Presenilin 1 Mutation in an African American Family Presenting With Atypical Alzheimer Dementia

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Background: Alzheimer disease (AD) is characterized by memory and visuospatial deficits with relative sparing of personality. Mutations in 3 genes (presenilin 1 and 2 and amyloid precursor protein) are associated with presenile AD. Presenilin 1 gene mutations have not been described in African Americans.

Methods: We studied an African American family with autosomal dominant rapidly progressive dementia and psychosis occurring early in the fifth decade of life. We performed neurologic evaluations, psychometrics, and neuroimaging. We sequenced the amyloid precursor protein gene, presenilin 1 and 2, and tau in affected and unaffected family members. One patient underwent a brain biopsy and subsequent autopsy.

Results: Personality change, auditory and visual hallucinations, delusions, memory impairment, word-finding difficulties, and subsequent rigidity, dystonia, myoclonus, and mutism developed in 2 brothers. Neuropsychometric testing in one was consistent with frontotemporal dementia or atypical AD. Neuroimaging studies showed diffuse cortical involvement. A clinical diagnosis of familial non-Alzheimer dementia was made. However, results of temporal lobe biopsy in one revealed amyloid neuritic plaques, and autopsy results confirmed the diagnosis of AD. Gene sequencing revealed a presenilin 1 point mutation (M139V) cosegregating with the disease. A tau polymorphism in exon 7 (A178T) was found in an affected brother and unaffected relatives.

Conclusions: We report the first documented presenilin mutation in African American patients presenting with early personality change, psychosis, and memory loss with preserved praxis. The M139V mutation can present differently between kindreds, with some features suggestive of a frontal lobe syndrome. The M139V mutation can lead to atypical AD, and genetic background may have a role in determining the phenotype of genetically defined AD.

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Each patient underwent standardized neuropsychometric testing as reported below. The brothers underwent evaluation in different institutions and therefore with different testing batteries.

INVESTIGATIONS

Both brothers underwent routine laboratory screening, measurement of titers for Lyme disease antibody and rapid plasma reagin level, VDRL testing, enzyme-linked immunosorbent assay for human immunodeficiency virus, lumbar puncture, computed tomography, and magnetic resonance imaging. Electroencephalography was performed on patient 2 but not patient 1. Positron emission tomography with fluorine F 18-labeled deoxyglucose was performed on patient 1, and single-photon emission computed tomography with technetium Tc 99m-hexamethylpropylene amine oxime on patient 2.

PATHOLOGY

A diagnostic brain biopsy was performed on patient 2 in January 1991. The cerebral isocortex and underlying white matter of tissue samples from the middle left temporal gyrus were examined by staining with hematoxylin-eosin, hematoxylin-eosin–Luxol fast blue, hematoxylin for white matter, and Congo red. Isocortex and underlying white matter samples were also examined by staining with Bielschowsky and Bodian silver impregnations. Deep-frozen tissue was examined by staining with toluidine blue O stain. Formalin-fixed and paraffin-embedded sections from the middle frontal, superior and middle temporal, precentral, and angular gyri; hippocampus; amygdala; basal forebrain; and biopsy site in the left temporal lobe were stained with thioflavine S and examined under a fluorescence microscope. Selected sections were also stained and examined with a modified Bielschowsky silver stain.

