Argyrophilic Grain Disease in Demented Subjects Presenting Initially With Amnestic Mild Cognitive Impairment

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Abstract
A previous autopsy study of patients with amnestic-type mild cognitive impairment (MCI) suggested an overrepresentation of argyrophilic grain disease (AGD). We studied 34 patients who had diagnoses of amnestic MCI during progression to dementia and who came to autopsy. Neuropathologic evaluation included routine histochemical and immunohistochemical methods, including a 4-repeat tau-specific marker (ET3). AGD was found in association with a variety of neuropathologic diseases in 18 (53%) cases but was the primary pathologic finding in only one (3%) case. ET3 allowed the detection of AGD in 5 additional cases missed using standard techniques. Cases with AGD were significantly older than those without (mean, 94 vs 84 years; p < 0.004, rank sum test). No significant differences were found between groups for other demographic variables, association of AGD with neuropathologic findings of Alzheimer disease, Lewy body, or cerebrovascular disease, or global measures of cognitive function, although there was a nonsignificant trend towards worsening cognitive status in cases with AGD. AGD is a common pathologic finding in subjects who have been diagnosed with amnestic MCI.

Key Words: Argyrophilic grain disease, Dementia, Mild cognitive impairment, Tau.

INTRODUCTION
Argyrophilic grain disease (AGD) is a common neuropathologic finding in both demented as well as cognitively normal individuals in published autopsy series (1–12). The diagnosis of AGD is based on the demonstration of 3 main pathologic features, including the presence of argyrophilic grains, coiled bodies, and Braak group I tangles, commonly referred to as “pretangles”, in limbic projection neurons (3, 5, 8, 9). Associated pathologic lesions include ballooned neurons, bush-like astrocytes, and, rarely, superficial laminar spongiosis in the temporal neocortex as well as cortical and subcortical gliosis in the entorhinal cortex and parahippocampal gyrus (3, 5, 8, 9, 13). The characteristic features of argyrophilic grains and other AGD-associated lesions are described in greater detail elsewhere (1–13).

Prevalence rates ranging from 6% to 9% in unselected autopsy series place AGD second only to Alzheimer disease (AD) as the most common of the recognized tauopathies (3, 6, 8, 9). Autopsy series on selected cases have shown that AGD can be found in 35% to 43% of individuals with clinical dementia where it is often found in association with other neuropathologically distinct forms of dementia (2, 7). Although clearly representing distinct pathological entities (based on morphologic characteristics at both the light and electron microscopic levels, immunohistochemical staining characteristics, biochemical analyses, and specific anatomic involvement), many series have demonstrated a high rate of co-occurrence of AGD with AD pathology (1–12, 14). Still other studies have suggested that AGD may be found in association with other common tauopathies such as cortico-basal degeneration, frontotemporal lobar degeneration, progressive supranuclear palsy, and tangle-predominant dementia (4, 6, 14–17). Additional reports have demonstrated AGD in cases of Parkinson disease, dementia with Lewy bodies, multiple system atrophy, and Creutzfeldt-Jakob disease (2–4, 6, 9, 18, 19). AGD has also been shown to have a high rate of co-occurrence with hippocampal sclerosis (20). AGD may act independently or in concert with AD or other pathologic features to produce the clinical signs and symptoms of dementia (2, 14, 20–23).

A recent report suggested that AGD may be at least one of the pathologic substrates of the amnestic type of mild cognitive impairment (amnestic MCI) (24). Three of the 11 cases included in this series were found to have characteristic features of AGD. The focal involvement of AGD in hippocampi and other limbic structures necessary for learning and memory lends credibility to the hypothesis that AGD may...
play a role in the development and/or progression of amnestic MCI. If this hypothesis were true, subjects progressing through amnestic MCI to clinical dementia would be expected to display a high frequency of AGD. In contrast, the available data suggest that the majority of subjects progressing through amnestic MCI to dementia develop both the clinical and pathologic features of AD (24–31). These studies, however, have not systematically looked for the possible co-occurrence of AGD in these cases.

The present study examines AGD in a case series of demented subjects who presented clinically with amnestic MCI, progressed to dementia, and eventually came to autopsy. Histopathologic examination used both standard neuropathologic techniques and the novel 4-repeat tau-specific monoclonal antibody ET3 (32).

