Chromosome 3 linked frontotemporal dementia (FTD-3)

S. Gydesen, MD; J.M. Brown, MD; A. Brun, MD; L. Chakrabarti, DPhil; A. Gade, PhD; P. Johannsen, MD, PhD; M. Rossor, MD; T. Thusgaard; A. Grove, MD; D. Yancopoulou; M.G. Spillantini, PhD; E.M.C. Fisher, PhD; J. Collinge, MD; and S.A. Sorensen, MD, DMS

Abstract—*Background:* The authors have identified and studied a large kindred in which frontotemporal dementia (FTD) is inherited as an autosomal dominant trait. The trait has been mapped to the pericentromeric region of chromosome 3. *Methods:* The authors report on the clinical, neuroimaging, neuropsychological, and pathologic features in this unique pedigree collected during 17 years of study. *Results:* Twenty-two individuals in three generations have been affected; the age at onset varies between 46 and 65 years. The disease presents with a predominantly frontal lobe syndrome but there is also evidence for temporal and dominant parietal lobe dysfunction. Late in the illness individuals develop a florid motor syndrome with pyramidal and extrapyramidal features. Structural imaging reveals generalized cerebral atrophy; $H_2{}^{15}O$-PET scanning in two individuals relatively early and late in the disease shows a striking global reduction in cerebral blood flow affecting all lobes. On macroscopic pathologic examination, there is generalized cerebral atrophy affecting the frontal lobes preferentially. Microscopically, there is neuronal loss and gliosis without specific histopathologic features. *Conclusions:* FTD-3 shares clinical and pathologic features with other forms of FTD and fulfills international consensus criteria for FTD. There is involvement of the parietal lobes clinically, radiologically, and pathologically in FTD-3 in contrast to some forms of FTD. This more diffuse involvement of the cerebral cortex leads to a distinctive, global pattern of reduced blood flow on PET scanning.

NEUROLOGY 2002;59:1585–1594

Several groups have reported patients presenting with features of frontal lobe or temporal lobe dysfunction in whom pathologic examination reveals mild frontal lobe atrophy with neuronal loss and gliosis without specific histopathologic features.[1-6] Consensus statements have been published delineating the clinical and pathologic features of such cases and naming them frontotemporal dementia (FTD).[7,8] In a large series, 8 to 10% of all patients with presenile dementia had this syndrome[9]; other series are in broad agreement with this figure.[5,6,10] These studies show that FTD is one of the common causes of presenile dementia.

In series of FTD, 20 to 50% of cases have a family history of dementia affecting a first-degree relative,[5,9,10] strongly suggesting that genetic factors play a major role in the etiology of this disease. It is now established that the disease in some of these families is caused by mutations within the tau gene.[11] Most studies suggest that tau mutations account for between 9 and 14% of all familial FTD,[12-14] although some studies suggest higher prevalences of tau mutations in this group.[15,16] The genetic cause of the remaining FTD pedigrees is not known. We published data in 1995 assigning the disease locus in a Jutland FTD pedigree to the pericentromeric region of chromosome 3.[17] One other locus has been proposed on chromosome 9, for FTD with motor neuron disease.[18] We now present clinical, neuropsychological, neuroimaging, and pathologic details of the Jutland FTD pedigree.

Clinical and pathologic features in some individuals in this family were reported in 1987[19] and briefly updated in 1998 and 1999.[20,21] We now present clinical details on all 22 affected individuals and the results of autopsy examination of two affected individuals. We include structural and functional im-

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the November 26 issue to find the title link for this article.

From the Frontotemporal Dementia Research in Jutland Association (FreJA),, Denmark; Institute of Medical Genetics (Drs. Gydesen and Sorensen, and T. Thusgaard), The Panum Institute, University of Copenhagen, Denmark; Department of Psychiatry (Dr. Gydesen), Central Hospital, Holbaek, Denmark; Department of Neurology (Dr. Brown), Addenbrooke's Hospital, Cambridge, United Kingdom; Department of Neuropathology (Dr. Brun), University Hospital, Lund, Sweden; MRC Prion Unit (Drs. Chakrabarti, Fisher, and Collinge), Department of Neurodegenerative Disease, Institute of Neurology, London, United Kingdom; Department of Neurogenetics (Drs. Chakrabarti, Fisher, and Collinge), Imperial College Medical School, London, United Kingdom; Department of Psychology (Dr. Gade), Copenhagen University, Denmark; Memory Disorders Clinic (Dr. Gade), University Hospital, Copenhagen, Denmark; Department of Neurology and PET Centre (Dr. Johannsen), Aarhus University Hospitals, Denmark; Dementia Research Group (Dr. Rossor), National Hospital for Neurology, Queen Square, London, United Kingdom; Department of Pathology (Dr. Grove), Holstebro Hospital, Denmark; and Brain Repair Centre and Department of Neurology (D. Yancopoulou and Dr. Spillantini), University of Cambridge, United Kingdom.

Sponsored by the Foundation of Else and Svend Madsen, Denmark; the Eli Lilly Psychiatric Research Foundation, Denmark; The Medical Research Council, UK; and The Wellcome Trust, UK.

Received December 28, 2001. Accepted in final form July 9, 2002.

Address correspondence and reprint requests to Dr. J.M. Brown, Department of Neurology, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ, UK; e-mail: jmb75@medschl.cam.ac.uk

aging studies and neuropsychological data on two recently studied individuals.

Patients and methods. The proband (III-17) was seen in an outpatient clinic in 1983. The family tree was traced with the help of family members and local doctors. Medical records have been obtained for historical cases; new cases have been assessed as they presented. Clinical assessments have been performed on at risk individuals over the age of 40 years. Permission for postmortem examinations has been obtained from affected individuals. Informed consent was obtained from patients when possible and also from their first-degree relatives according to the declaration of Helsinki and approved by the Ethical Committee of Northern Jutland, Denmark.

Affected and at risk individuals were assessed by a neurologist (J.M.B.) and a psychiatrist (S.G.), usually in the patient's home. The Mini-Mental State Examination (MMSE) was administered[22] and a series of bedside tests of higher cognitive functions were performed based on the Queen Square Screening Test for Cognitive Deficits booklet.[23] There has been a paucity of formal neuropsychological assessments in this family; affected individuals tended to come to the attention of both the research group and local departments late in the disease course. Two cases were neuropsychologically tested 7 and 5 years after onset, when their MMSE scores were 8 and 16. In the last year neuropsychological tests and scales with Danish norms[24,25] have been administered by one of the authors (A.G.).

Imaging methods. Seven CT scans, one MRI scan, and two PET scans have been performed in affected individuals. The protocol for the PET scans followed the Helsinki declaration and was approved by The Aarhus County Research Ethics Committee. Informed consent was obtained from a close relative and the patient.

PET data acquisition. Regional cerebral blood flow (rCBF) was measured in Patients III-20 and III-22 using O-15-water and the ECAT Exact HR47 PET-camera (Siemens/CTI, Knoxville, TN). The calculated radiation dose was 0.74 mSv. A transmission scan was followed by 10 minutes dynamic data acquisition together with arterial blood sampling. Images were reconstructed with correction for scatter and filtered to a resolution of 4.6 mm full-width at half maximum. Voxel maps of CBF were calculated[26] and spatially aligned[27] in the Talairach coordinate system.[28] Standard volumes of interest (VOI) based on normal control probability maps were applied.