GENETICS

Tau exons 1 through 5, 7, and 9 through 13 and presenilin 1 exons 3 through 12 were amplified from genomic DNA from individuals with primers designed from flanking intron sequence (tau exons 4a, 6, and 8 are essentially absent in human brain messenger RNA and were not analyzed). For both genes, we used 50 ng of DNA in a 50-mL reaction mixture containing 20 pmol of each primer, 0.2mM deoxynucleotide triphosphates, and 1 U of Taq polymerase (QIAGEN, Valencia, Calif). All reaction mixtures included 5×Q solution (QIAGEN). Amplifications were performed oil free in touchdown thermal cyclers (Hybaid, Cambridge, England). Conditions were 35 cycles of 94°C for 30 seconds, 60°C to 50°C touchdown annealing for 30 seconds, and 72°C for 45 seconds with a final extension of 72°C for 10 minutes. All products were purified using a polymerase chain reaction purification kit (Qiagen; QIAGEN). For each exon, 100 ng of product was sequenced in both directions using the Big Dye kit (PerkinElmer, Inc, Wellesley, Mass) and relevant polymerase chain reaction primers in accordance with the manufacturer's protocol. Sequencing was performed on an automated sequencer (ABI37796; ABI, Foster City, Calif) and processed using Factura and Sequence Navigator software (PerkinElmer, Inc). Standard apolipoprotein E genotyping was also performed in both patients.

REPORT OF CASES

Patient 1

In 1996, a credit analyst aged 45 years presented with a 3-year history of personality change, memory difficulty, delusions, and hallucinations. At 42 years of age, he began to make errors in managing funds and signing letters at work. These errors necessitated termination of his employment at 43 years of age. During the next 2 years, he became increasingly compulsive about exercise and achieved black belt status in martial arts. By 45 years of age, he had experienced a dramatic decline in his daily functioning. His daughter discovered that he was no longer housecleaning or paying bills. He was inappropriate and jovial, and visual and auditory hallucinations and delusions developed. His mood was labile, and he showed no insight into his condition. He required constant reminding of recent events, and language function declined. He was unable to complete a coherent sentence and had difficulty recalling the names of family members. He later became disoriented to time and place.

On examination, he was mute, distractible, and uncooperative but placid. Speech was rapid and demonstrated clear signs of thought disorder, particularly loose associations and a rambling, tangential quality. He was energetic and flirtatious during the examination and repeatedly spoke about his clothing, which he believed to have been stolen by “a man.” He also reported seeing “blue animals—like with electricity moving through them.” Results of the neurologic examination revealed spontaneous myoclonus in the right more than the left arm. No stimulus-sensitive myoclonus was observed. The patient had positive grasp, snout, palpomental, and glabellar reflexes and hyperreflexia. He had spasticity and rigidity in the neck, arms, legs, and trunk.

There was no apparent family history of schizophrenia outside the context of dementing illness. Medical history was notable for casual alcohol use on weekends for 8 years until 30 years of age. There was no history of other drug abuse or head injury. Family history was notable for a brother (patient 2) who died of a similar illness, and a father (also of African American background) with early-onset dementia with psychosis who had died in his sixth decade of life. One daughter had bipolar disorder.

Patient 2

A forklift operator, aged 42 years, with a history of ongoing daily alcohol abuse presented with personality change and memory impairment. In February 1990 he began to neglect his child, whereas previously he had pampered him. He started losing items around the home and became violent and agitated. He forgot to buy items in a grocery store. He began to curse. During the course of 8 months, he experienced a progressive decline in functioning and required assistance for activities of daily living. His wife described him at the time as “more like a child, he needed reminding to eat.” He partially prepared food, yet insisted that it was cooked. He became

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depressed and spoke of dying. He displayed diminished language production and comprehension. He discontinued alcohol use in June 1990. Serum vitamin B₁₂ level was noted to be slightly below normal, and he started supplementation with cyanocobalamin, folic acid, and thiamine hydrochloride.

At 43 years of age, complex partial seizures with secondarily generalized events developed. He became uncooperative and exhibited episodes of violent psychotic behavior, characterized by auditory and visual hallucinations and paranoia. He lost his job. His medical history was notable for 2 previous head injuries, with loss of consciousness for 15 minutes in one without apparent residual deficits.