MATERIALS AND METHODS

Subjects

We identified all subjects enrolled in the Mayo Alzheimer’s Disease Patient Registry (ADPR)/Alzheimer’s Disease Research Center (ADRC) programs who were diagnosed with MCI from 1993 to 2001, prospectively followed, converted to dementia, and underwent neuropathologic examination (33). These subjects were age 65 or older and recruited while cognitively normal from various sources, including the Division of Community Internal Medicine and the referral practice of the Behavioral Neurology Section in the Department of Neurology at the Mayo Clinic in Rochester, Minnesota. These studies have been approved by the Mayo Institutional Review Board.

Clinical Evaluation

Initial clinical evaluation included detailed history and examination by a staff behavioral neurologist. Formal neuropsychometric testing included Mini-Mental Status Examination (34), Mattis Dementia Rating Scale (35), and Clinical Dementia Rating (CDR) (36) during annual evaluations while the subjects were followed prospectively. Clinical criteria for the diagnosis of amnestic MCI included a memory complaint, generally intact cognitive functions and activities of daily living, evidence of cognitive dysfunction with predominant memory involvement on formal testing, not demented (37). We used definitions from Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised or Fourth Edition (DSM-IV) for the diagnosis of dementia and the National Institute on Neurologic and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria for AD (38, 39). The transition to dementia was documented as the time of first diagnosis of dementia according to DSM-IV criteria, which required decline in a nonmemory cognitive domain in addition to the amnestic deficits characteristic of amnestic MCI and evidence for functional impairment by history, CDR, or other elements of the examination. ApoE genotyping was performed on blood samples according to established protocols (40). Neuroimaging protocols used to assist with the determination of consensus diagnoses included either standard computed tomography or preferably magnetic resonance imaging with coronal sections through the hippocampi, medial temporal lobes, and limbic structures (41). Clinical diagnosis was determined by a consensus committee comprised of behavioral neurologists, neuropsychologists, nurse specialists, and a geriatrician after review of all available data. All subjects diagnosed with amnestic MCI subsequently progressed to clinical dementia, died, and had a neuropathologic evaluation were included in the study. Only one patient meeting these criteria was excluded from the analysis because the autopsy findings were rendered uninterpretable by the coincident development of a high-grade infiltrative astrocytoma.

Neuropathologic Evaluation

The brains were processed according to the protocol of the Mayo Alzheimer’s Disease Research Center Neuropathology Core based on the recommendations of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) (42). After removal, the brain was divided into right and left hemibrains. The left hemibrain was fixed in 10% buffered formaldehyde for 2 weeks. Brain areas sampled included midfrontal gyrus, inferior parietal lobule, superior temporal gyrus, anterior cingulate gyrus, hippocampus at the level of the lateral geniculate body, amygdala and entorhinal cortex at the level of the mammillary bodies, nucleus basalis, cerebellum, dorsomedial thalamus with subthalamic nucleus, and midbrain with substantia nigra. Histochemical and immunostains were performed on paraffin sections from the fixed hemibrain after gross brain sectioning. Routine histochemical stains performed on all sections included hematoxylin and eosin (H&E), modified Bielschowsky silver impregnation, and Gallyas staining. Immunohistochemistry was performed on selected brain sections with antibodies specifically recognizing hyperphosphorylated tau (AT8, 1:1000 dilution; Endogen, Woburn, MA), 4-repeat tau (ET3, recognizing exon 10 of the tau protein specifically, a gift of Dr. Peter Davies) (32), β-amyloid (6F/3D, 1:10 dilution; Novocastra Vector Labs, Burlingame, CA), and α-synuclein (LB509, 1/200 dilution; Zymed, South San Francisco, CA). β-amyloid and phosphorylated tau staining was performed on sections, including occipital cortex (Brodman’s area 17), hippocampus at the level of the lateral geniculate body, and nucleus basalis. The 4-repeat tau antibody was used to facilitate the identification of argyrophilic grains on sections of both hippocampus and amygdala. α-synuclein immunohistochemistry was used to identify Lewy bodies and neurites in the anterior cingulate gyrus, hippocampus, amygdala, and midbrain, including the substantia nigra and locus ceruleus.