Pathologic methods. The fixed brain specimens from Cases II-12 and III-13 were sliced coronally. The brain slices were embedded in paraffin, sectioned in whole brain sections at 6 microns, and stained with hematoxylin–eosin, Luxol fast blue, Cresyl violet, and Gallyas and Campbell silver methods, and in selected areas with antibodies to tau (AT8), glial fibrillary acidic protein (GFAP), prion protein, beta amyloid, and ubiquitin.

Results. *Clinical and neuropsychological results.* The pedigree is shown in figure 1 and clinical details are summarized in table E-1 on the *Neurology* Web site (go to www.neurology.org). The onset of the disease is insidious and estimates of the age at onset often vary between informants. The average age at onset is 57 years. The average age at onset in individuals who have inherited the disease from their father is lower (53 years) compared to maternally inherited cases (59 years).

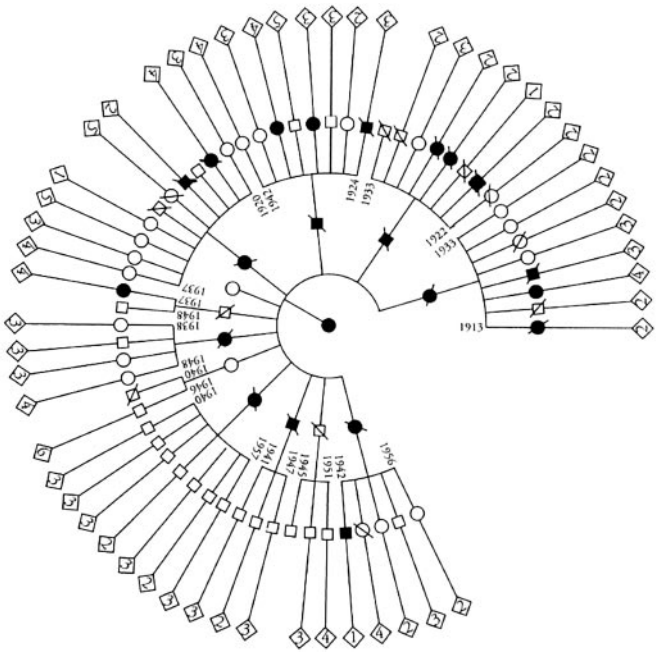

Figure 1. Pedigree of large Jutland family with presenile dementia. The year of birth for the first and last born in each sibship are given. The patients with presenile dementia are marked with black dots. The numbers in the outer line are number of sibs in the sibship.

The pattern of inheritance is autosomal dominant with high penetrance (II-6 died in a road traffic accident before the average age at onset of symptoms of dementia). Virtually all individuals still reside in Jutland, facilitating follow-up. There have been no genetically relevant consanguineous marriages, and there is no family history of presenile dementia in the spouses of affected individuals.

Earlier studies[17] suggested that anticipation of the age at onset was a feature of the disease in this family. Anticipation is an increase in severity or decrease in age at onset as a disease passes from one generation to the next. Anticipation in the age at onset was seen in cases of paternal transmission but not when the disease was inherited through the maternal line (these differences were highly statistically significant when analyzed).[17] Cases diagnosed since this time have not supported our previous conclusion and reduced the significance of this result; two recent paternally inherited cases have had a later age at onset than their father.

Typically the disease starts with a subtle personality change. Affected individuals become less concerned about others and less kempt. They become disinhibited in their speech and may show inappropriate emotional responses. Hyperorality is a common feature, encompassing mouthing of nonfood objects, overeating sweet foods, and chain smoking. Patients are restless. Dyscalculia is an early feature in a few individuals and in III-3 was a presenting complaint. Patients lack insight into their illness. There are no physical signs in the cranial nerves, limbs, or gait early in the disease.

The progression of the disease is steady and behavioral problems may become prominent. Individuals may be apa-

thetic or occasionally aggressive. Urinary incontinence is common. Spontaneous speech declines, although repetition and reading from a text is relatively preserved. Stereotyped behavioral routines are frequent.

Some patients seen 5 or more years into the illness have developed a florid motor syndrome with a combination of parkinsonian features, dystonia, pyramidal signs, and myoclonus. In the terminal stages these motor problems confine the patient to bed. All patients who have developed this motor syndrome have at some stage been exposed to neuroleptics, although often at low doses. Withdrawal of the neuroleptics fails to stop progression of the motor syndrome. No patients have had seizures. The average duration of the illness was 8 years, and death was usually from pneumonia or other intercurrent illness.

Clinical details of 22 affected individuals are reported in the online Appendix (access the supplementary data on the *Neurology* Web site). Two representative clinical histories are included in this section. These are typical cases, one seen early (III-22) and one seen late (III-20) in the course of the illness. Neuropsychological results are included for III-22.

Case reports. *Case III-20.* Case III-20 was a textile worker who became slower in her work and more forgetful in her late 40s. By the time she was referred to a psychiatrist at age 59, she was unkempt, depressed, apathetic, and irritable. She had no insight into her illness. Her memory for recent events was poor. Her behavior deteriorated and she began to spend money excessively, chain smoke, and drink more beer. She was aggressive toward her husband. As her illness progressed she developed word finding difficulties, dressing difficulties, and route-finding problems.

She was first seen at age 61, 7 years into her illness. She was distractible and tried to evade cognitive testing. She was disinhibited, laughed excessively, and joked inappropriately: "Ha, ha, you must be German." She had good recall of autobiographical details; for example, she knew her children's birthdays.

She scored 20/30 on the MMSE. She was orientated in place but not in time. She could register and recall three objects. She could name pictures and household objects correctly initially but then perseverated in her responses. She had no visuospatial problems. She was dyscalculic. There was evidence of apraxia: she was unable to copy gestures and would not mime actions. She could not perform alternating hand movements. On physical examination she had brisk tendon reflexes with an extensor left plantar response. Her gait was stooped and stiff.

She was seen again the following year while on neuroleptic medication. She had deteriorated sharply. She was restless and continuously walked around the outside of her house in a stereotyped fashion. She collected other people's cups. She was almost mute and used abbreviated words; for example, "ret" for "cigarette" and "af" for "kaffe" (coffee). She was incontinent of urine. If cigarettes were available she would chain smoke. She ate sweet foods to excess. She kept food in her mouth for long periods without swallowing. Her gait was shuffling with flexed arms. She had facial hypomimia with nuchal and limb rigidity with cogwheeling. She had bilateral grasp reflexes. All reflexes were exaggerated and both plantar responses were extensor. She had a vasovagal attack following examination of the plantar responses.

