Severe Involvement of Ambient Gyrus in Dementia with Grains

YUKO SAITO, MD, PHD, KENICHI NAKAHARA, MD, PHD, HIROSHI YAMANOUCHI, MD, PHD, AND SHIGEO MURAYAMA, MD, PHD

Abstract. Argyrophilic grains are detected as punctate or filiform structures in the neuropil of the medial temporal lobe, and dementia with grains (DG) is defined as a form of dementia with argyrophilic grains as the only explainable cause. We found argyrophilic grains in 43.2% of our 190 serial autopsy brains (mean age, 79.7 yr) from a community-based geriatric hospital, but only 20% of these argyrophilic grain-positive brains fulfilled the criteria for DG. To determine if there are structural differences between cognitively normal cases with argyrophilic grains (CNG) and DG, we studied 14 brains with CNG and 15 brains with DG. All cases of DG had severe atrophy of the ambient gyrus (the junction between temporal lobe and amygdala) with spongiosis, neuronal loss, and gliosis, as well as many grains, pretangles, coiled bodies, and tau-immunoreactive astrocytes. Comparable changes were not present in the ambient gyrus of CNG brains. The temporal neocortex and hippocampus were relatively spared in DG, in contrast to Alzheimer disease. Our study suggests that selective severe involvement of the ambient gyrus may explain the clinical manifestations of a limbic-type dementia in DG.

Key Words: Aging; Dementia with grains; Immunocytochemistry; Senile dementia; Tau; Tauopathy.

INTRODUCTION

Argyrophilic grains are punctate or filiform structures in the neuropil and are best demonstrated with Gallyas-Braak (G-B) silver staining (1). Argyrophilic grains are most abundant in the CA1 subfield of hippocampus, the entorhinal and transentorhinal cortex and adjacent temporal isocortex, the amygdala, the hypothalamic lateral tuberal nuclei, the rectus gyrus, and the septal nuclei (2). Argyrophilic grain dementia or dementia with grains (DG) is defined by Braak and Braak (2, 3) as a form of senile dementia that has only argyrophilic grains as a morphological cause of dementia. In their series of 56 brains from patients with adult-onset dementia and no cerebrovascular disease, 8 had argyrophilic grains, 8 had argyrophilic grains with changes of Alzheimer disease (AD), and 40 had AD (3). Argyrophilic grains are immunoreactive with anti-tau antibodies (4–6), and DG may be classified as a form of tauopathy.

Argyrophilic grains are also reported in cognitively normal subjects (7–9) and in a large variety of neurodegenerative disorders in the aged population, including AD, progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies, Pick disease, multiple system atrophy, Parkinson disease, amyotrophic lateral sclerosis, and the neurofibrillary tangle-predominant form of dementia (4, 8, 10, 11). The term argyrophilic grain disease has been applied to brains with abundant argyrophilic grains, and the term DG to the subgroup of patients with argyrophilic grain disease and a definite clinical history of dementia (9, 12).

Multiple studies support the independence of DG from AD. These data include 1) a higher frequency of the ε2 genotype of apolipoprotein E (apoE) (13, 14) in DG than AD; 2) the constant finding of αβ-crystallin-positive ballooned neurons in the amygdala in DG (15); 3) the presence of abundant tau-immunoreactive astrocytes in DG (16); and 4) the preferential deposition of neocortical diffuse plaques rather than neuritic plaques in DG (17). Despite these genotypic and immunohistochemical differences, the clinical presentation of DG largely overlaps that of AD, such that the clinical distinction between the two is difficult (18).

We recently performed G-B staining and tau immunocytochemistry on brains from serial autopsy cases in our institute and found a relatively high frequency of argyrophilic grains in these brains. However, only a small percentage of the argyrophilic grain-positive cases fulfilled the clinical and pathological criteria for DG. Further analysis of the brains containing argyrophilic grains revealed that severe involvement of the ambient gyrus was limited to brains showing both argyrophilic grains and a clinical history of dementia. The purposes of the current study are to establish the significance of ambient gyrus degeneration in DG and to document the relative frequency of DG among dementing disorders in the aged population.