Routine neuropathologic evaluation included assessment of Khachaturian criteria (43), CERAD criteria (42), National Institute on Aging (NIA)–Reagan criteria (44), and Braak staging of neurofibrillary pathology (45). Clinical information was available to the neuropathologist to assist in the final determination of CERAD assignment (42). Size, location, and histologic age of large and small vessel infarcts were recorded. Acute or subacute infarcts were not considered clinically significant with respect to chronic antemortem neurologic features. Microvascular disease, microinfarcts,
amloid angiopathy, and intracranial atherosclerosis were assessed using semiquantitative grading scales according to the National Alzheimer Coordinating Center protocol (available at https://www.alz.washington.edu/NONMEMBER/PDF/nped2004.pdf). The presence or absence of vascular contributions to cognitive decline in these subjects was then dichotomized as either being present or absent according to consensus agreement between 2 examining neuropathologists (JEP and DWD). Lewy body pathology was analyzed on α-synuclein-immunostained sections and categorized as brainstem, limbic, or neocortical.

AGD was visualized with Gallyas stain and the AT-8 and ET-3 monoclonal antibodies (32) and included as a pathologic diagnosis only if there was significant involvement of the medial temporal lobe (entorhinal cortex, hippocampus, parahippocampal gyrus, and amygdala), Braak group I tangles in limbic projection neurons, as well as evidence of more than one distinct pathologic process, (Fig. 1). The overall morphology and anatomic distribution of the pathologic features of AGD in this case series was similar to that reported previously in unselected case series.

AGD was found in isolation in only one of 34 total dementia cases. AGD was found in association with AD in 13 cases, Lewy body disease in 2 cases, and one case each of Lewy body disease and frontotemporal lobar degeneration (tau-negative, ubiquitin-positive inclusions) in this series.

Twenty-eight (82%) subjects were found to have evidence of more than one distinct pathologic process, including AGD, AD, vascular disease, and Lewy body disease (Table 2). Vascular lesions, including large and small vessel infarcts, microvascular infarcts and severe arteriosclerosis, and severe amyloid angiopathy were found in 12 cases (9 with AD, 2 with tangle predominant dementia, and one with Lewy body disease). In no case was vascular disease seen in isolation or considered to be the sole cause of dementia. Lewy bodies in brainstem and limbic regions were found to coexist with AD pathology in 4 cases and with hippocampal sclerosis in 2 cases.

### Statistical Methods

Rank sum and chi-squared tests were used to compare both quantitative and categorical aspects of the clinical and neuropathologic findings. p values less than 0.05 were considered statistically significant.

### RESULTS

#### Demographic, Genetic, and Clinical Analyses

The cause of death was related to the complications of end-stage dementia or vascular disease in the majority of cases (respiratory/pneumonia, n = 18; cardiac/myocardial infarction, n = 6; stroke, n = 5; ischemic bowel, n = 1; renal failure, n = 1, not determined, n = 3). Demographic data, ApoE2 and E4 allele frequencies, and clinical measures from last evaluation before death and autopsy on the 34 subjects are shown in Table 1. The study subjects were enrolled for a mean 83.8 months and no subject was followed for less than 2 full years. Duration of MCI and or dementia did not differ between cases with AGD and those without (Table 1).

#### Neuropathologic Diagnosis

Standard Bielschowsky and Gallyas histochemistry and AT8 immunostaining detected AGD in 13 of the 34 cases studied (38%). ET3 immunohistochemical staining allowed for the detection of AGD in 5 additional cases (18 of 34 total [53%]). ET3 recognized all of the hallmark lesions of AGD, including argyrophilic grains, coiled bodies, bush-like astrocytes, pretangles, and ballooned neurons (Fig. 1). The overall morphology and anatomic distribution of the pathologic features of AGD in this case series was similar to that reported previously in unselected case series.

#### Between-Group Comparisons

Demographic variables and neuropathologic features were compared between subjects with and without AGD.