When reassessed at age 66 she was in full-time care. Her neuroleptics had been stopped 2 years previously and she was on a benzodiazepine. She was mute. She walked continuously in a stereotyped fashion with ritualized touching of objects. She now needed help eating. She carried her left arm extended. Her gait was festinant and stiff. Her knees were held partially flexed and she was tilted to the left. She had gait ignition failure but once walking had a reasonable stride. She experienced difficulty turning. She was not able to find her own room. She had marked orofacial dyskinesiae. Ocular pursuit movements were full. Limb signs were essentially unchanged. She rooted to visual stimuli. She was seen four more times over the next 5 years. Her gait had become more flexed and tilted with dystonic posturing of her left hand and arm. On examination she had stimulus sensitive myoclonus in the left hand. Her orofacial dyskinesiae had become more pronounced with involuntary protrusion of her tongue. She had become bed-bound with the left arm flexed and the right extended, and both legs flexed. She had marked limb rigidity and additional pyramidal signs and release reflexes.

Case III-22. Case III-22 was first seen at age 56 when she was cognitively normal. Eight years later her relatives felt she had developed the family disease. She had developed symptoms of depression following the death of her husband in her late 50s but had improved on citalopram. At age 63, she had developed symptoms of apathy and fatigue and was felt to be depressed again. Six months before being seen she began to develop cognitive symptoms. She became irritable and less careful in what she ate and less able to look after her house. She gave up reading books and became repetitive in her questioning. She would accumulate food, buying certain items like flour and juice repeatedly and then not using them. Her problems were slowly progressive. She scored 28/30 on the MMSE, failing to recall one of three remembered items and failing in one part of the three-part command. Physical examination was unremarkable. She was mildly apraxic for copying meaningless postures and showed body part substitutions in miming actions. She could not learn alternating hand postures.

Case III-22 was neuropsychologically tested in several sessions in her home from October 2000 to January 2001, soon after diagnosis and presumed onset. Concurrent MMSE scores were 26 and 28. Her Danish Adult Reading Test (DART) score was 25/50, indicating an average premorbid intellectual level. On a test battery specifically designed for AD,[21] she generally scored 1.5 to 3 SD below normal controls, with visual perception as the only cognitive domain in the normal range. The only disproportionate impairment was in famous faces, where she failed to recognize 12 of 20 well-known public figures. On a more demanding test battery,[20] most test scores were significantly below expected levels (based on regression equations with age, sex, education, and DART as predictor terms), again indicating a rather generalized intellectual decline. Of note, however, was intact learning and intact delayed recall on a 15-item paired associates learning task, corroborating a clinical impression of intact day-to-day memory. Tests of frontal lobe function indicated some se-

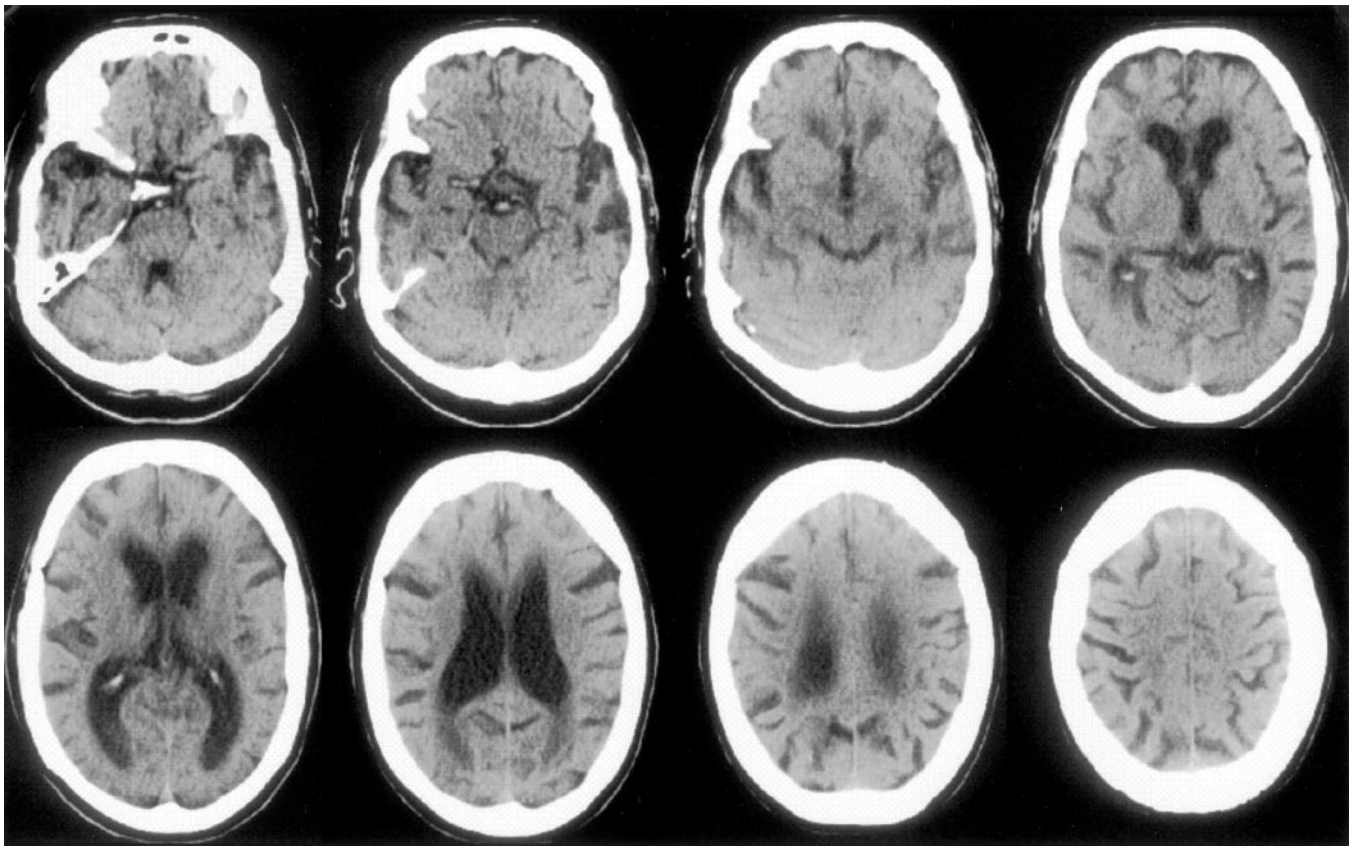

Figure 2. CT scan of Subject III-22 shows a moderate degree of atrophy.

lective deficits. For instance, the patient failed grossly in the modified Wisconsin Card Sorting Test, attaining only two of six sets and committing a total of 35 errors in 48 cards. She could not explain simple proverbs. Some of her cognitive estimates were far off the mark: the height of the Round Tower (a church tower in Copenhagen) was estimated at "millions," corrected to "more than 3,000 meters." Stroop color interference naming was unremarkable. She was mildly impaired in category fluency tests, naming 13 animals in a minute, but more impaired on letter fluency, naming only four or five words beginning with S, P, or A in 1 minute. She named 18 of 30 objects in the Boston Naming Test. Nondominant parietal functions were not selectively impaired. She copied a cross, a star, and a cube normally and copied the complex Rey figure with only minor omissions (31/36 points). She could copy block designs with four blocks but failed with nine blocks. She was severely impaired in drawing a clock face from memory, but copied it much better.