MATERIALS AND METHODS

Cases

One hundred and ninety postmortem brains submitted for morphological examination in our department from June 1999 to May 2000 were the basis of the present work. The brains were from consecutive autopsy cases that included permission for brain examination at Tokyo Metropolitan Geriatric Hospital, an institution that provides community-based medical services.
Clinical information was obtained from medical charts and from interviews with relevant physicians and caregivers. The Mini-Mental State Examination (MMSE) (19) or the Hasegawa dementia scale (20, 21) were used for evaluation of cognitive function and the clinical dementia rating scale (CDR) (22) was used for grading of dementia. The Hasegawa dementia scale is a screening tool for cognitive decline in the elderly and has the same sensitivity and specificity as the MMSE (21).

Neuropathology

Routine Pathology: The right medial temporal lobe was selected at the time of autopsy and divided into 3 portions. The 3 portions were placed in 4% paraformaldehyde fixative for histochemical and immunocytochemical studies, half-strength Karnovsky fixative for electron microscopy, and liquid nitrogen for snap-freezing for biochemical and molecular pathology studies, respectively. The remainder of the brain was fixed in 20% buffered formalin for further morphological study. Multiple areas from the formalin-fixed brain were embedded in paraffin, serially sectioned at 6-μm, and stained with hematoxylin and eosin (H&E) and Klüver-Barrera. Areas examined included bilateral temporal poles, amygdala at the level of ambient gyrus, anterior and posterior hippocampus with entorhinal and transentorhinal areas, left rectal gyrus and septal area, the left frontal, temporal, parietal, and cingulate cortex as recommended by CERAD (23). Also sampled were the left primary motor area, visual cortex, basal ganglia at the level of mammillary body, thalamus at the level of red nucleus, subthalamic nucleus, hypothalamus, midbrain, upper and middle pons, medulla oblongata, cerebellar vermis, dentate nucleus, and the cervical, thoracic, and lumbar spinal cord. Selected sections were stained with Congo red and various silver stains, including Gallyas-Braak (G-B) (24), modified methenamine silver (MMS) (25), Bielschowsky, and Bodian methods.

Immunocytochemistry: The various anti-tau antibodies employed and their epitopes were as follows: AT8, phosphorylated Ser-202/Thr-205 (monoclonal; Innogenetics, Tense, Belgium); AP422, phosphorylated Ser-422 (polyclonal; a gift from Dr. Y. Ihara); Alz50, amino acids 5–51, 312–322 (monoclonal; a gift from Dr. P. Davies); and PHF1, Ser-396/404, (monoclonal; a gift from Dr. P. Davies). Also employed were antibodies raised against gial fibrillar acidic protein (GFAP) (polyclonal; Dako, Carpinteria, CA); HLA-DR (CD68, Dako); Aβ1–42 (polyclonal, IBL, Maebashi, Japan); Alz50, amino acids 5–51, 312–322 (monoclonal; a gift from Dr. T. Iwasuibo); α-crystallin (polyclonal; a gift from Dr. H. Mori) and ubiquitin (polyclonal; Dako).

Abbreviations: CDR, clinical dementia rating before suffering from the last fatal illness; ApoE, apolipoprotein E; MMSE, mini mental state examination; HDS-R, Hasegawa dementia scale revised; Interval, the interval between the last mental examination and death; N/A, not available due to the patient’s refusal; BW, brain weight; NFT, neurofibrillary tangles, Braak staging (42); SP, senile plaques, Braak staging (42); AG, argyrophilic grains; AA, amyloid angiopathy; CC, clinical course staging (42); SP, senile plaques, Braak staging (42); AG, argyrophilic grains; AmG, ambient gyrus; pSub, posterior subiculum; mTp, medial temporal pole; aCg, anterior cingulate gyrus.