### TABLE 1. Demographic and Clinical Variables and the Incidence of AGD

<table>
<thead>
<tr>
<th></th>
<th>AGD (n = 18)</th>
<th>No AGD (n = 16)</th>
<th>Total (n = 34)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at death (range)</td>
<td>92.6 (73–105)</td>
<td>84.4 (68–94)</td>
<td>88.7 (68–105)</td>
<td>p = 0.004</td>
</tr>
<tr>
<td>Mean education (range)</td>
<td>13.1 (8–16)</td>
<td>14.38 (8–18)</td>
<td>13.5 (8–18)</td>
<td>p = 0.21</td>
</tr>
<tr>
<td>Gender (F:M)</td>
<td>13:5</td>
<td>10:6</td>
<td>23:11</td>
<td>χ2 = 0.55 (NS)</td>
</tr>
<tr>
<td>Mean duration of MCI</td>
<td>3.10</td>
<td>3.06</td>
<td>3.08</td>
<td>p = 0.34</td>
</tr>
<tr>
<td>Mean duration of dementia</td>
<td>3.49</td>
<td>2.95</td>
<td>3.23</td>
<td>p = 0.74</td>
</tr>
<tr>
<td>ApoE2 allele frequency</td>
<td>0.06</td>
<td>0.06</td>
<td>0.06</td>
<td>χ2 = 1.00 (NS)</td>
</tr>
<tr>
<td>ApoE4 allele frequency</td>
<td>0.17</td>
<td>0.28</td>
<td>0.22</td>
<td>χ2 = 0.26 (NS)</td>
</tr>
<tr>
<td>Mean MMSE (range)</td>
<td>16.18 (9–21)</td>
<td>19.18 (12–27)</td>
<td>17.68 (9–27)</td>
<td>p = 0.21</td>
</tr>
<tr>
<td>Mean CDR (range)</td>
<td>2.32 (0.5–3)</td>
<td>1.76 (0.5–3)</td>
<td>2.07 (0.5–3)</td>
<td>p = 0.08</td>
</tr>
<tr>
<td>Mean DRS (range)</td>
<td>93 (74–108)</td>
<td>104 (67–120)</td>
<td>91 (67–120)</td>
<td>p = 0.06</td>
</tr>
</tbody>
</table>

Gender and ApoE allele frequency analyzed by χ2 test. Age, education, duration of MCI and dementia, MMSE, CDR, and DRS scores at last evaluation before death analyzed by rank sum test.

AGD, argyrophilic grain disease; NS, not significant; MMSE, Mini-Mental Status Examination; CDR, Clinical Dementia Rating; DRS, Dementia Rating Scale.
FIGURE 1. (A) Argyrophilic grains in hippocampal pyramidal layer with ET3 (inset higher magnification of argyrophilic grains from amygdala). (B) Pretangles in CA2 show diffuse and granular perikaryal ET3 immunoreactivity. (C) Ballooned neuron in amygdala (hematoxylin & eosin). (D) Ballooned neuron shows ET3 immunoreactivity at the cell margin. (E) Oligodendroglial coiled bodies in temporal white matter show ET3 immunoreactivity. (F) Bushy ET3-immunoreactive astrocyte from amygdala. Original magnifications: (A) 200×; (B–F) 400×.

FIGURE 2. (A) Hippocampal sclerosis shows selective neuronal loss in CA1 and subiculum with preservation of neurons in CA3 and the end plate. Insets show higher magnification of CA3 and the end plate. Insets show grain-like ET3-immunoreactivity in CA1 (hematoxylin & eosin; original magnification: 1×; insets: 400×). (B) α-synuclein positive Lewy bodies and Lewy neurites in the amygdala. Original magnification: 200×. Inset shows higher magnification of grain-like AT8-immunoreactivity in the entorhinal cortex. Original magnification: 400×. (C) AT8-immunoreactive grains, neurofibrillary tangles, and pretangles in progressive supranuclear palsy. Inset shows AT8-immunoreactive globose tangle in the subthalamic nucleus. Original magnification: 400×.
Subjects with AGD were significantly older than those without the pathologic features of AGD (Table 1). No between-group differences were found for education, gender, duration of MCI, duration of dementia, or ApoE2 or E4 allele frequency (Table 1).

No significant associations between AGD and the presence or absence of Alzheimer, Lewy body, or vascular lesions were found (Table 2). More detailed analysis of AD pathology using Khachaturian, CERAD, NIA-Reagan, and Braak staging again failed to demonstrate a significant difference between cases with and without AGD (Table 3).

Between-group comparisons for MMSE, CDR, and Dementia Rating Scale (DRS) at first diagnosis of MCI, first evaluation at transition to dementia, or last evaluation before death failed to show significant differences between subjects with and without AGD (Table 1, data shown is from last evaluation before death). Three of the cases without AGD (19%) remained CDR 0.5 at death compared with only one of the cases that demonstrated AGD pathology (6%). All 4 of these cases met NIA-Reagan criteria for intermediate or high probability AD, and one case without AGD was considered to have had significant coexistent vascular pathology. There appeared to be a trend toward worsening cognitive status in the presence of AGD that could not be readily explained by an increased presence and or severity of AD, Lewy body disease, or vascular disease in the subjects with AGD (Tables 2 and 3). To investigate whether this trend in worsening cognitive status was related to the significantly advanced age of the subjects with AGD, correlative analyses were performed. Age did not appear to be significantly associated with measures of cognitive function in any of these analyses (data not shown).

