Mutations in the amyloid precursor protein (APP) gene cause one form of early onset familial Alzheimer’s disease (AD). One such family has been studied genetically and neuropathologically and represents the basis of the present report. Four siblings with the APP717 Val to Ile mutation, aged 59, 65, 61 and 64 years, apolipoprotein E (APOE) genotyped 2, 4 (first three) and 2, 3 respectively, had severe AD, Braak stage VI with frequent neurofibrillary tangles in the primary visual cortex, Brodmann area 17. The first one also met McKeith criteria for the limbic stage of dementia with Lewy bodies but did not have substantia nigra Lewy bodies. The second two met McKeith criteria for the neocortical stage of dementia with Lewy bodies and both had substantia nigra Lewy bodies. The fourth had AD but no Lewy bodies. A cousin without the APP717 mutation who was APOE 3, 4, developed dementia at age 60 and died at age 75. She had severe cerebrovascular atherosclerosis, less severe AD, Braak stage V, with sparing of area 17. She also had Lewy bodies in the substantia nigra and in the cortex and met McKeith criteria for neocortical stage of dementia with Lewy bodies. Extrapyramidal features were present in all five. Lewy bodies have been described in 53% of reported autopsies on individuals with the APP717 Val to Ile mutation coincident with dementia and AD neuropathologic changes. These observations suggest an association between the chromosome 21 APP mutation and Lewy body formation, possibly mediated by other environmental or genetic factors.

Key words Alzheimer’s disease · Dementia with Lewy bodies · Parkinson’s disease · APP717 gene mutation · Beta amyloid

Introduction

Pathologically, Alzheimer’s disease (AD) occurs together with Parkinson’s disease (PD) much more frequently than can be explained by chance alone [21]. PD is characterized clinically by extrapyramidal signs such as rigidity, bradykinesia and resting tremor, and pathologically by neuronal loss, gliosis and Lewy bodies within the substantia nigra (SN). Lewy bodies in the nigra occur in about 5% of the normal population, but when observed in the setting of clinical parkinsonism, are considered diagnostic of PD [11]. PD is confirmed at autopsy in only approximately 75% of cases of clinical parkinsonism [9, 20]. The other 25% exhibit a variety of other pathologic processes including AD.

AD has been shown to be associated with a number of different genes. One of these, apolipoprotein E (APOE), a susceptibility gene, increases the risk of development of AD and decreases the age of onset [8] but does not cause the disease. In 60–90% of cases, AD strikes during the sixth decade of life or later [50] and the APOE-4 allele is associated with 40–60% of all AD cases [44, 51].

In contrast, early-onset familial forms of AD are pathogenic in an autosomal dominant fashion with mutation in the genes causing the disease. The genes that fall into this category include presenilin 1 on chromosome 14 [47], presenilin 2 on chromosome 1 [42], and amyloid precursor protein (APP) on chromosome 21 [15]. Mutations in the familial AD genes are associated with onset of symptoms one to two decades earlier than in late-onset sporadic AD.

Here, we report the neuropathologic features of a family with dementia and the APP717 Val to Ile mutation.
Four individuals had the mutation, one did not. At autopsy, all exhibited senile plaques and neurofibrillary tangles and four had Lewy bodies.

## Methods

Nurse coordinators of the Bryan Alzheimer’s Disease Research Center (ADRC) autopsy and tissue donation program at Duke University Medical Center were contacted by a non-affected sibling of Family 372. Members of the Genetics Core of the Bryan ADRC collected extensive background information from the family. Additional participants of Duke Family 372 were recruited by methods approved by the Institutional Review Board. In cases where a subject was unable to provide informed consent for participation in clinical studies and tissue donation, permission was obtained from next of kin. Family members have been and continue to be followed clinically via telephone contact or field visits as individual circumstances permit.

Four family members died in North Carolina locations remote from Duke University and were autopsied at those sites. Their brains were bisected, half frozen, half fixed in 10% buffered formalin, and sent to Duke University for neuropathology and distribution to other researchers. Case 3 was examined at Duke University according to the Rapid Autopsy Protocol [22].

Mutation analysis of this family has been previously reported [43]. For the purpose of the present study, the APP gene from autopsied family members was sequenced using single-strand PCR followed by standard Sequenase sequencing of the PCR product, verifying the previously reported findings.

