Prevalence and Disease Associations of Argyrophilic Grains of Braak

P. Martinez-Lage, MD, PhD and D.G. Munoz, MD, FRCP(C)

Abstract. Braak's argyrophilic grains (BAG) are spindle-shaped structures originally described in patients with dementia. We have determined that the prevalence of BAGs in an unselected series of 300 consecutive autopsies of subjects over the age of 30 is 5.6%, or 11.7% if only subjects older than 65 are considered. All the 17 subjects identified were older than 65, 6 received other neuropathological diagnoses of degenerative disease, and 11 did not. Only 2 of the latter had shown clinical evidence of mental impairment. Braak's argyrophilic grains were associated with balloononed neurons, superficial linear spongiosis, and gliosis of entorhinal cortex and amygdala. Subcortical neurofibrillary tangles were consistently found in patients with dementia, but not in other subjects.

In a separate series studying the prevalence of BAG in neurodegenerative diseases, we found a strong, but not universal association with progressive supranuclear palsy, and to a lesser degree with the lobar atrophies (Pick's disease and corticobasal ganglionic degeneration). Numerous BAG were present in occasional cases of diffuse Lewy body disease, multiple systems atrophy, and motor neuron disease. We conclude that rather than defining a single disease, BAG constitute lesions that accompany several degenerative diseases, but also occur in normal elderly subjects, and rarely in demented subjects without other major histological findings.

Key Words: Dementia; Pick's disease; Progressive Supranuclear Palsy; Tau.

INTRODUCTION

Braak's argyrophilic grains (BAG) were first reported by Helko and Eva Braak as a novel neuropathological finding in patients with dementia (1, 2). They were described as small, silver-stained, spindle-shaped structures scattered in the neuropil, distinct from neuropil threads. BAG were often interconnected by fine argyrophilic threads issuing from their pointed poles. In most instances BAG were accompanied by elongated argyrophilic glial cytoplasmic inclusions, termed coiled bodies, mainly located in the subcortical white matter. While in some patients these findings were associated with neuritic plaques, neurofibrillary tangles, and neuropil threads characteristic of Alzheimer disease, in 10 cases BAG were interpreted as the only neuropathological correlate of dementia. After reporting an additional case, Inagaki et al suggested the term "Braak's disease or argyrophilic grain dementia" to designate this new illness (3).

Despite the apparently high frequency of BAG in a demented population (35% of cases in Braak's original series), only isolated case reports of the condition have been published. A study reported "mild" or "moderate" BAG in patients with progressive supranuclear palsy, Pick's disease, and corticobasal ganglionic degeneration (4), and another mentioned them in a patient with senile hippocampal sclerosis (5). Hence, questions regarding the frequency of BAG and coiled bodies in the general autopsy population and whether they represent and define a distinct disorder remain open. To address these issues, we have reviewed a series of unselected consecutive autopsies performed in a University Hospital over a period of 2 years, as well as groups of patients with different neurodegenerative disorders in search of these peculiar neuropathological markers.

MATERIALS AND METHODS

The study was divided into 2 parts. First, to determine the prevalence of BAG in a general autopsy population, the brains of all 300 subjects older than 30 that came to autopsy in our center during 1993 and 1994 were reviewed. The series included 133 females and 167 males with a mean age of 61.30 years, S.D. 15.84 years. One-hundred and forty-five subjects were older than 65. Brains were fixed in 10% formalin for 7 to 13 days. To screen for the presence of BAG, paraffin-embedded blocks of the hippocampus/entorhinal cortex were sectioned and stained with the Bielschowsky method. This particular anatomical region was chosen since Braak and Braak described the highest density of BAG in these areas in all cases. We determined that the Bielschowsky stain, a routine in our laboratory, is as effective as the Gallyas method to detect BAG. For cases where BAG was observed, sections from frontal, parietal, occipital, insular, and temporal cortices, amygdaloid complex, basal ganglia, nucleus basalis, thalamus, hypothalamus, brainstem, and cerebellum were stained with hematoxylin-eosin and Gallyas method (6), and processed for immunohistochemistry, in order to investigate the anatomical distribution and association with other lesions (neuronal loss, gliosis, spongiosis, senile plaques, neurofibrillary tangles, granulo-vacuolar degeneration, Pick bodies, balloononed neurons. Lewy bodies).