**DISCUSSION**

The present study demonstrates a high frequency of AGD in subjects initially diagnosed with amnestic MCI who progressed to dementia. Previous reports from our group have documented the presence of AGD in 31% of cognitively normal individuals and have suggested that AGD can be found in increasing frequency and may contribute to the underlying neuropathologic substrate of subjects who died with a clinical diagnosis of amnestic MCI (24). We have found that this trend continues as subjects progress from amnestic MCI to clinical dementia.

The precise contribution of AGD to cognitive decline as one progresses from normal cognition through amnestic MCI and eventually to dementia is difficult to determine in many cases with complex or multiple distinct pathologic features. AGD may represent a primary pathologic process in certain cases, contributing to the early memory impairment characteristic of amnestic MCI. In other cases, AGD could be a secondary pathologic process, aggravating cognitive decline and hastening the transition from MCI to dementia. It is also possible that AGD may play little role in the cognitive decline seen in subjects with other complex or mixed pathologic features that may be the primary determinant of clinical dementia. It should not be understated that the presence of AGD as a coexistent pathologic process in 53% of the cases in this series does not necessarily imply causality for cognitive decline at any stage in the development of dementia.

Although AGD in combination with other pathologic findings was quite frequent in our series, it was found in isolation in only one case (3%). This contrasts with previously reported frequencies of AGD in dementia autopsy series of 35% to 43% (2, 7, 22). In one of these studies, Braak et al found the frequency of AGD to be 35% but could demonstrate AGD as the sole pathologic feature in only 12.5% of cases (2). Analysis of AT8- and Gallyas-stained sections in the present series identified AGD at a similar frequency (38%). Again, similar to the findings of Braak et al, the majority of cases with AGD in the present series demonstrate mixed pathologic features rather than pure AGD in isolation. The small number of subjects in this report limits any conclusions that could be drawn regarding frequency or prevalence of isolated AGD in this autopsy series.
Nonetheless, the finding of isolated AGD in a subject that was diagnosed with amnestic MCI suggests that AGD is one of the neuropathologic substrates of amnestic MCI and may further contribute to MCI in cases in which it coexists with other distinct pathologic processes. Previous analysis of cases that came to autopsy with the clinical diagnosis of MCI demonstrated AGD in isolation as well as with coexistent vascular lesions, hippocampal sclerosis, and/or low-grade AD pathology (24). The anatomic specificity of AGD pathology for the hippocampi and other components of the limbic system make it an attractive candidate as a potential causative or contributing factor in the very focal clinical memory deficits seen in amnestic MCI.

Previous studies have demonstrated AGD in both cognitively normal as well as demented subjects, suggesting that AGD in isolation may not necessarily correlate with cognitive impairment and should not be regarded as inevitably deleterious (3, 6, 10, 14). Several of these same studies, however, have demonstrated that the extent of pathology or association with AD pathology may be the primary determinant of the clinical presentation (6, 7, 10, 14, 22). This is analogous to the finding of moderate AD-type pathology in many cognitively intact subjects (6, 29, 31, 46–52). In this context, AGD may contribute to the clinical presentation of amnestic MCI and/or dementia by either progressing sufficiently in isolation, or, as more commonly seen in the present study, combining with other pathologic features in other anatomic areas to produce the complex neuropathologic findings seen across the cognitive spectrum from mild memory impairment to full-blown dementia.

Cognitive measures, including the MMSE and DRS, tended to be lower and CDR scores higher in those subjects with AGD compared with those without. Although this trend did not reach statistical significance, it was seen across all global measures of cognitive function. Although it remains possible that this trend is more closely related to the presence and severity of coexistent AD, Lewy body disease, and vascular disease in this series, we were unable to find evidence for a disproportionate burden of these pathologic features in the AGD cases sufficient to explain this trend. It is possible that this trend represents the clinical contribution of AGD to the cognitive symptoms and development of dementia seen in these subjects as has been suggested by others (14). Further studies addressing these issues with larger numbers of subjects are needed to further define the constellation of clinical deficits associated with AGD.

