Familial Early-Onset Dementia With Tau Intron 10 + 16 Mutation With Clinical Features Similar to Those of Alzheimer Disease

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Background: Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) owing to the tau intron 10 + 16 mutation usually occurs with a prototypical frontotemporal dementia phenotype with prominent disinhibition and affective disturbances.

Objective: To report a new FTDP-17 pedigree with the tau intron 10 + 16 mutation demonstrating a clinical phenotype suggestive of Alzheimer disease.

Design: Case reports.

Setting: Regional neuroscience centers in northwest England.

Patients: We examined 4 members of a kindred in which 8 individuals were affected in 3 generations.

Results: All 4 patients reported memory difficulty. Marked anomia was also present, but behavioral disturbances were conspicuously absent in the early stages of disease. All patients had an initial clinical diagnosis of Alzheimer disease. No mutations were found in the presenilin or amyloid precursor protein genes. Pathologic examination of the proband showed features typical of FTDP-17, and tau gene analysis showed the intron 10 + 16 mutation.

Conclusions: This pedigree illustrates the phenotypic variability of tau intron 10 + 16 mutations. In pedigrees with a clinical diagnosis of Alzheimer disease but without presenilin or amyloid precursor protein gene mutations, tau gene mutations may be found.

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FRONTOTEMPORAL DEMENTIA (FTD) with parkinsonism linked to chromosome 17 (FTDP-17) results from mutations in the gene encoding the microtubule-associated protein tau. Approximately 40 pathogenic mutations and several polymorphisms have been described (Alzheimer Disease and Frontotemporal Dementia Mutation Database: http://www.molgen.ua.ac.be/Admutations).1,2 Clinical heterogeneity is a feature of FTDP-17.3,4 In addition to prototypical behavioral features of FTD, cases have been reported with the phenotype of progressive supranuclear palsy,5 idiopathic Parkinson disease,6 corticobasal degeneration,7 Alzheimer disease (AD),8,9 and respiratory failure10 as well as with neuropathologic features typical of progressive supranuclear palsy and corticobasal degeneration.5,10 Clinical heterogeneity may be seen with the same tau mutation: for example, R406W may be manifested with late-onset memory deficits similar to AD3 or as early-onset rapidly progressive FTD.11 Other tau mutations have a more homogeneous phenotype; for example, the +16 mutation in the intron after exon 10 has been described in several kindreds with disinhibition and affective disturbances characteristic of FTD developing in the fourth to sixth decades of life,12-17 although progressive subcortical gliosis was the pathologic finding in 1 of these.13 We report another pedigree with the +16 mutation without behavioral disturbances but with AD-like clinical features.

REPORT OF CASES

Four subjects, 3 brothers and their cousin, were seen during a 6-month period (August 1, 1997, to January 5, 1998). From the family history, 4 other affected individuals were identified. Thus, 8 individuals in 3 generations fulfilled criteria for autosomal-dominant inheritance (Figure 1).
A 45-year-old man and his wife reported a 3-year history of progressively worsening memory difficulties such as recalling the names of persons and objects and difficulty using familiar household appliances such as the dishwasher. He made errors recounting autobiographic information such as when he had lost his job. There was a family history of early-onset dementia. His mother (II-2) was said to have had AD with onset at age 43 to 44 years and death at age 51 years. Her sister (II-3) and brother (II-4) were also reported to be affected, as was their maternal grandmother (I-2); all died in their mid 40s to early 50s.

Clinical examination showed no abnormal neuropsychologic signs and there were no behavioral features of disinhibition. Bedside neuropsychologic testing showed word-finding difficulties with circumlocutions. The Mini-Mental State Examination (MMSE) score was 8 (of a possible 30), with disorientation in time (1 point, 5 items) and place (1 point, 5 items), impaired 5-minute recall (0 points, 3 items), and naming problems (0 points, 2 items), but preserved ability to draw intersecting pentagons. Formal neuropsychologic assessment showed a 15-point discrepancy on the Wechsler Adult Intelligence Scale, Revised (WAIS-R) between verbal and performance IQ in favor of nonverbal abilities. He performed at the first percentile on verbal memory for immediate and delayed recall and was similarly impaired on visual delayed recall, also evident on recall of the Rey Complex Figure Test, although copy was satisfactory. Severe impairment was evident on the Graded Naming Test (0 points, three items), but preserved ability to draw intersecting pentagons. Structural brain imaging (computed tomography and magnetic resonance imaging) showed generalized atrophy, relatively increased around the sylvian fissures and midtemporal lobes. The electroencephalogram showed normal findings. The cerebrospinal fluid findings showed only a mildly elevated protein level (0.049 g/dL [to convert to grams per liter, multiply by 10.0]).