Immunohistochemistry was performed by the avidin-biotin-peroxidase method, utilizing Vector Elite kits, as previously described (7). The antibodies utilized include the mouse monoclonals NF2F11, directed against phosphorylated heavy and midweight neurofilament proteins (8), and tau-2, against tau (9, 10), as well as rabbit polyclonal antiserum raised against GFAP (7), and bavine red blood cell ubiquitin conjugated to keyhole limpet hemocyanin (11). Clinical information was collected

From the Departments of Pathology and Clinical Neurological Sciences, University of Western Ontario and London Health Sciences Center, London, Ontario, Canada.

Correspondence to: Dr. D. G. Munoz, Department of Pathology, University of Western Ontario, London, Ontario, Canada N6A 5C1.

Vol. 56, No. 2
February, 1997
pp. 157-164
TABLE 1

Demographic Characteristics, Cognitive Status, and Major Neuropathological Findings in the 16 "Incidental" Cases with Argyrophilic Grains

<table>
<thead>
<tr>
<th>Number</th>
<th>Age</th>
<th>Sex</th>
<th>Mental status</th>
<th>BW</th>
<th>Major autopsy findings</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>F</td>
<td>Dementia</td>
<td>870</td>
<td>PD (Classic)</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>M</td>
<td>PPA, dementia</td>
<td>1,090</td>
<td>CBGD</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>F</td>
<td>Dementia</td>
<td>1,200</td>
<td>CBGD</td>
</tr>
<tr>
<td>4</td>
<td>86</td>
<td>F</td>
<td>Dementia</td>
<td>1,050</td>
<td>PSP</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>F</td>
<td>Dementia</td>
<td>1,300</td>
<td>PSP</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>M</td>
<td>Dementia</td>
<td>1,150</td>
<td>DLBD</td>
</tr>
<tr>
<td>7</td>
<td>84</td>
<td>M</td>
<td>Dementia</td>
<td>NA</td>
<td>Arteriosclerosis</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>F</td>
<td>Disoriented, poor ADL</td>
<td>1,040</td>
<td>Lewy bodies (substantia nigra)</td>
</tr>
<tr>
<td>9</td>
<td>79</td>
<td>M</td>
<td>(−)</td>
<td>1,360</td>
<td>Mild senile changes</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>M</td>
<td>(−)</td>
<td>1,500</td>
<td>Arteriosclerosis</td>
</tr>
<tr>
<td>11</td>
<td>72</td>
<td>M</td>
<td>(−)</td>
<td>1,300</td>
<td>(−)</td>
</tr>
<tr>
<td>12</td>
<td>71</td>
<td>M</td>
<td>(−)</td>
<td>1,110</td>
<td>Infarct (right basal ganglia)</td>
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<td>13</td>
<td>80</td>
<td>F</td>
<td>(−)</td>
<td>1,380</td>
<td>(−)</td>
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<tr>
<td>14</td>
<td>79</td>
<td>F</td>
<td>(−)</td>
<td>920</td>
<td>Mild senile changes</td>
</tr>
<tr>
<td>15</td>
<td>74</td>
<td>F</td>
<td>(−)</td>
<td>1,280</td>
<td>(−)</td>
</tr>
<tr>
<td>16</td>
<td>81</td>
<td>M</td>
<td>(−)</td>
<td>1,330</td>
<td>(−)</td>
</tr>
<tr>
<td>17</td>
<td>78</td>
<td>F</td>
<td>(−)</td>
<td>1,120</td>
<td>(−)</td>
</tr>
</tbody>
</table>

ADL: Activities of daily living; AD: Alzheimer disease; BW: Brain weight; CBGD: Corticobasal ganglionic degeneration; PD: Pick's disease; PPA: Primary progressive aphasia; PSP: Progressive supranuclear palsy; (−): no significant abnormalities.

from hospital charts supplemented in some cases by telephone interviews of relatives to determine the presence of dementia or cognitive impairment.

The second part of the study was designed to investigate whether BAG characterize a distinct clinicopathological entity or are best understood as a new lesion within an established disease or group of diseases. For this purpose, we studied the brains of subjects with several neurodegenerative diseases, including 6 patients with classical Pick's disease; 6 patients with corticobasal ganglionic degeneration, 3 of whom presented with primary progressive aphasia; 10 cases of progressive supranuclear palsy; 6 cases with multiple system atrophy; 13 cases of motor neuron disease without dementia and 2 cases with dementia and motor neuron disease; 3 subjects with Huntington's disease; 7 patients with Creutzfeld-Jakob disease; 9 cases with diffuse Lewy body disease; and 18 cases with Alzheimer disease. All these brains were obtained from the University of Western Ontario Dementia Study and the Neuropathology Service brain banks. Details of history and neurological exam by at least one academic neurologist were available in all cases, but only some had quantitative neuropsychological testing. Tissue samples were processed and studied as described in the first part of the study.