AGD was found to coexist with other tau-related diseases such as AD and progressive supranuclear palsy, as well as tau-independent degenerative diseases such as Lewy body dementia and hippocampal sclerosis. These same associations have been shown in many other studies (1–12, 14). No dominant association of AGD with any specific pathologic feature or process was seen in this study; rather, AGD appeared to be independently distributed across coexistent pathologies in this series. The association of AGD with hippocampal sclerosis is intriguing because both pathologies may increase in frequency with advancing age (3, 20). Two cases of hippocampal sclerosis were present in this series; however, only one was found to have coexistent AGD. Clearly, larger-scale studies will be needed to further explore the potential associations of AGD with hippocampal sclerosis or other distinct degenerative disease states.

Previous studies have also demonstrated that AGD is frequently found in association with low-grade, Braak stage I–III, neurofibrillary degeneration of the AD type (1–3, 5, 6, 8–11, 14, 32, 53). Consistent with this, we found the Braak stage tended to be lower in those subjects with AGD, although this was not statistically significant, and the full spectrum of pathology from Braak stage I through VI was found in AGD cases. It is possible that AGD and low-grade neurofibrillary pathology may act additively in the development of dementia in cases in which the individual pathologic features of either AGD or neurofibrillary pathology are not sufficient to explain the extent of cognitive impairment seen clinically.

There are several possibilities that may explain why the overall frequency of AGD, as a coexistent pathologic process, in this series is higher than that reported in previous dementia autopsy series (53% as opposed to 35–43%) (2, 7). Our case series was, on average, older than that published in previous series (1–12, 14, 22, 32, 53). Prior work has demonstrated that the frequency of AGD increases with advancing age (2, 46, 53), a finding that is replicated in the present study. The relatively advanced age of the subjects analyzed in the present study may represent a potential source of bias favoring an elevated estimate of AGD prevalence.

It is also noteworthy that the average duration of MCI in this series was only slightly greater than 3 years. This contrasts to previous work suggesting a conversion rate from MCI to dementia of approximately 12% per year (54, 55). As such, our series may be enriched in “rapid” converters to dementia. This accelerated rate of conversion could be related to the complex neuropathologic features seen in the majority of these cases. AGD may have contributed to the rapid development of dementia in this series. Subjects passing through a diagnosis of amnestic MCI to dementia with a more typical rate of progression may tend to have a lower frequency of coexistent neuropathologic diagnoses. If future studies bear this out, the prevalence of AGD in demented subjects initially presenting with amnestic MCI would be expected to decrease significantly from that seen in the present study.

An additional explanation for the high rate of AGD seen in this series centers on our active search for AGD pathology in these cases. Because of the similarities in immunohistochemical reactivity and anatomic specificity of AGD and AD changes, the identification of AGD can often be masked by the presence of even low-grade neurofibrillary degeneration. Recent reports have shown that argyrophilic grains are largely comprised of 4-repeat tau isoforms in contrast to the neurofibrillary degeneration of AD, which contains all 6 known tau isoforms (53, 56–58). Using the 4-repeat anti-tau monoclonal antibody ET3, we were able to significantly enhance the detection of AGD over that found using our standard phosphorylation-dependent, repeat-independent anti-tau immunohistochemistry.

The standard neuropathologic protocol used in this study includes routine sections derived from the left hemisphere in all cases. Asymmetric pathologic features are prominent in corticobasal degeneration and frontotemporal...
lobar degeneration, and can also be seen less commonly in individual cases of AD and dementia with Lewy bodies. The single case of frontotemporal dementia in this series did not have coexistent AGD, limiting the potential bias of unilateral pathologic analysis in this asymmetric degenerative disease state. Hemispheric symmetry in AGD has not been previously addressed in the literature. Our experience with AD, dementia with Lewy bodies, and AGD in cases from other series (with sections available from both hemispheres) suggests that these pathologic processes are relatively symmetric in the majority of cases (unpublished data). Nonetheless, the possibility of asymmetric pathologic features biasing our data and conclusions confounds the present study and merits further study.

It is likely that an increasing awareness of AGD, recognition of its unique neuropathologic features, and more widespread use of repeat-specific anti-tau antibodies will lead to an increased appreciation of the role of AGD in the development of clinical dementia associated with a wide variety of neuropathologic conditions, including a potential role in the development of the early cognitive deficits seen in amnestic MCI.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Dr. Peter Davies for supplying the ET-3 monoclonal antibody used in this study.

REFERENCES


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