Scoring for Lewy body is as follows: 0 = none; 1 = a few Lewy bodies without neuronal degeneration; 1 = following diagnostic rating protocol by Consensus Guidelines for Dementia with Lewy bodies (32). Scoring for AA is as follows: 0 = none; 1 = mild; 2 = moderate with degenerative changes in the arterial walls; and 3 = severe with hemorrhage. Scoring of argyrophilic grains is based on number of grains in a ×400 field as follows: 1 = 20–50 grains; 2 = 50–100 grains; and 3 = >100 grains. Scoring for degeneration: + = mild (gliosis is only detectable by GFAP immunostaining); ++ = moderate (gliosis is easily seen with H&E stain); and +++ = severe (neuronal loss with rarefaction of the tissue is prominent).
Serial 6-μm-thick sections of right and left temporal pole, ambient gyrus, anterior and posterior hippocampus, and mid-brain were prepared for immunocytochemical study. Sections were pretreated by heating in a microwave oven for the anti-psosyn antibody and LB509, and by incubation with formic acid for anti-Aβ1-42 and Aβ 11–28 antibodies, as previously reported (26). The sections were then processed using an automatic immunostaining apparatus for single or double immunostaining (27, 28) (Ventana NX20; Ventana, Tucson, AZ).

Molecular Pathological Study: Genomic DNA was extracted from the kidney, which was snap-frozen at autopsy, and apoE genotyping was determined by PCR (29). There were 1,107 of 1,227 serial autopsy cases starting January 27, 1995 examined, including 181 of the 190 cases in the present series. Genotypes and allelic frequencies were statistically analyzed by χ² test or the Fisher exact test, with p < 0.01 interpreted as significant.

Diagnostic Criteria of Each Type of Dementia

The diagnosis of DG was based on Jellinger’s definition (30): 1) widespread occurrence of minute, spindle- or comma-shaped, argyrophilic tau-immunoreactive structures distinct from neurofilament threads and predominantly located in the hippocampus and related limbic areas, including the amygdala; 2) accompanying clinical evidence of dementia; and 3) absence of other morphological causes of dementia. The diagnosis of the neurofibrillary tangle-predominant form of dementia was also based on Jellinger’s definition (10) and includes the following: 1) tangles restricted to hippocampus, entorhinal and transentorhinal areas and fitting Braak tangle stage III or IV; 2) the frequency of tangles being extensive and usually greater than that seen in AD; and 3) the frequency of senile plaques being the same or less than that found in normal age-matched controls. NIA-Reagan criteria (31) and consortium criteria (32) were adopted for the diagnosis of AD and dementia with Lewy bodies, respectively. The diagnosis of vascular dementia was based on the State of California AD Diagnostic and Treatment Centers criteria (the “California criteria”) (33) and/or the National Institute of Neurologic Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria (34).

Selection of DG and CNG

Fifteen pure DG cases were identified after employing the following neuropathological exclusion criteria: 1) presence of plaque staging of Braak C; 2) presence of tangle staging of more than Braak III; 3) presence of prominent amyloid angiopathy; or 4) presence of major vascular pathology. Fourteen CNG cases were identified. These 14 cases had none of the exclusionary neuropathological findings and had definite evidence of normal cognitive function until the last admission, as documented by the clinical charts and by the attending physicians, nurses, and caregivers.