RESULTS

Prevalence of BAG

Among 300 consecutive autopsies of subjects older than 30, 17 brains (5.6% of the total, or 11.7% of those older than 65) showed the abnormalities under study. Six brains had additional specific diagnosis of neurodegenerative disease (1 classical Pick's disease, 1 classical corticobasal ganglionic degeneration, 1 corticobasal ganglionic degeneration presenting as PPA, 2 progressive supranuclear palsy, and 1 diffuse Lewy body disease) and were included in the second part of the study; the remaining 11 did not. The clinical features and major neuropathological findings are summarized in Table 1. All cases were older than 68 years of age.

Only one subject (case 7) of the 11 without significant lesions other than BAG carried a clinical diagnosis of dementia (specifically Alzheimer disease), although another (case 8) had evidence of mental deterioration. She was disoriented at the time of admission and had required assistance at home for her daily activities in the previous months. Both cases showed small numbers of neurofibrillary tangles in the hippocampus, entorhinal cortex, and basal temporal neocortex, accompanied by diffuse plaques and rare neuritic plaques. Among the remaining 8 subjects no evidence of cognitive impairment was described in their hospital charts, which included an assessment of activities of daily living as part of the admission procedure.

Morbidity and Immunohistochemistry

Both the Bielschowsky and Gallyas staining methods revealed the presence of BAG throughout the hippocampus, amygdaloid complex, and other cortical and subcortical structures (see below). In most cases both techniques revealed similar numbers and structures of BAG; occasionally the Bielschowsky stain showed considerably more BAG, and in cases of Pick disease BAG failed to stain with Gallyas (see below). With either stain, BAG appeared as small argyrophilic structures with some variation in size and shape, including the characteristic spindles, but also straight or kinked rods, commas or cigarlike profiles (Fig. 1a). About 20 to 40% of BAG
displayed drumstick or drop-shaped branches or excrescences on their surface. In many instances one or both extremes of the grain ended in a thin, thread-like structure that extended to interconnect several other grains. BAG were usually freely scattered throughout the neuropil, but with some frequency, clusters of 4 to 10 free or interconnected grains could be observed (Fig. 1c).

Most BAG were labeled by tau-2, although in a non-homogeneous, often granular pattern, rather than the solid and excrescence-bearing profiles observed with the silver stains (Fig. 1b, d). In addition, many BAG showed a nonimmunoreactive core (Fig. 1e). Immunoreactivity to anti-ubiquitin antibodies was observed in only 10 to 20% of grains. BAG were not stained with anti-phosphorylated neurofilament or anti GFAP antibodies.

**Topographical Distribution of BAG**

The distribution is presented in a diagram in Figure 2, and a semiquantitative assessment of BAG density in Table 2. All cases, by definition, had BAG in the hippocampal formation, although they were not seen in the fascia dentata and only rarely in sectors CA4 or CA3. Rare BAG could be detected in CA2 along with some argyrophilia and granulo-vacular degeneration in the pyramidal cells in 8 cases. The highest density of BAG was observed throughout sector CA1 and subiculum, where they could be seen in all layers: stratum oriens, pyramidale, radiatum, and lacunosum-moleculare. Moderate numbers of BAG were seen in the parasubiculum but none was present in the presubiculum. The distribution of BAG in the entorhinal cortex followed both a vertical modular and a laminar pattern, favoring layer pre-β, but also present in layer pre-α, as well as in the deep layers under the lamina dissecans (Fig. 3a). The density of BAG decreased toward the collateral sulcus, and no BAG were seen in the fusiform gyrus. An antero-posterior gradient was observed in the entorhinal cortex, BAG being more abundant anteriorly. BAG were also abundantly present in the amygdaloid complex, especially in the paralaminar and ventrolateral nuclei of the basolateral portion and less so in the ventromedial and ventrolateral nuclear groups.