The patient acknowledged intellectually the possibility of having developed the "family disease," and she acknowledged and welcomed the assistance given by her daughter, but denied any perception of intellectual decline. Two behavioral rating scales were administered with a daughter. The Frontal Behavioral Inventory[29] indicated mild aspontaneity, decreased flexibility and reasoning, and moderate disorganization (20/72). On the Neuropsychiatric Inventory,[30] scores of two or more were registered on anxiety, apathy, and depression/dysphoria (12/120). These results concurred with clinical impressions. She would act the hostess, but tended to commit small errors in her kitchen, and her repertoire in conversation was limited. The patient seemed to be cognitively stable over the time period she was tested. According to her daughter, she worsened over the ensuing months, and a slight decline in MMSE was recorded 3 months later.

Neuroimaging results. CT scans on several individuals and MRI scans on III-28 showed generalized cortical atrophy without white matter changes. Figure 2 shows serial sections of a CT scan performed on Subject III-22.

CBF-PET results. The rCBF of Patient III-22 at age 64 (MMSE = 24) was normal in the primary visual cortex, thalami, basal ganglia, cerebellum, and in a small area of the right lateral frontal cortex. The peak rCBF was 70 mL/100 g/min in the cerebellum. All other cortical regions had a pronounced and extensive rCBF deficit with the most prominent flow deficits in the frontal, parietal, and temporal lobes (figure 3 and table 1).

The rCBF of III-20 at age 70 years (MMSE = 0) was normal in the primary visual cortex, thalami, putamen, and cerebellum, with a global peak value in the cerebellum of 62 mL/100 g/min. The rCBF of all other cortical regions was severely impaired, with the most prominent flow deficits in parietal, anterior-frontal, and lateral temporal cortices (see figure 3 and table 1).

Pathologic results. Three postmortem examinations were performed prior to 1987[19] and are summarized in the Appendix on the *Neurology* Web site (go to www.neurology.org). The brains were not available for re-examination. All three showed cerebral atrophy with a frontal preponderance. None of the autopsy examinations revealed plaques, tangles, or inclusion bodies. Two additional postmortem examinations have been performed. Table 2 contains a summary of the pathologic findings.

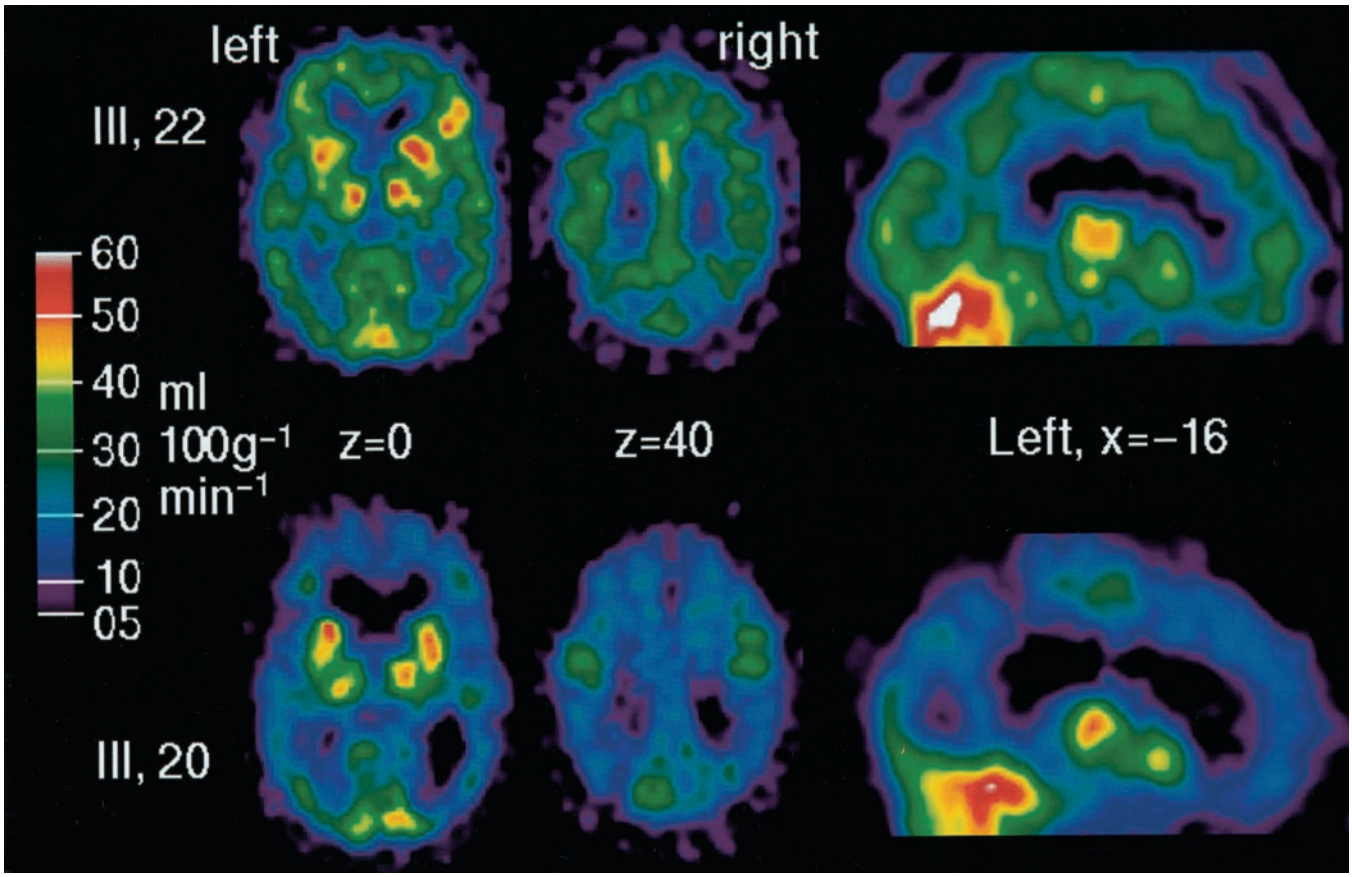

Figure 3. Regional cerebral blood flow (rCBF) maps of Patients III-22 (top row: age 64; Mini-Mental State Examination [MMSE] = 24) and III-20 (lower row: age 70; MMSE = 0). Note normal CBF values in the cerebellum, basal ganglia, and thalami of both patients. The rCBF values from both patients are identically scaled as indicated by the color bar. Slices are in the Talairach coordinate system: Z coordinates indicate number of millimeters above a plane through the anterior and posterior commissures. "X = −16" indicates a sagittal slice 16 mm from midline in the left hemisphere.

Case II-12. The brain weighed 900 grams at autopsy. The left hemisphere was available for neuropathologic study (the right one was frozen in slices). Macroscopy showed global atrophy more marked frontally. No focal abnormalities were seen. There was cortical degeneration and pallor of the white matter with secondary dilatation of the lateral ventricles.

Microscopy showed fibrillar marginal sclerosis of the membrana limitans piae. The cortical laminae showed microvacuolation, neuronal loss, and astrocytic gliosis. In

Table 1 *The rCBF averaged over selected large volumes including both gray and white matter*

	III-22 (aged 64, MMSE = 24)		III-20 (aged 70, MMSE = 0)	
Area	R hemisphere	L hemisphere	R hemisphere	L hemisphere
Frontal	34	34	24	23
Temporal	30	29	20	20
Parietal	32	32	24	22
Occipital	27	26	21	19
Hippocampal formation	34	31	23	22
Lingual gyrus	39	39	27	31
Basal ganglia	37	38	36	35
Thalamus	31	32	23	26
Cerebellum	47	46	39	41
White matter	30	32	19	24

Values are expressed in mL/100 g/min.

rCBF = regional cerebral blood flow; MMSE = Mini-Mental State Examination.