RESULTS

Relative Frequency of DG among Demented Population

One hundred and one of the 190 autopsied cases (53.2%) had clinically documented dementia. The brains from these demented cases were pathologically classified as follows: 28 cases of vascular dementia, 52 cases of degenerative dementia, 3 cases of mixed dementia, and 18 cases of other causes. The 52 cases of degenerative dementia included 22 cases of AD, 15 cases of DG, 6 cases of dementia with Lewy bodies, 2 cases of neurofibrillary tangle-predominant form of dementia, 1 case of

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>CDR</th>
<th>ApoE</th>
<th>BW (g)</th>
<th>NFT</th>
<th>SP</th>
<th>AmG</th>
<th>pSub</th>
<th>LB**</th>
<th>AA</th>
<th>Deg. AmG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>M</td>
<td>3/4</td>
<td>1</td>
<td>1410</td>
<td>I</td>
<td>A</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>M</td>
<td>3/4</td>
<td>1</td>
<td>1370</td>
<td>I</td>
<td>B</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>M</td>
<td>3/3</td>
<td>1</td>
<td>1360</td>
<td>I</td>
<td>A</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>+/-</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>M</td>
<td>3/3</td>
<td>1</td>
<td>1490</td>
<td>I</td>
<td>B</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>M</td>
<td>3/3</td>
<td>1</td>
<td>1055</td>
<td>O</td>
<td>B</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>+/-</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>M</td>
<td>3/3</td>
<td>1</td>
<td>1450</td>
<td>I</td>
<td>B</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>M</td>
<td>3/3</td>
<td>1</td>
<td>1120</td>
<td>I</td>
<td>O</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>83</td>
<td>M</td>
<td>3/3</td>
<td>1</td>
<td>1280</td>
<td>I</td>
<td>A</td>
<td>3</td>
<td>1</td>
<td>i</td>
<td>1</td>
<td>+/-</td>
</tr>
<tr>
<td>9</td>
<td>75</td>
<td>F</td>
<td>3/3</td>
<td>1</td>
<td>1135</td>
<td>I</td>
<td>B</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>F</td>
<td>3/3</td>
<td>1</td>
<td>1200</td>
<td>I</td>
<td>O</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>+/-</td>
</tr>
<tr>
<td>11</td>
<td>79</td>
<td>F</td>
<td>3/3</td>
<td>1</td>
<td>1160</td>
<td>I</td>
<td>A</td>
<td>1</td>
<td>0</td>
<td>i</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>80</td>
<td>F</td>
<td>2/3</td>
<td>1</td>
<td>1270</td>
<td>I</td>
<td>B</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>82</td>
<td>F</td>
<td>3/3</td>
<td>1</td>
<td>1220</td>
<td>I</td>
<td>A</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>+/-</td>
</tr>
<tr>
<td>14</td>
<td>84</td>
<td>F</td>
<td>3/3</td>
<td>1</td>
<td>1160</td>
<td>I</td>
<td>B</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Abbreviations for Table 2 are the same as for Table 1, except that scoring of degeneration of ambient gyrus (Deg. AmG) is as follows: – = no tau-immunoreactive astrocytes; +/- = less than 5 tau-immunoreactive Gallyas-negative astrocytes in a section of the ambient.

* No grains found in medial temporal pole or anterior cingulate gyrus in these CNG cases.

** LB = Lewy bodies in brainstem and amygdala. No Lewy body is observed in the cerebral cortex in these cases.
progressive supranuclear palsy, 4 cases of AD plus dementia with Lewy bodies, 1 case of DG plus dementia with Lewy bodies, and 1 case of DG plus progressive supranuclear palsy.

Argyrophilic grains were seen in 81 of the 190 cases (42.6%). Forty-seven (46.5%) of the 101 cases with dementia had argyrophilic grains, and 34 (38.2%) of the 89 cases without dementia had grains. The age distribution of argyrophilic grains was as follows: 60 to 69 yr, 3 of 14 cases (21.4%); 70 to 79 yr, 26 of 73 cases (35.6%); 80 to 89 yr, 38 of 74 cases (51.4%); 90 to 99 yr, 14 of 28 cases (50%); and 100 to 103 yr, 0 of 1 case.