BAG were particularly abundant in the superficial layers of the insular and pyriform cortices, and present in

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**Fig. 1.** a. Numerous BAG scattered individually and in small clusters in the neuropil of the CA1 sector of the hippocampus. Note the absence of other neurofibrillary pathology in the neuronal cell bodies in the background. Bielschowsky. Bar = 100 μm. b. Same area as a. BAG are decorated by the tau-2 antibody. A solitary neurofibrillary tangle is labeled by an arrow. Bar = 150 μm. c. Same area and stain as a. Under high power, thin threads connecting series of BAG are evident (arrow). Bar = 15 μm. d. In contrast to the solid profiles observed with silver stains, tau immunoreactivity of BAG (arrows) often demonstrates a discontinuous, granular pattern, particularly evident in a cluster of which one grain is labeled by an arrow. CA1 sector. Tau-2 immunostain. Bar = 15 μm. e. Tau-2 immunostain reveals a hollow core in some BAG. CA1. Bar = 15 μm.
low to moderate densities in the claustrum. Only rare BAG were detected in the frontal regions in 2 cases, and never in parietal or occipital cortices. The hypothalamus showed BAG in multiple nuclei, including the walls of the III ventricle, the mammillary bodies (Fig. 3b), and especially the lateral tuberal nucleus.

BAG were very rarely seen in the basal ganglia except in one case in which they were abundantly present in the medial portion of the globus pallidus. BAG were not detected in the thalamus, subthalamic, or red nuclei, but were occasionally present in the substantia nigra, periaqueductal gray, and locus ceruleus. No BAG were found in other brainstem nuclei, or in the cerebellum.

**Associated Lesions**

Ten cases, including all but one of the patients with dementia, demonstrated prominent superficial linear spongiosis in frontal and temporal neocortex, as well as in the entorhinal cortex and posterior parahippocampal gyrus (Fig. 4a). There was moderately severe gliosis of the latter two structures, as well as the amygdala, as demonstrated by GFAP immunostains (Fig. 4b). Ballooned neurons, highlighted by their expression of phosphorylated neurofilament proteins, were commonly seen in the entorhinal cortex and the frontal cortex, especially in cases with associated dementia (Fig. 4c). Hippocampal neurofibrillary tangles were found in 13 cases (Table 2). Gallyas stain and tau immunohistochemistry revealed globose neurofibrillary tangles in one or several subcortical structures (striatum, globus pallidus, subthalamic nucleus, periaqueductal gray, substantia nigra) in all the 6 patients with a diagnosis of neurodegenerative disease. The presence of numerous neurofibrillary tangles in the subthalamic nucleus, and a few in the substantia nigra in the patient with diffuse Lewy body disease (case 6), was unexpected. Only 3 of the 11 cases with no additional neurodegenerative diagnosis showed subcortical globose neurofibrillary tangles: in case 7 (demented) neurofibrillary tangles were seen in the substantia nigra, locus ceruleus, and midline nuclear group of the thalamus, but not in the globus pallidus, subthalamic nucleus, periaqueductal gray, or olive, whereas in case 8 (mentally impaired) they were restricted to the locus ceruleus, and in case 12 (no clinical diagnosis) they were restricted to the periaqueductal gray.

In all cases, BAG were accompanied by argyrophilic glial cytoplasmic inclusions consisting of elongated, curvaceous, often branched profiles known as coiled bodies (Fig. 4d). They had a fibrillar substructure, and often surrounded a rounded glial nucleus, usually identifiable as oligodendroglia by virtue of its membership in a nuclear row or fascicle. They were immunoreactive for tau, but not for ubiquitin, neurofilament, or GFAP. Coiled bodies were usually seen in the white matter and occasionally in the neuropil, in the areas where BAG were present.

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**TABLE 2.**

Neuropathological Findings in the 17 cases with BAG Found in the Unselected Autopsy Series

<table>
<thead>
<tr>
<th>Number</th>
<th>SP</th>
<th>NFTh</th>
<th>NFTs</th>
<th>BN</th>
<th>SS</th>
<th>BAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>−</td>
<td>−</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>2*</td>
<td>−</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>3*</td>
<td>−</td>
<td>−</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
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<td>4*</td>
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<td>++</td>
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<td>+</td>
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<td>5*</td>
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<td>+</td>
<td>++</td>
<td>+</td>
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<td>7*</td>
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<td>+</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>8*</td>
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<td>+</td>
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<td>+</td>
<td>++</td>
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<td>+</td>
<td>−</td>
<td>+</td>
<td>+++</td>
<td>+</td>
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<td>+</td>
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<td>11</td>
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</tr>
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<td>13</td>
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<td>+</td>
<td>−</td>
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</table>