A clinical diagnosis of probable early-onset familial Alzheimer disease (EOFAD) was made on the basis of clinical diagnostic criteria. He was treated with cholinesterase inhibitors (ChEIs), with some initial improvement (MMSE score increased to 13). Neurogenetic testing showed no mutation in the genes encoding the amyloid precursor protein, presenilin-1, presenilin-2, or prion protein. During the next 2 years, his condition gradually progressed, particularly affecting language function, which became extremely sparse. Behavioral features appeared during the next year, with restlessness, wandering, and hyperorality but no verbal or physical aggression. Progressively, he developed urinary incontinence and mild parkinsonism and became mute. A trial of memantine hydrochloride therapy had no effect. He became bedbound and died 7 years after diagnosis. Consent for postmortem examination was obtained.

### PROBAND’S BROTHERS (III-2 AND III-3) AND COUSIN (III-9)

The proband’s next older brother (III-2) was seen at age 42 years with a 3-year history of memory and language difficulties. His MMSE score was 26, with 3 points lost for 5-minute recall. Neuropsychologic assessment (WAIS-R) showed uniform depression of subtest scores, with generalized intellectual loss, particularly for nonverbal functions. He exhibited severe impairment on tests of verbal and visual memory for immediate and delayed recall, performing below the fifth percentile on all measures. He demonstrated no impairment on the Rey Complex Figure Test but exhibited impairment on recall. Severe impairment was evident on the Graded Naming Test (1 point of a possible 30), Stroop Test (below the second percentile), and Verbal Fluency Test (below the first percentile). Structural computed tomographic brain imaging showed generalized atrophy disproportionately affecting the temporal lobes. A clinical diagnosis of probable EOFAD was made. Neurogenetic testing showed no amyloid precursor protein, presenilin-1, presenilin-2, or prion protein mutation. Therapeutic trials of ChEIs and memantine therapy had no effect. Three years after diagnosis, he was effectively mute and behavioral deterioration with disinhibition was noted. Later, he became apathetic and had occasional falls.

The next eldest brother (III-3) was seen at age 40 years and reported forgetting names. Symptoms progressed over the next 3 years. Neuropsychologic assessment (WAIS-R) showed severe impairments on all measures of verbal and visual memory for immediate and delayed recall (below the first percentile). Severe impairment was evident on the Graded Naming Test (1 point of a possible 30) and the Stroop Test (between the second and fourth percentiles), and his score was within the low normal range on the Verbal Fluency Test (11th to 22nd percentile). Structural computed tomographic brain imaging showed global atrophy. Based on the initial findings and the family history, a clinical diagnosis of EOFAD was made. Trials of ChEIs and memantine therapy were not helpful. Behavioral features (agitation and undressing) emerged after 4 years.

Their cousin (III-9), son of the proband’s maternal uncle (II-4), was seen at age 48 years with a 2-year history of difficulty remembering new information. Repetitive questioning was a feature. He got lost walking home the short distance from the hospital. He was unable to perform simple money transactions. His MMSE score was 26, with disorientation in time, impaired recent memory, naming, and visuospatial tasks. Primitive reflexes (grasp, pout, and palmomental) were evident on examination. Computed tomographic brain imaging showed marked atrophy, especially of the temporal lobes. A clinical diagnosis of EOFAD was made. Therapeutic trials of ChEIs...
and memantine therapy were not helpful. He later developed urinary incontinence, made repeated attempts to leave the house or care facilities, and exhibited mild features of parkinsonism.

**NEUROPATHOLOGIC FINDINGS (III-1)**

Macroscopically, the proband’s brain showed bilateral frontotemporal atrophy, severe at the temporal pole and relatively sparing the superotemporal lobe (Figure 2). The hippocampal formation (Ammon’s horn) was mildly atrophic. The caudate nucleus and putamen were atrophic, the caudate appearing flattened in profile. The substantia nigra and locus coeruleus were underpigmented, the former markedly so. There was no evidence of cerebrovascular disease.