Comparative Study of Brains with DG and CNG

The profiles of the DG and the CNG cases are summarized in Tables 1 and 2. The DG cases included 7 males and 8 females, with ages ranging from 79 to 98 yr (mean age, 86.5 yr) and brain weights ranging from 990 g to 1,390 g (mean weight, 1,212 g). Five DG cases (cases 3, 5, and 7–9) were almost free of other senile changes. By comparison, the CNG cases included 8 male and 6 female, with ages ranging from 68 to 84 yr (mean age, 76.4 yr) and brain weights ranging from 1,055 g to 1,490 g (mean weight, 1,263 g).

Macroscopically, the DG brains showed atrophy of the medial temporal lobe, whereas the CNG cases had no significant abnormalities. The temporal lobe atrophy in the DG brains was greater anteriorly and was accentuated at the junction between temporal lobe and amygdala, such that the ambient gyrus (35–37) was constantly involved (Fig. 1A, B). The posterior hippocampus and entorhinal areas were relatively spared.

Microscopically, the distribution of argyrophilic grains was much more restricted in the CNG brains than in the DG brains. In 8 of 14 CNG cases, argyrophilic grains were limited to the ambient gyrus and anterior CA1 area, with accompanying oligodendroglial coiled bodies in the subcortical white matter. In the remaining 6 cases the argyrophilic grains had a wider distribution, extending to the posterior CA1, subiculum and transentorhinal area, and the basal and lateral subnuclei of the amygdala. Also present in these latter 6 cases of CNG were pretangles in...
the dentate gyrus and hippocampal CA2 subfield, tau-immunoreactive astrocytes (16) preferentially present around the uncal horn and in the amygdala, and rare ballooned neurons in the basal and lateral subnuclei of the amygdala. In contrast, the DG brains uniformly showed a much wider distribution of argyrophilic grains (Fig. 2A), with grains extending as far as the medial side of the temporal pole (Fig. 3).

Another distinctive histopathological difference between the DG and CNG cases was the presence of a superficial spongiosis associated with the argyrophilic grains (Fig. 2B) in the DG brains. The spongiosis was most prominent in the ambient gyrus, but was also present in the cortical subnuclei of the amygdala, in the entorhinal and transentorhinal areas, and in the subiculum. As the spongiosis became more severe, the argyrophilic grains became less numerous. A reactive tau-immunopositive astrocytosis, best demonstrated by double immunostaining with AT8 and GFAP (Fig. 2C), always accompanied the spongiosis. The CNG brains had only scattered AT8-immunoreactive astrocytes in the middle layer of the ambient gyrus in some cases (Table 2).

Pathological changes in the dentate gyrus, a predilection site for pretangles (38), showed some overlap between DG and CNG cases. The DG brains had abundant numbers of AT8-immunoreactive pretangles but no grains in dentate gyrus, as previously reported (38). Eight of the CNG brains (CNG cases 1, 2, 4, 6, 7, 9, 11 and 12) had...
no pretangles, 4 (CNG cases 3, 5, 10 and 13) had rare pretangles, and 2 (CNG cases 8 and 14) had numbers of pretangles comparable to those in DG brains.

Tau-immunoreactive ballooned neurons and coiled bodies were usually associated with grains. Ballooned neurons were most frequent in the basal and lateral subnuclei of amygdala, and coiled bodies were most frequent in the subcortical white matter of the affected area. Double immunostaining with AT8 and anti-αB-crystallin antibody showed peripheral localization of the AT8-immunoreactivity and central accumulation of the αB-crystallin epitope (Fig. 2D). AT8-immunoreactive granulovacuolar degeneration (39) was frequently seen in the areas abundant with grains and often associated with swollen neurons.

ApoE Genotyping

The results of apoE genotyping are summarized in Table 3. The genotype distributions and allele frequencies between the DG cases and the background were significantly different ($\chi^2 = 14.4$ and $14.5$, $p < 0.005$ and $p < 0.001$, respectively). The frequency of ε2 allele in the DG cases was significantly increased when compared with the background (26.7% vs 3.9%, $p < 0.01$ [Fisher exact test]) and with the AD cases (16.7% vs 0%, $p < 0.01$ [Fisher exact test]), but not when compared with the CNG cases (16.7% vs 3.6%, $p = 0.195$ [Fisher exact test]). In contrast, the frequency of ε4 allele in the DG cases was significantly decreased compared with the AD cases (0% vs 27.3%, $p < 0.005$ [Fisher exact test]). There was no significant difference in distribution of genotypes or frequencies of alleles between cases with and without argyrophilic grains ($\chi^2 = 3.9$ and 3.6, $p = 0.27$, and $p = 0.16$, respectively).

