showed various results, including increases, decreases, and no change (62). In the present study, although we could not show an isolated effect of AGD pathology on the occurrence of depression in our subjects, we estimate that AGD-related pathology in the amygdala or limbic region may be an aggravating factor of PSD. Surdhar et al (63) showed that amygdala volumes are significantly smaller in patients with Parkinson disease with mild depressive symptoms than in healthy controls. A detailed neuropathologic study of AGD or other neurodegenerative diseases in aged individuals who have committed suicide may be useful for exploring the mechanism of the occurrence or progression of PSD and other depressive states leading to suicide.

Progressive supranuclear palsy is a rare neurodegenerative disease; major clinical signs include supranuclear gaze palsy, bradykinesia, rigidity, postural instability, and frontotemporal cognitive dysfunction (64). Progressive supranuclear palsy is characterized by neuronal degeneration with NFT in the globus pallidus, subthalamic nucleus, mesencephalic tectum, substantia nigra, dentate nucleus, and pontine tegmentum (23). Four-repeat tau–positive tufted astrocytes are major diagnostic hallmarks, especially for differentiation from CBD (65). Depressed mood occurs in approximately 20% of patients with PSP (66), but no suicides have been reported in patients with PSP. In a recent case-control study, Bloise et al (67) found depression that met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria and was considered to be related to PSP in 8 of 15 patients; the depression occurred more frequently in patients with PSP than in controls. Atypical cases of PSP, in which psychiatric symptoms appeared in the early phase, have also been reported (68, 69). The mechanism of psychiatric disorders in PSP has been proposed to be dysfunction of orbitofrontal circuits, with preferential involvement of the mesofrontal targets of striatal projections (70). However, this circuit is usually associated with behavioral disturbance, personality changes, irritability, and apathy, rather than depression (71). Besides injuries to this circuit, coexisting AGD (as in our Case 8) might also influence the occurrence of major depression in cases of comorbid PSD and PSP. In addition, our 2 subjects with PSP did not show any neurologic signs before the onset of stroke; therefore, these may have been rare cases of early PSP. Although neuronal loss was localized to the substantia nigra, we found considerable tauopathy in almost all regions commonly associated with PSP. Thus, careful examination of forensic autopsy cases may provide information about the pathology of rare neurodegenerative diseases at preclinical or early clinical stages.

Our study has certain limitations. First, the study population consisted of a small sample of patients with PSD, including those who had committed suicide. Second, because the diagnosis and treatment of our cases were provided by different neurologists and psychologists at different hospitals, the clinical evaluations were not as uniform as they would have been in a single-center study. Third, we were unable to evaluate the subjects’ education level, which is a known influence risk for PSD (5), or other psychobiologic factors such as physical disability, ineffective coping skills, and lack of social resources.

In conclusion, overlapping 4-repeat tauopathy may be a risk factor for suicide in subjects with PSD without preexisting clinical psychiatric disorders or prominent dementia before the occurrence of stroke. We believe that the presence of other neurodegenerative diseases should not preclude a postmortem diagnosis of PSD. Both stroke and 4-repeat tauopathy, especially AGD, occur frequently in older persons; thus, the presence of both in some patients would not be unexpected. Longitudinal studies including detailed pathologic examinations are needed to clarify the mechanism and risk factors of PSD-related suicide.

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