On examination, he had a vacant euphoria and a constant smile. He was passive, apathetic, inattentive, and disoriented to time, place, and situation. He had telegraphic speech and impaired comprehension. Object naming, reading, spelling, and repetition were impaired. He had rare neologisms and literal paraphasias. Recurrent, continuous, and stuck-in-set perseverations were observed. Short- and long-term memory were severely compromised. Anosognosia, alexia, agraphia, finger agnosia, right/left disorientation, and acalculia were evident. Constructional dyspraxia was evident, but limb praxis was preserved. Bedside cognitive testing indicated left hemisphere and bifrontotemporal dysfunction. Ophthalmoplegia and nystagmus were absent, and results of cranial nerve, motor, and coordination examinations were normal. Gait was narrow based with no ataxia. Babinski and frontal release signs were absent. Diagnostic considerations were frontotemporal dementia, atypical AD, Creutzfeldt-Jakob disease (prompting brain biopsy), and Wernicke-Korsakoff syndrome. In January 1991, a brain biopsy was performed.

By 48 years of age, he was abulic but occasionally muttered unintelligible phrases. Snout, glabellar, palmo-mental, and grasp reflexes were evident. Tendon jerks, finger and toe flicking, and tapping of the forehead and mouth elicited stimulus-sensitive cortical myoclonus. He became incontinent and required a gastrostomy tube. He died at 49 years of age of bronchopneumonia. An autopsy was performed.

**NEUROPSYCHOMETRICS**

Patient 1 had an initial Mini-Mental State Examination score in January 1996 of 24 of 30, which declined to 14 of 30 during the course of 6 weeks, probably related to inattention. Formal neuropsychometric testing in January 1996 showed poor executive functioning, deficits in abstract thought, impaired verbal functioning, voluminous speech, an inability to learn new information, and deficits in confrontation naming. He exhibited profound memory impairment, with performance at or below the second percentile on the logical memory and visual reproduction subsets of the Wechsler Memory Scale–Revised, on measures of immediate and delayed recall. Recognition memory was severely impaired, and he was easily distractible during testing. His performance on the block design subset of the Wechsler Adult Intelligence Scale–Revised was impaired (scoring in the ninth percentile), as was his performance on the Hooper Visual Organization Test (13 of 30). Measures of verbal functioning showed difficulty with confrontation naming. The Boston Naming Test score was 38 of 60, greater than 4 SDs below the mean score for his age group; the Animal Naming Test score was 11. Frontal lobe functioning was severely impaired, with 14 responses in 20 minutes on the Wisconsin Card Sorting Test, despite strong encouragement. Performance on the Trail-Making Test part A was below the 10th percentile. Part B performance was below the first percentile. Deficits in abstract thought on the proverb subset of the Wechsler Adult Intelligence Scale–Revised were evident, as was perseverative behavior on the vocabulary subset. The patient’s praxis was unimpaired, with a perfect score on the Western Apraxia Examination.

Patient 2 underwent primarily bedside cognitive evaluation as described in the case report. He exhibited a pattern of decreased awareness and concern, dysfluency, and delusional psychosis. His Mini-Mental State Examination score was 13 of 38 in June 1990, 18 of 30 in July 1990, and 12 of 30 in August 1990. The Boston Naming Test score was 40, and the Animal Naming Test score was 9. In August 1990, the patient was administered the following (scores in parentheses): Clinical Dementia Rating Scale (1.66), Hachinski Ischemic Scale (3), Hamilton Depression Scale (14), Blessed Dementia Scale (8), and Karnofsky Scale (60).

**IMAGING**

Magnetic resonance imaging in patient 1 showed moderate generalized atrophy and mild leukoaraiosis. The positron emission tomography study on patient 1 showed bilateral decreased tracer accumulation in the frontal and temporoparietal regions. Results of computed tomography on patient 2 were read as normal. The single-photon emission computed tomography study on patient 2 showed multiple bilateral perfusion defects. Multiple sharply defined defects involving the right and left posterior frontal and parietal lobes were evident, with defects greater on the left than the right side. Bilateral temporal lobe defects were also noted.