Table 2 *Pathologic features of frontotemporal dementia–3*

	Individual				
Characteristic	II-3	II-9	II-10	II-12	III-13
Age at death, y	64	65	61	76	61
Brain weight, g				900	960
Frontal atrophy	++	+	++	+	++
White matter change	++	+	+	+	++
Inclusion bodies	−	−	−	−	−
Vascular changes	+			+	+

+ = feature present; ++ = feature abundant; − = feature absent.

parts this was limited to the supragranular layers but in many areas it also involved the deeper layers to include the whole cortical thickness. Cortical changes were most marked in the anterior parts of the brain but spared the amygdala, hippocampus, and striatum. Milder changes were also found in the parietal and basal temporal cortex. There were no degenerative changes in the occipital lobe although there was a single microinfarct. Ubiquitin staining showed corpora amylacea and occasional extracellular deposits but no inclusions or degenerating structures. There was diffuse loss of myelin in the white matter with astrocytosis. The thalami were normal, as was the substantia nigra with no Lewy bodies or other inclusions. There were multiple minute subependymal glial proliferations protruding into the third ventricle. There were no plaques, tangles, dystrophic neurites, or argyrophilic inclusions. There was sparse tau immunostaining of age-related neurofibrillary tangles. The cerebellar cortex was largely preserved although there was some loss of Purkinje cells compatible with the patient's age. In the spinal cord the anterior horn neurons were well preserved. In the medial posterior tracts there was some mild myelin loss.

Case III-13. The brain weighed 960 grams after fixation. Macroscopy showed atrophy of the frontal lobes more marked on the left with moderate widening of the frontal horns of the lateral ventricles. The lower prefrontal region including Broca's area was particularly affected. There was no "knife edge" appearance as in classic Pick's disease. The remainder of the brain showed no convincing atrophy. There was no atheroma of the major vessels. Other parts of the brain were unremarkable, including the amygdala, hippocampi, and basal ganglia. The substantia nigra showed a slight depigmentation.

On microscopy the atrophic cortex showed microvacuolation, mild gliosis, and loss of neurons (figure 4). These changes were often restricted to the supragranular layers but also involved the deeper layers focally. There were no plaques, tangles, amyloid deposits, or Pick cells. Ubiquitin staining showed only corpora amylacea and occasional extracellular deposits but no inclusions or degenerating structures. Cells of microglial nature and some reactive astrocytes as well as occasional macrophages had a diffuse, slight ubiquitin cytoplasmic positivity. In neurons there was a granular positivity in the cytoplasm corresponding to lipofuscin deposits, but neuronal nuclei never showed ubiquitin-positive inclusions of the type seen in Huntington disease and only occasional nuclear membrane indentations. There was sparse tau immunostaining of age-related neurofibrillary tangles in neurons. Other techniques including silver methods failed to reveal nuclear inclusions.

The white matter showed moderate widespread loss of myelin staining with astrocytosis but without macrophages (figure 5). This was most marked in the corpus callosum and deep periventricular white matter. There was a moderate status cribrosus with some iron-laden macrophages. Some vessels in the white matter showed a narrowing, fibrohyaline arteriolosclerosis. The striatum and thalamus were unremarkable except for a slight vacuolation of the thalamus on one side. The amygdala and the hippocampal formations were unremarkable. The substantia nigra contained many intact neurons and scarce extracellular pigment deposited interstitially. The pons, including the locus coeruleus, medulla oblongata, and the cerebellum, was normal. In the cervical cord, there was a

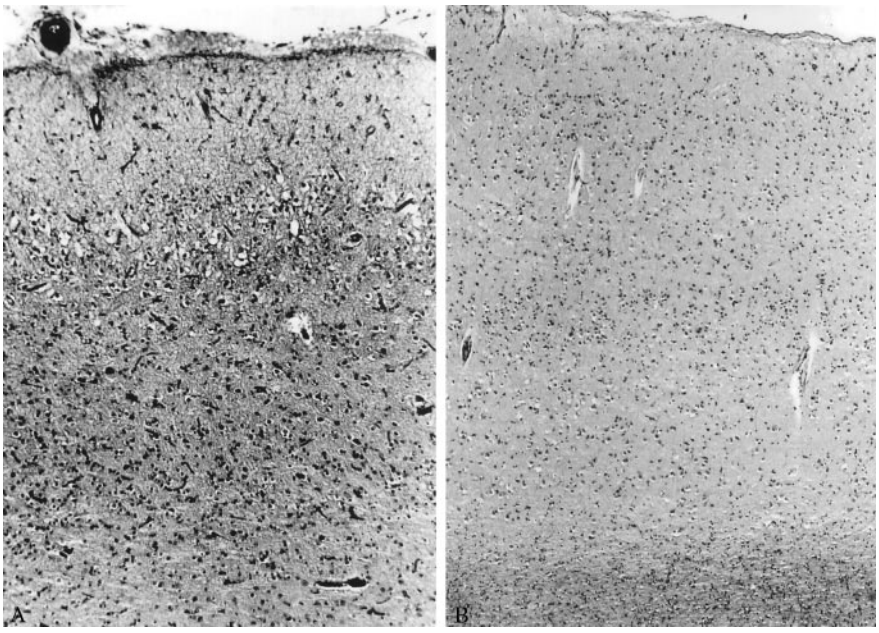

Figure 4. (A and B) Frontal cortex. Original magnification ×100. Hematoxylin and eosin staining. A shows gliosis of lamina 1 and microvacuolation of lamina 2 and 3 with increased cell density of deeper portions of lamina 3, due to gliosis. These changes are more easily appreciated when comparing the same layers from the spared occipital cortex (B) in the same case, where there are only perineuronal vacuoles due to postmortem artifacts.