The first two cases that presented for autopsy in 1989 and 1991 have been described previously [36, 30]. For consistency, all five cases were re-examined by one neuropathologist (C.M.H.) and a second researcher (C.K.R.). At the time that all five cases were re-examined, a substantial quantity of the tissue from the early cases had been dispersed from the Kathleen Bryan Brain Bank to other researchers. Only one original SN slide, stained with Luxol fast blue/hematoxylin and eosin (LFB/H&E) was available for case 1.

Archival blocks were sectioned and additional tissue sections submitted including mid-frontal, inferior parietal, superior temporal, and occipital cortices (Brodmann areas 17 and 18), coronal hippocampus with adjacent temporal neocortex at the level of the lateral ventricle, amygdala with entorhinal cortex, basal ganglia and insula, thalamus, SN, cerebellum, anterior and postero cingulate gyrus including deep white matter. Sections were embedded in paraffin and cut at 8 μm. Routine archived tissue sections had been stained with LFB/H&E, a modified King silver stain, Congo Red for visualization of vascular amyloid, and a beta amyloid (Aβ) immunostain pretreated with 99% formic acid, Congo Red for vascular amyloid angiopathy. Immunohistology slides were counterstained with hematoxylin for visualization of nuclei.

Neuritic plaque frequency was graded according to CERAD criteria [13] and neurofibrillary change was staged according to Braak and Braak [4]. Cortical sections and transentorhinal cortex were examined and scored for Lewy body frequency according to McKeith criteria for the evaluation of dementia with Lewy bodies [34].

The literature was reviewed for reports of Lewy bodies in individuals with (1) known APP AD mutations, (2) Down’s syndrome, and (3) hereditary cerebral hemorrhage with amyloidosis of the Dutch type (HCHWA-D), a familial form of amyloid angiopathy linked to a mutation in APP approximately 20 codons away from the APP AD mutation.

## Results

Family members are labeled cases 1–5 according to the order in which they appeared at autopsy (see Table 1, first three columns, for different patient identification schemes from a previous publication [36] and the pedigree).

All five family members were profoundly demented. Their symptoms included severe disorientation and memory loss, dyscalculia, behavioral disturbances such as aggression and wandering, and apraxia followed by a complete loss of mobility.

Several family members declined detailed neurological examination by Bryan ADRC physicians. Histories of parkinsonism were extracted from private physician records and discussion with family members interested in our studies. All known parkinsonian symptoms are described herein. Clinical features of four family members examined at autopsy have been previously described [36]. Briefly, case 1 displayed twitching movements in all her limbs at about age 55 years. Physical examination of case 2 at age 60 revealed a poverty of facial expression, mild myoclonus, and moderate generalized increased tone with cogwheeling in the upper limbs. Case 3 showed marked bradykinesia with masked facies and waxy rigidity of all extremities at age 41. Treated with neuroleptics, she displayed dystonic posturing. Neurologic examination of case 4 revealed “extrapyramidal features” which were attributed by her physician to neuroleptic medication. This patient was also noted to have fluctuating insight into her

<table>
<thead>
<tr>
<th>Case ID</th>
<th>Pedigree</th>
<th>Age at death (years)/sex</th>
<th>Age at onset (years)</th>
<th>Disease duration (years)</th>
<th>APP mutation</th>
<th>Braak stage</th>
<th>APOE genotype</th>
<th>Brain weight (g)</th>
<th>SN Lewy bodies</th>
<th>Cortical Lewy bodies</th>
<th>McKeith stage</th>
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<tbody>
<tr>
<td>1</td>
<td>U 0106</td>
<td>59/F</td>
<td>49</td>
<td>10</td>
<td>Yes</td>
<td>VI</td>
<td>2.4</td>
<td>960a</td>
<td>No</td>
<td>Yes</td>
<td>Limbic</td>
</tr>
<tr>
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<td>W 0102</td>
<td>65/F</td>
<td>50</td>
<td>15</td>
<td>Yes</td>
<td>VI</td>
<td>2.4</td>
<td>986a</td>
<td>Yes</td>
<td>Yes</td>
<td>Neocortical</td>
</tr>
<tr>
<td>3</td>
<td>T 0001</td>
<td>61/F</td>
<td>41</td>
<td>20</td>
<td>Yes</td>
<td>VI</td>
<td>2.4</td>
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</tr>
<tr>
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<td>15</td>
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<td>64/F</td>
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<td>17</td>
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<td>VI</td>
<td>2.3</td>
<td>768a</td>
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a Estimated by doubling weight of one fixed hemisphere