**LABORATORY**

Electroencephalography performed on patient 2 showed diffuse background slowing and bilateral frontal theta activity indicative of diffuse cerebral dysfunction. Results of laboratory investigations were within reference ranges.

**PATHOLOGY**

A stereotactic brain biopsy of the left temporal lobe of patient 2 was performed in January 1991 and showed numerous neuritic plaques, which met criteria of the Consortium to Establish a Registry for Alzheimer’s Disease for a diagnosis of AD. On postmortem examination in July 1997, more frequent neuritic plaques and NFTs and a marked increase in the number of neuritic amyloid plaques when we compared the initial biopsy site with the same...
site at autopsy 6 years later (Figure). Frequent NFTs were found in the hypothalamus, and moderate neuronal loss was evident in the substantia nigra. Surviving nigral neurons occasionally exhibited NFTs but no Lewy bodies.

GENETICS

We found the presenilin 1 M139V point mutation in both brothers. This mutation was not present in any of the unaffected relatives. We found a tau polymorphism/mutation in exon 7 (A178T) in only 1 of the affected brothers (patient 1) and in other unaffected family members. The A178T mutation introduces an extra proline-directed phosphorylation site in the hyperphosphorylated site found in the tauopathies. Both patients were homozygous for apolipoprotein E3.

We herein report, to our knowledge, the first documented occurrence of a presenilin mutation in an African American family. The genetic analysis of our 2 patients disclosed a known presenilin 1 mutation, M139V, cosegregating with the disease. Our patients presented with early personality change, psychosis, memory impairment, and relative preservation of praxis, which is somewhat atypical for AD. Taking the results of bedside evaluation and neuropsychometric and neuroimaging studies together, a clinical diagnosis of non-Alzheimer dementia was made.

Although patient 1 exhibited some features consistent with a diagnosis of frontotemporal dementia (early decline in interpersonal conduct, impaired regulation of conduct, emotional blunting, loss of insight, decline in hygiene and grooming, distractibility, impersistence, pressure of speech, primitive reflexes, rigidity, and impairment on executive tasks), the presence of early memory impairment, constructional dyspraxia, and nonspecific functional neuroimaging findings was more in keeping with AD. Patient 2 likewise met some of the criteria for a diagnosis of frontotemporal dementia (early decline in interpersonal conduct, impairment of regulation of conduct, mental rigidity, distractibility, perseveration, and economy of speech), but early memory impairment, constructional dyspraxia, and background slowing on electroencephalography were less consistent with a diagnosis of frontotemporal dementia. The clinical picture in patient 2 was complicated by ongoing alcohol abuse. However, he continued to deteriorate clinically after the discontinuation of alcohol use. Neither patient exhibited a classic AD phenotype, as the behavioral changes preceded or coexisted with the memory impairment. Overall, both patients exhibited a mixed nonspecific pattern of progressive dementia with features of prominent behavioral change, early memory impairment, preservation of limb praxis, and psychosis.

Binetti et al reported on the clinical differences and overlap between patients with Pick disease and AD in a cross-sectional and longitudinal study. Caregiver reports of personality change and language impairment were significantly more common in Pick disease than in AD in their cohort. Deficits in memory were commonly reported by caregivers in both groups, but significantly more often in AD. On results of cognitive testing, patients with Pick disease had a superior performance on measures of explicit memory and visuospatial functioning when compared with those with AD. These authors concluded, however, that despite these differences on cognitive testing results, substantial overlap exists and, therefore, limits the diagnostic value of cognitive testing.