DISCUSSION

Our postmortem examination of the brains from 190 serial autopsies at a geriatric hospital revealed that the incidence of argyrophilic grains increased with age and peaked at 50% in subjects over 80-yr-old. The argyrophilic grains were limited to the medial temporal lobe, with the ambient gyrus being preferentially involved. Thus, argyrophilic grains are an age-related morphological change, like neurofibrillary tangles and senile plaques, and have a unique and highly restricted topographical distribution in the brain.
The preferential accumulation of the e2 allele of apoE in DG is consistent with the previously reported genotypic analyses and contrasts with the preferential accumulation of the e4 allele in AD (13, 14). These genotypic data underscore the distinctness of DG from AD. The data also suggest that the pathogenesis of argyrophilic grains is not influenced by apoE genotypes. We cannot find significant genotypic difference between CNG and DG in this study. Further studies, including the objective staging of the appearance of argyrophilic grains in a large series of autopsy cases with DG and CNG, may be important for determining the biological significance of argyrophilic grains and their role in the pathogenesis of DG.

ACKNOWLEDGMENTS

The authors thank Drs. Peter Davies, Takeshi Iwatsubo, Hiroshi Mori and Yasuo Ihara for the donation of their antibodies; Mr. Naoo Aikyo, Ms. Masako Maeda, Ms. Mieko Yamazaki, Ms. Sachiko Sugita, Ms. Chieko Kanai, Ms. Hiroko Matsuoka and Mr. Yoshihiro Fujita for technical support; Professor Kinuko Suzuki for encouraging and advising this study, and Professor Thomas W. Bouldin for editing the manuscript. This study was supported by grants-in-aid from Tokyo Metropolitan Institute of Gerontology. A part of this study was presented at the 76th Annual Meeting of the American Association of Neuropathologists Inc. held in Atlanta, Georgia, June 2000.

REFERENCES


TABLE 3

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>DG (15)</th>
<th>CNG (14)</th>
<th>AD (22)</th>
<th>With grains</th>
<th>Without grains</th>
<th>Background (1107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>e2/e3</td>
<td>5 (33.3%)</td>
<td>1 (7.1%)</td>
<td>0</td>
<td>11 (13.6%)</td>
<td>9 (8.2%)</td>
<td>86 (7.8%)</td>
</tr>
<tr>
<td>e3/e3</td>
<td>10 (66.7%)</td>
<td>11 (78.6%)</td>
<td>13 (59.1%)</td>
<td>57 (70.4%)</td>
<td>76 (69.7%)</td>
<td>846 (76.4%)</td>
</tr>
<tr>
<td>e3/e4</td>
<td>0</td>
<td>2 (14.3%)</td>
<td>6 (27.3%)</td>
<td>9 (11.1%)</td>
<td>16 (14.7%)</td>
<td>160 (14.5%)</td>
</tr>
<tr>
<td>e4/e4</td>
<td>0</td>
<td>0</td>
<td>3 (13.6%)</td>
<td>0</td>
<td>3 (2.8%)</td>
<td>15 (1.3%)</td>
</tr>
<tr>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (4.9%)</td>
<td>5 (4.6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: DG: dementia with grains; CNG: argyrophilic grain disease without cognitive impairment; AD: Alzheimer disease. Significant differences were detected between DG and AD and between DG and background for the e2 allele, and between DG and AD for the e4 allele.


Received December 20, 2001
Revision received May 20, 2002
Accepted May 22, 2002