SP: Senile plaques (hippocampus); NFTh: neurofibrillary tangles (hippocampus); NFTs: Neurofibrillary tangles, subcortical; BN: ballooned neurons (entorhinal/frontal cortex); SS: superficial spongiosis (entorhinal/frontal cortex); BAG: Braak's Argyrophilic Grains; (*): cases with dementia or cognitive impairment; +: mild; ++: moderate; +++: severe; −: absent.
and always in no more than moderate numbers. For example, coiled bodies were mainly distributed in the alveus, but some were present in the neuropil of the pyramidal layer in sector CA1 and subiculum, and were also seen in the amygdala and in both external and extreme capsules.

Associated Diseases

When the prevalence of BAG in neurodegenerative diseases was investigated (Table 3), these lesions were found to be predominantly associated with progressive supranuclear palsy (Fig. 5a). They were very abundant in the hippocampus in 7 cases, where they were not intermingled with neuropil threads, and in the entorial cortex in an additional patient. However, BAG were absent from 2 typical progressive supranuclear palsy cases. Braak's argyrophilic grains were seen in 5 of 6 classical Pick's disease cases (Fig. 5b), and in 5 of 5 corticobasal ganglionic degeneration cases, but they were far less abundant and admixed with numerous argyrophilic threads. In 2 Pick's disease cases, both BAG and Pick bodies were unstained by the Gallyas method, but were prominent in the Bielschowsky silver stain (Fig. 4c, d).

The BAG seen in 3 of 6 cases of multiple system atrophy were small, rare, and associated with neuropil threads. Another multiple system atrophy case displayed numerous BAG. Because of the presence of neurofibrillary tangles in the periaqueductal gray, the diagnosis of progressive supranuclear palsy was considered, but the numerous crescent-shaped glial inclusions of multiple system atrophy type argued for the latter diagnosis. A few BAG were present in all 3 cases of hippocampal sclerosis in the elderly (5), but only in the area of abnormality. Although most cases of amyotrophic lateral sclerosis did not show BAG, a nondemented and 1 of 2 demented cases had abundant BAG, not admixed with other argyrophilic abnormalities. The same was true in 1 of 13 cases of diffuse Lewy body disease. Two others had BAG in the context of neuropil threads. No case of Huntington's disease or Creutzfeldt-Jakob disease showed any BAG. Although the exuberance of neuropil threads in Alzheimer disease made it difficult to rule out the presence of any BAG, we could not identify any with certainty a different situation from the intermingling observed in Pick's disease, corticobasal ganglionic degeneration, and some cases of diffuse Lewy body disease.
TABLE 3

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total</th>
<th>−</th>
<th>+</th>
<th>++</th>
<th>+++</th>
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</thead>
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<td>Pick’s disease</td>
<td>6</td>
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<td>3</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Corticobasal ganglionic degeneration</td>
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<td>0</td>
<td>4</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Progressive supranuclear palsy</td>
<td>10</td>
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<td>1</td>
<td>1</td>
<td>6</td>
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<tr>
<td>Multiple system atrophy</td>
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<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Motor neuron disease</td>
<td>13</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Dementia with motor neuron disease</td>
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</table>

- − = Absent; + = Sparse; ++ = Abundant; +++ = Very abundant.

**DISCUSSION**

Once described by Braak and Braak (1, 2), BAG are easy to identify in routine silver stains. Rather than an isolated substrate for dementia, we most commonly found BAGs in asymptomatic elderly individuals, as in our cases 9–17. In fact, Table 2 of Braak and Braak (2) shows 2 individuals (Cases 2 and 5) who had no apparent impairment of mental functions. It is thus important to determine the pathological correlates of mental deterioration in these patients. Although previous reports do not mention any evidence of tissue damage in association with BAG, we found distinct superficial linear spongiosis in temporal and frontal cortex in more than half of the cases. Gliosis was obvious in the entorhinal cortex and amygdala. Although the latter two findings, along with ballooned neurons, were more common in patients with dementia, there are important exceptions. Case 5 did not have superficial spongiosis, and case 8 did not show ballooned neurons. The family of case 16 denied at posthumous interview any mental abnormality, in spite of evidence of substantial damage to entorhinal cortex and amygdala that could be expected to interfere with memory functions at least. The finding that in this series best separated demented from nondemented patients was the presence of subcortical globose neurofibrillary tangles, which extended beyond their expected appearance in progressive supranuclear palsy, corticobasal ganglionic degeneration, and Pick’s disease cases to include the diffuse
PREVALENCE OF ARGYROPHILIC GRAINS