Presenile AD due to the substitution of valine for methionine at codon 139 of the presenilin 1 gene has been previously described in British and German families. A German patient with the M139V mutation of the presenilin 1 gene followed up for 7 years had a phenotype somewhat similar to our patients, characterized by social withdrawal and early euphoria. Myoclonus and generalized seizures also occurred. Progressive frontal and temporal cortical atrophy was found on imaging studies. Impaired visuospatial functioning was evident. No evidence of psychosis was noted. An earlier age of onset (38 years) was noted compared with our patients (42 and 45 years). The 2 British families were different from the aforementioned German patient and our patients. The British patients had relative preservation of naming, reading, and object recognition, even with profound cognitive impairment. Praxis was abnormal in moderately affected subjects, and myoclonus appeared early. The British patients exhibited early memory impairment, acalculia, frontal and temporoparietal hypometabolism on positron emission tomography, and large numbers of senile plaques at autopsy. One exhibited early aggressive-
n ess and mood disturbance.\textsuperscript{4} The age of onset differed between the 2 British pedigrees, showing no overlap in range (36-40 vs 42-48 years). This was not attributable to apolipoprotein E genotype. Finckh et al\textsuperscript{7} identified another German patient with the M139V mutation of the presenilin 1 gene (age of onset, 32 years) in whom prominent extrapyramidal phenomena, ataxia, and incontinence developed. Later manifestations included generalized seizures, akinetic mutism, and frequent myoclonic jerks. No significant behavioral dyscontrol or psychosis was reported. Two affected family members exhibited senile plaques and NFTs at autopsy.\textsuperscript{7}

The clinical phenotype in our 2 patients, although similar, may have been confounded by comorbid conditions. Patient 2 had a history of alcohol abuse and discontinued alcohol use 4 months after onset of symptoms. Korsakoff syndrome could have clouded the clinical picture, although confabulation was not prominent. The contribution of previous head injury in patient 2 is also unclear. However, no residual clinical deficits or evidence of trauma were found on results of neuroimaging. Unfortunately, formal neuropsychometrics and magnetic resonance imaging were not obtained with patient 2 to permit comparison with his brother. The single-photon emission computed tomography findings showed nonspecific hypoperfusion.

The significance of the tau polymorphism (A178T) in this family with AD remains unclear. Patient 1 (with the A178T mutation) had clinical onset at 45 years of age; patient 2 (without the A178T mutation), at 42 years of age. We do not have brain tissue from patient 1 to compare NFTs containing phosphorylated tau and amyloid deposition with the findings at autopsy in patient 2. It is likely that this tau polymorphism had little phenotypic effect, but this remains to be confirmed.

A markedly increased neuritic amyloid plaque number was observed when the temporal lobe biopsy site in patient 2 was compared with the same site at autopsy. This plaque number increase paralleled the observed clinical decline. The strong association between increased plaque density and clinical deterioration in this case supports the concept that deposition of amyloid is the primary problem in the pathogenesis of familial AD secondary to presenilin mutations.

We report the first evidence of a presenilin mutation in African American patients. In previously reported cases of the M139V mutation in the presenilin 1 gene, clinical features suggestive of a frontal lobe syndrome appear to be present in varying degrees. The M139V mutation may present differently between kindreds of different ethnic background. Our patients presented with early personality change, psychosis, and relative preservation of limb praxis, in addition to early memory loss. We suggest that genetic background may play a role in the clinical phenotype of patients with genetically determined neurologic diseases, and this is of both scientific interest and clinical importance.

CONCLUSIONS

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Author contributions: Study concept and design (Drs Rippon and Lynch); acquisition of data (Drs Rippon, Halvorsen, Chin, Hutton, Houlden, Hardy, and Lynch and Mr Baker); analysis and interpretation of data (Drs Rippon, Halvorsen, Chin, Hutton, Hardy, and Lynch and Messrs Crook and Baker); drafting of the manuscript (Drs Rippon, Halvorsen, Chin, and Lynch); critical revision of the manuscript for important intellectual content (Drs Halvorsen, Chin, Hutton, Houlden, Hardy, and Lynch and Messrs Crook and Baker); statistical expertise (Dr Hutton); obtained funding (Drs Hardy and Lynch); administrative, technical, and material support (Drs Rippon, Halvorsen, Chin, Houlden, Hardy, and Lynch and Messrs Crook and Baker); and study supervision (Drs Chin and Lynch).

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