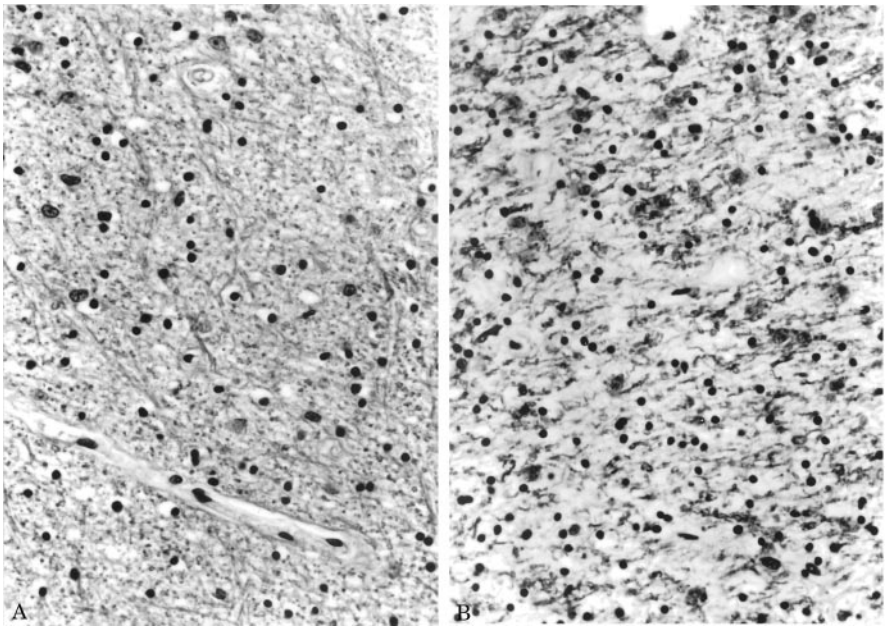

Figure 5. (A and B) Frontal white matter. Original magnification ×200. (A) Hematoxylin and eosin staining. This shows gliosis with increased numbers of larger, lighter astrocytic nuclei. (B) Luxol fast blue staining. This shows reduced staining for myelin.

suspicion of demyelination of the posterior tracts; there was preservation of anterior horn neurons.

Discussion. FTD, as recently redefined in an international consensus statement, encompasses a wide spectrum of different clinical and pathologic phenotypes, including semantic dementia, dementia of frontal type, dementia lacking distinctive histopathology, progressive supranuclear palsy, and corticobasal degeneration, among others.[8] All affected individuals in this family fulfill clinical and pathologic consensus criteria for FTD[7] and we have named this disease FTD-3. The more global character of the clinical, psychological, imaging, and pathologic features in this family with abnormalities outside the frontal and temporal lobes raises doubt as to whether the family should be included under the rubric of FTD.[7] We included them as a form of FTD as the overwhelming majority of the early clinical and psychological features are typical for FTD. This family is closest phenotypically to the form of FTD described originally as dementia lacking distinctive histologic features[5] and now renamed dementia lacking distinctive histopathology (DLDH).[8] Clinical and pathologic changes in DLDH and other forms of FTD are not always limited to the temporal and frontal lobes.

The disease in this family is inherited as an autosomal dominant trait with high penetrance. Linkage analysis has located the disease locus to the centromeric region of chromosome 3[17]; therefore, we have named this disease FTD-3. Earlier evidence for anticipation of the age at onset with paternal inheritance has weakened with data from two new cases. We have assessed the Huntington disease, dentatorubralpallidolysial atrophy, and some of the SCA genes and found no expansion mutations.

The dementia in this family typically starts with a slowly progressive frontal syndrome with subtle early personality and behavior changes. Hyperorality affected a number of individuals, suggesting temporal lobe dysfunction. Dyscalculia is a common problem, as has been reported in FTD previously.[4,9] There are two possible explanations for this: that a frontal type of dyscalculia is represented, as suggested in other individuals with FTD,[31] or that the dyscalculia reflects dominant parietal lobe pathology. In FTD-3 there are pathologic changes within the parietal lobes and both frontal and parietal lobe disease may contribute to the dyscalculia. Visuospatial skills are normally well preserved until late in the illness. Motor features appear later in the illness and, as in Pick's disease, can be asymmetric.[32] The motor features in three recently examined cases eventually became florid with features reminiscent of corticobasal degeneration. The appearance of such features very late in the course of the disease clearly distinguishes FTD-3 from corticobasal degeneration but suggests there may be a link between corticobasal degeneration and FTD-3.

No individuals had seizures. Some patients developed myoclonus late in the illness. Although myoclonus has been an exclusion criterion for FTD,[7] it can be seen late in the disease. A few individuals had fainting episodes. There are reports of abnormal lability of blood pressure in patients with frontotemporal dementias.[7]

Neuropsychological investigations in this family are at an early stage. Test results from patients in advanced stages of dementia are of limited value in differentiating between types, and so far only one patient has been tested in an early stage. The test results of Case III-22 indicate surprisingly severe and generalized deficits in view of her MMSE score (26 or 28). Her day-to-day memory appeared fully intact and some memory tests were performed well. An impression of intact episodic memory in early

stages of the disease has also been given in retrospective interviews of caregivers of other patients (work in progress), setting the disease sharply apart from AD.

The structural imaging shows a global pattern of atrophy. The extensive rCBF deficits on PET scanning were pronounced and spread over most of the cerebrum involving all secondary cortices. This is even more striking in the mildly affected subject (Case III-22) who had an MMSE of 24 at the time of scanning. As the rCBF was normal in the primary visual cortex and the cerebellum, the marked reduction in blood flow cannot be attributed to a primary vascular problem but must reflect a decline in metabolism in the affected areas. This is the case with other degenerative dementias. Cortical blood flow in three individuals from this pedigree was measured in 1987[19] using ^{133}Xe and 16 channel scintillators on each hemisphere. This study showed a similar reduction in global blood flow in two of the three patients (the third had an increase in blood flow). The global reduction in cerebral blood flow in the mildly affected III-22 suggests that the blood flow changes occur early in the course of the disease. Furthermore, although FTD-3 may present with clear frontal lobe symptoms, the CBF results indicate widespread deficits at an early stage, including but not confined to the frontal lobes.

Five postmortem examinations have been performed and all have revealed a similar pattern of macroscopic and microscopic neuropathology. On macroscopic examination there is global cortical and central atrophy, which always includes the frontal lobes. On microscopy, all five cases show neuronal loss and gliosis but none shows any of the characteristic inclusion bodies or staining seen in AD, classic Pick's disease, prion disease, dementia with Lewy bodies, corticobasal degeneration, Huntington's disease, or motor neuron disease (MND) with dementia. Immunostaining shows some tau deposition but not in a pattern suggestive of a tauopathy.[33] The pathology shows marked similarities to that described originally under the rubric of frontal lobe degeneration of non-Alzheimer type (FLD)[2] and more recently renamed FTD-7. The pathologic changes are more extensive in both distribution and depth than in typical FLD. White matter changes are also found. These may be secondary to the cortical disease or may represent coincident small vessel disease.

A number of families in which FTD is inherited as an autosomal dominant trait have been shown to be linked to chromosome 17[34]; such families are now described as chromosome 17 linked frontotemporal dementia with parkinsonism (FTDP-17). In many of these families mutations have been described in the tau gene.[15,35,36] Clinical and pathologic comparisons between chromosome 3 linked FTD-3 and chromosome 17 linked FTDP should be regarded as preliminary until more families are described and all the relevant mutations identified. The clinical spectrum of chromosome 3 linked and of chromosome 17 linked FTD overlap—patients with a typical frontal dementia and mild or absent parkinsonian features could have either disease.

Patients with prominent parkinsonian features early in the disease may be more likely to have FTDP-17, but the wider clinical spectrum of the chromosome 17 linked families may simply reflect the larger number of cases described. Similarly, a wider spectrum of pathologic changes have been described in chromosome 17 linked FTDP, including the presence of Pick cells and Pick bodies, which are absent from the Jutland cases. Individuals with FTD-3 do not show the characteristic tau accumulations seen in FTDP-17. Functional neuroimaging studies of rCBF in FTDP-17 showed marked rCBF reduction in the frontal regions only,[37] which is quite different from the result in FTD-3.