Microscopically, the neocortex in the midfrontal gyrus, the superior and middle temporal gyri, and the inferoparietal lobe showed neuronal loss and gliosis with layer II microvacuolation. Tau immunohistochemistry showed rare cortical neurofibrillary tangles, primarily in the deep cortical layers, but more widespread granular neuronal immunopositivity. Glial coillike tau structures were also seen. No cortical ballooned neurons, Pick bodies, motor neuron disease–type inclusions, Lewy bodies, or Aβ-positive amyloid plaques were seen. Frontal, temporal, and parietal white matter showed prominent glial tau immunopositivity, primarily in the form of oligodendroglial coillike structures (Figure 3). Low numbers of neurofibrillary tangles and other tau-positive neuronal inclusions were seen in the hippocampus, but moderate to high numbers of grainlike and threadlike structures were seen in the background neuropil in CA1 and the subiculum (Figure 4). Some pyramidal neurons contained Hirano bodies. The striatal structures contained moderate numbers of neurofibrillary tangles with more striking glial tau pathologic features in its associated white matter. The substantia nigra showed neuronal depletion with moderate numbers of neurofibrillary tangles and neuropil threads but no Lewy bodies.

The pathologic findings were judged consistent with FTDP-17, similar to those previously described in individuals with the +16 mutation. Genetic testing confirmed the tau exon 10 +16 splice site mutation in the proband (Figure 5).

**COMMENT**

All 4 patients from this kindred with autosomal-dominant early-onset dementia (mean age at onset, 42 years; age range, 39-46 years) exhibited forgetfulness. This symptom, corroborated by family members, encompassed both orientation and autobiographic information, and semantic loss. In 3 patients, neuropsychologic assessment confirmed the marked memory deficits at disease onset. Prototypical features of FTD such as restlessness, disinhibition, hoarding behavior, routines, and rituals were not noted initially. All patients initially had a diagnosis of probable EOAD, but no mutations in genes known to be associated with EOAD were identified. All received ChEIs and memantine therapy, without clinical benefit. Behavioral and psychologic symptoms more in keeping with a diagnosis of FTD emerged later in the course of illness; mild parkinsonism was observed in 2 patients (III-1 and III-9). At postmortem examination, the proband demonstrated tau-positive inclusions typical of FTDP-17, and tau gene analysis revealed the intron 10 +16 mutation.
In retrospect, the profound anemia early in the course of disease might have suggested the correct diagnosis. Naming is relatively preserved in some EOAD presenilin-1 gene mutations. The AD-like phenotype has been described in association with certain tau mutations (R406W and P301L), but all previously reported kindreds with the +16 mutation have had a typical and relatively homogeneous FTD clinical phenotype with behavioral and linguistic features. Memory loss has been noted during the disease course in some kindreds with the +16 mutation, but this may reflect semantic loss or be attributable to inattention and strategic impairments secondary to frontal lobe dysfunction. In contrast, our patients had no obvious behavioral disinhibition when first seen or when undergoing neuropsychologic assessment, but they did have poor autobiographic memory.

Eight kindreds with the +16 mutation have been reported from northwest England and north Wales. On the basis of geographic clustering and haplotype analysis, these 8 families may share a common founder. Whether our Liverpool kindred is related to these families remains to be determined. The age at onset in this family was younger, and the phenotype when they were first seen was different. Causes of phenotypic heterogeneity in families with the tau mutation have not been identified. The apolipoprotein E genotype does not seem to have a role.

Our clinical experience suggests that screening for tau mutations, as well as amyloid precursor protein, presenilin-1 and presenilin-2, may need to be considered in patients having a clinical diagnosis of EOAD. This situation may reciprocate that in certain presenilin-1 mutations with typical autosomal-dominant FTD phenotype. Certain presenilin-1 mutations have been reported to develop with either the AD or FTD phenotype, for example, M139V. On occasion, the FTD phenotype has prompted analysis of the tau gene before a presenilin-1 mutation has been identified.  

**References**

16. Pickering-Brown SM, Richardson AMT, Snowden JS, et al. Inherited frontotem-


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