Fig. 5. a. Numerous BAG in the absence of other hippocampal neurofibrillary pathology in a case of progressive supranuclear palsy. CA1 sector, Bielschowsky. Bar = 100 μm. b. BAG, individually and in clusters (open arrows) are scattered in the neuropil between Pick body-containing neurons (filled arrows) in the CA1 sector of the hippocampus in a case of Pick's disease. Bielschowsky. Bar = 100 μm. c. Pick bodies in CA1 in another case of Pick's disease are prominent in the Bielschowsky stain. BAG are barely visible in the background at this magnification. Bar = 200 μm. d. Same area as c, stained by Gallyas with light green counterstain, demonstrating the absence of argyrophilic deposits. Bar = 200 μm.

Lewy body disease case, and the case of “pure” BAG with dementia.

Only one case (7) in the unselected autopsy series combined established dementia with relatively isolated BAG, the pattern described in the original Braak and Braak report (case 8 may also qualify even if a formal diagnosis of dementia was not made). In all other cases with dementia in the unselected series BAG were found in association with specific neurodegenerative diseases, thus raising the question of the role of BAG in this group of maladies. In determining the prevalence of BAG in neurodegenerative diseases in the second part of the study, we found a remarkable association of BAG with progressive supranuclear palsy, much greater than with any other disease in this series. It is conceivable that BAG may represent a limbic manifestation of progressive supranuclear palsy, a disease known for the case-to-case variation of involved areas (12). The similar ultrastructure of the fibrillar constituents of BAG and globose neurofibrillary tangles of progressive supranuclear palsy (13) would be consistent with this hypothesis. Masliah et al (13) described 5 patients with dementia in whom BAG were combined with tau-positive, but thioflavin S-negative neurofibrillary tangles and threads in subcortical nuclei and hippocampus, and raised the differential diagnosis of dementia with BAG vs an atypical form of progressive supranuclear palsy. Our progressive supranuclear palsy patients had classical motor presentation and histopathological findings, and thus differ from those reported by Masliah et al (13). It is of interest that impairment of upper gaze was recorded in the patient with dementia with BAG presented by Itagaki et al (3). Our case of multiple system atrophy with prominent BAG had periaqueductal neurofibrillary tangles, and thus shares progressive supranuclear palsy features, similar to others reported in the literature (14). However, although the distribution of subcortical neurofibrillary tangles in case 7 is reminiscent of progressive supranuclear palsy, absence of subcortical neurofibrillary tangles was the rule among our cases with BAG and no other neurodegenerative diagnosis, and 2 classical progressive supranuclear palsy cases did not show any grans. Therefore, it seems that the process inducing the formation of subcortical progressive supranuclear palsy-type neurofibrillary tangles is often associated, but not identical with the process responsible for the development of BAG.

Most cases of classical Pick's disease showed BAG, albeit in modest numbers, a result consistent with Ikeda
et al (4), but different from the findings of Braak and
Braak (2). Although the reason for the discrepancy is
uncertain, it is clear that the Gallyas stain often fails to
recognize both Pick bodies and BAG in Pick’s disease.
In addition, in both Pick’s disease and corticobasal gan-
glionic degeneration, BAG are intermingled with threads,
and thus more difficult to recognize. Although present in
some cases of amyotrophic lateral sclerosis with demen-
tia, BAG are not consistently found in this condition.
Feany et al (15) have recently emphasized that a number
of neuronal and glial neurofibrillary lesions are shared
among Pick’s disease, corticobasal ganglionic degenera-
tion, and progressive supranuclear palsy, albeit at differ-
ent frequencies. It is possible that BAG represent one
such entity, a lesional element shared by several non-
Alzheimer dementias. The concept of BAG as a mani-
festation of progressive supranuclear palsy is a testable
hypothesis that may be worth future research. Braak’s
argyrophilic grains are not prominent lesions in most
cases of Alzheimer disease, but full examination of their
presence and significance in this disease awaits the de-
velopment of methods for differential staining of BAG
and neuropil threads.

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Received July 29, 1996
Revision received October 28, 1996
Accepted October 28, 1996