Several pedigrees with similarities to FTD-3 both clinically and pathologically have been published.[9,38] These pedigrees are not of sufficient size to allow positional cloning to determine whether they are also linked to chromosome 3. Inheritance in these families is consistent with an autosomal dominant pattern, the families fulfill consensus criteria for FTD, and the pathologic changes and their topographic distribution in the family reported in 1981[38] are strikingly similar to those in FTD-3. Once the causative mutation is discovered in FTD-3, these pedigrees, the very numerous smaller FTD pedigrees,[14,39] and individuals with DLDH can be screened for mutations within the same gene. One other familial degenerative dementia has been mapped to a nearby region of chromosome 3.[40] Individuals in this pedigree have late onset familial AD and their disease is distinct from FTD-3 clinically and pathologically.

Similar pathologic changes to FTD-3 are seen in the brains of individuals with MND plus dementia, and families have been reported in which frontotemporal dementias and MND cosegregate.[41] Recently two families have been described in whom FTD is inherited as an autosomal dominant trait and who on pathologic examination have typical tau-negative, ubiquitin-positive inclusion bodies.[42,43] None of the 22 affected individuals with FTD-3 have shown typical clinical features of MND. Pathologically, the recently examined cases do not show the tau-negative, ubiquitin-positive inclusion bodies described in MND dementia.[44] Linkage studies in FTD-3 have excluded the *SOD1* gene,[45] and recent work has suggested that familial MND plus dementia is linked to chromosome 9.[18] Therefore, clinically, pathologically, and genetically, FTD-3 appears distinct from MND dementia.

Currently, three genetically and pathologically distinct groups of familial FTD can be recognized: FTDP-17, which has distinctive tau pathology and is produced by mutations in the *tau* gene; FTD-3, which lacks distinctive histopathology and is linked to chromosome 3; and familial MND dementia, which has tau-negative, ubiquitin-positive inclusion bodies and appears to be linked to chromosome 9.

The assignment of the gene causing the dementia in this family to the pericentromeric region of chro-

mosome 3 is an important step in the genetic classification of frontotemporal dementias. There are similarities between individuals in this family and many patients with FTD, and it is possible that mutations or polymorphisms in the FTD-3 gene may account for a significant proportion of all FTD.

Postscript. Sections of the brains of 11-12 and 111-13 were stained with antibodies to tau, neuroserpin, and alpha-synuclein by M.G.S. and D.Y. No inclusions containing neuroserpin or alpha-synuclein were present. There was some tau immunostaining in neurons and glial cells as well as neuropil threads. The tau immunostaining was more prominent in 11-12 (the older patient who died at age 76).

Acknowledgment

The authors thank Birkehøj Nursing Home and the family for their help.

References

1. Clark AW, White CL, Manz HJ, et al. Primary degenerative dementia without Alzheimer pathology. Can J Neurol Sci 1986;13:462–470.
2. Brun A. Frontal lobe degeneration of non-Alzheimer type I. Neuropathol Arch Gerontol Geriatr 1987;6:193–208.
3. Gustafson L. Frontal lobe degeneration of non-Alzheimer type II. Clinical picture and differential diagnosis. Arch Gerontol Geriatr 1987;6:209–223.
4. Neary D, Snowden JS, Northen B, Goulding P. Dementia of frontal lobe type. J Neurol Neurosurg Psychiatry 1988;51: 353–361.
5. Knopman DS, Mastri AR, Frey WH, Sung JH, Rushtan T. Dementia lacking distinctive histologic features: a common non-Alzheimer degenerative dementia. Neurology 1990;40: 251–256.
6. Giannakopoulos P, Hob P, Bares C. Dementia lacking distinctive histopathology: clinicopathological evaluation of 32 cases. Acta Neuropathol 1995;89:346–355.
7. Brun A, Englund E, Gustafson L, et al. Clinical and neuropathological criteria for frontotemporal dementia. J Neurol Neurosurg Psychiatry 1994;57:416–418.
8. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojonowski JQ. Clinical and pathological diagnosis of frontotemporal dementia. Arch Neurol 2001;58:1803–1809.
9. Gustafson L, Brun A, Passant U. Frontal lobe degeneration of non-Alzheimer type. In: Rossor MN, ed. Unusual dementias. London: Balliere Tindall, 1992;559–582.
10. Neary D. Non Alzheimer's disease forms of cerebral atrophy. J Neurol Neurosurg Psychiatry 1990;53:929–931.
11. Poorkaj P, Bird T, Wijsman E, et al. Tau is a candidate gene for chromosome 17 frontotemporal dementia. Ann Neurol 1998;43:815–825.
12. Houlden H, Baker M, Adamson J, et al. Frequency of tau mutations in three series of non-Alzheimer degenerative dementias. Ann Neurol 1999;46:243–248.
13. Neary D, Snowden JS, Mann DM. Classification and description of frontotemporal dementias. Ann NY Acad Sci 2000;920: 46–51.
14. Poorkaj P, Grossman M, Steinbart E, et al. Frequency of tau gene mutations in familial and sporadic cases of non-Alzheimer dementia. Arch Neurol 2001;58:383–387.
15. Rizzu P, van Swieten JC, Joosse M, et al. High prevalence of mutations in the microtubule associated protein tau in a population study of frontotemporal dementia in the Netherlands. Am J Hum Genet 1999;64:414–421.
16. Morris HR, Khan N, Janssen JC, et al. The genetic and pathological classification of familial frontotemporal dementia. Arch Neurol 2001;58:1813–1816.
17. Brown J, Ashworth A, Gydesen S, et al. Familial non-specific dementia maps to chromosome 3. Hum Mol Genet 1995;4: 1625–1628.
18. Hosler BA, Siddique T, Sapp PC, et al. Linkage of familial amyotrophic lateral sclerosis with frontotemporal dementia to chromosome 9q21-q22. JAMA 2000;284:46–51.
19. Gydesen S, Hagen S, Klinken L, Abelskov J, Sorensen SA. Neuropsychiatric studies in a family with presenile dementia different from Alzheimer and Pick disease. Acta Psychiatr Scand 1987;6:276–284.
20. Brown J. Chromosome 3-linked frontotemporal dementia. CMLS 1998;54:925–927.
21. Ashworth A, Lloyd S, Brown J, et al. Molecular genetic characterisation of frontotemporal dementia on chromosome 3. Dement Geriatr Cogn Disord 1999;10(suppl 1):93–101.
22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
23. Warrington EK. The Queen Square Screening Test for Cognitive Deficits. London: National Hospital, 1989.
24. Mortensen EL, Gade A. On the relation between demographic variables and neuropsychological test performance. Scand J Psychol 1993;34:305–317.
25. Waldemar G, Bruhn P, Schmidt E, Kristensen M, Lassen NA, Paulson OB. Cognitive profiles and regional cerebral blood flow patterns in dementia of the Alzheimer type. Eur J Neurol 1994;1:81–89.
26. Ohta S, Meyer E, Fujita A, Reutens DC, Evans A, Gjedde A. Cerebral [^{15}O]water clearance in humans determined by PET: I. Theory and normal values. J Cereb Blood Flow Metab 1996; 16:765–780.
27. Collins DL, Neelin P, Peter TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J Comput Assist Tomogr 1994;18:192–205.
28. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Georg Thieme Verlag, 1988.
29. Kertesz A. The quantification of behavior in frontotemporal dementia. In: Kertesz A, Munoz DG, eds. Pick's disease and Pick complex. New York: Wiley, 1998.
30. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–2314.
31. Johanson A, Hagberg B. Psychometric characteristics in patients with frontal lobe degeneration of non-Alzheimer type. Arch Gerontol Geriatr 1989;8:129–137.
32. Brown J. Pick's disease. In: Rossor MN, ed. Unusual dementias. London: Balliere-Tindall, 1992;535–557.
33. Spillantini MG, van Swieten JC, Goedert M. Tau gene mutations in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Neurogenetics 2000;2:193–205.
34. Wilhelmsen K, Lynch T, Pavlou G, et al. Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to chromosome 17q 21–22. Am J Hum Genet 1994;55:1159–1165.
35. Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 1998;393:702–705.
36. Foster NL, Wilhelmsen K, Sima AA, Jones MZ, D'Amato CJ, Gilman S. Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. Conference Participants. Ann Neurol 1997;41:706–715.
37. Heutink P, Stevens M, Rizzu P, et al. Hereditary frontotemporal dementia is linked to chromosome 17q21-q22: a genetic and clinicopathological study of three Dutch families. Ann Neurol 1997;41:150–159.
38. Kim RC, Collins GH, Parisi JE, Wright AW, Chu YB. Familial dementia of adult onset with pathological findings of a "nonspecific" nature. Brain 1981;104:61–78.
39. Chow TW, Miller BL, Hayashi VN, Geschwind DH. Inheritance of frontotemporal dementia. Arch Neurol 1999;56:817–822.
40. Podulso SE, Yin X, Hargis J, Brumback RA, Marstrianni JA, Schwankhaus J. A familial case of Alzheimer's disease without tau pathology may be linked with chromosome 3 markers. Hum Genet 1999;105:32–37.
41. Gunnarsson L-G, Dahlbom K, Strandman E. Motor neuron disease and dementia reported among 13 members of a single family. Acta Neurol Scand 1991;84:429–433.

42. Kertesz A, Kawarai T, Rogaeva E, et al. Familial frontotemporal dementia with ubiquitin-positive, tau-negative inclusion bodies. Neurology 2000;54:818–827.
43. Kovari E, Leuba G, Savioz A, Saini K, Miklossy J, Bouras C. Familial frontotemporal dementia with ubiquitin inclusion bodies and without motor neuron disease. Acta Neuropathol 2000;100:421–426.
44. Cooper PN, Jackson M, Lennox G, Lowe J, Mann DMA. Tau, ubiquitin and alpha beta crystallin immunohistochemistry define the principal causes of degenerative frontotemporal dementia. Arch Neurol 1995;52:1011–1015.
45. Brown J, Gydesen S, Sorensen SA, et al. Genetic characterization of a familial non-specific dementia originating in Jutland, Denmark. J Neurol Sci 1993;114:138–143.

Incidence and outcome of mild cognitive impairment in a population-based prospective cohort

S. Larrieu, MSc; L. Letenneur, PhD; J.M. Orgogozo, MD; C. Fabrigoule, PhD; H. Amieva, PhD; N. Le Carret, MSc; P. Barberger–Gateau, MD, PhD; and J.F. Dartigues, MD, PhD

Abstract—*Objective:* To estimate the age-specific incidence rate of mild cognitive impairment (MCI) according to sex and educational level and to explore the course of MCI, particularly its progression to AD, in a population-based cohort. *Methods:* A community-based cohort of nondemented elderly people (Personnes Agées QUID [PAQUID]) was followed longitudinally for 5 years. MCI was defined as memory complaints with objective memory impairment, without dementia, impairment of general cognitive functioning, or disability in activities of daily living. Incidence rates were calculated using the person–years method. A descriptive analysis at the different follow-up times was performed to study the course of MCI. *Results:* At baseline, there were 58 prevalent cases of MCI (2.8% of the sample). During a 5-year follow-up, 40 incident cases of MCI occurred in 1,265 subjects at risk. The global incidence rate of MCI was 9.9/1,000 person–years. MCI was a good predictor of AD with an annual conversion rate of 8.3% and a good specificity, but it was very unstable over time: Within 2 to 3 years, only 6% of the subjects continued to have MCI, whereas >40% reverted to normal. *Conclusions:* Conventionally defined MCI has reasonable predictive value and specificity for AD. However, MCI was very unstable across time in this study. Furthermore, the definition of MCI seems to be too restrictive and should probably be extended to other categories of individuals also at high risk of developing AD.

NEUROLOGY 2002;59:1594–1599

The clinical course of AD is preceded by a period of time during which the affected patients experience subtle cognitive impairments but do not yet meet the criteria for dementia. The term "mild cognitive impairment" (MCI) was proposed to describe this transitional state between normal cognition and AD.[1,2] As an operational concept, the diagnosis of MCI is based on memory complaints with an objective deficit in memory performances but with normal general cognitive functioning and normal functional abilities, in the absence of diagnosed dementia.[2] Since 1999, and particularly in the USA, these criteria have been used by the scientific community, and a recent report of the Quality Standards Subcommittee of the American Academy of Neurology recommended them.[3] Several studies have been undertaken to follow up the natural course of MCI to determine the annual incidence of AD in affected subjects, the so-called "conversion rate."[3] As expected from the theory, most longitudinal studies of case series revealed a much increased risk of AD in MCI subjects, with a conversion rate ranging from 7 to 20%/year.[4-6]

The use of MCI may be important because new drugs are available for the treatment of AD, with the assumption that early treatment may be better. MCI subjects may constitute, as high-risk individuals, a particularly suitable population for preventive approaches, and clinical trials of drug therapies in MCI are in progress. Most studies on the natural history of MCI have been conducted on samples of subjects

From the Epidemiology Research Unit (Drs. Letenneur, Orgogozo, Fabrigoule, Amieva, Barberger–Gateau, and Dartigues, S. Larrieu and N. Le Carret), Institut National de la Santé et de la Recherche Médicale (INSERM) U 330; and Department of Neurology (Drs. Orgogozo and Dartigues), CHU Pellegrin, Bordeaux, France.

PAQUID Project was funded by Association pour la Recherche Médicale en Aquitaine (ARMA), Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS), Conseil Général de la Dordogne, Conseil Général de la Gironde, Conseil Régional d'Aquitaine, France Alzheimer, Institut National de la Santé et de la Recherche Médicale (INSERM), Mutuelle Générale de l'Education Nationale (MGEN), Mutualité Sociale Agricole (MSA), NOVARTIS Pharma, and SCOR Insurance Co.

Received January 28, 2002. Accepted in final form July 25, 2002.

Address correspondence and reprint requests to Sophie Larrieu, INSERM Unit 330, Case 11, Université Victor Segalen Bordeaux 2, 146 rue Léo Saignat, 33076 Bordeaux cedex, France; e-mail: Sophie.Larrieu@isped.u-bordeaux2.fr

