The Neuropathology of Chromosome 17–Linked Dementia

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We recently described a family with chromosome 17–linked dementia, characterized clinically by disinhibition-dementia-parkinsonism-amyotrophy complex. We report now the neuropathology of 6 affected family members. This included semiquantitative scoring of neuronal loss, gliosis, and spongiosis and immunocytochemical and ultrastructural characterization of neuronal and glial inclusions. The changes consisted of circumscribed neuronal loss, gliosis, and spongiosis of limbic neocortical areas and frontal, temporal, and occipital association areas. Similar changes were present in subcortical nuclei, most severe in the substantia nigra, but also involved the ventral striatum and amygdala. The hippocampus was spared except for degeneration of the afferent perforant tract, secondary to entorhinal nerve cell loss. Argyrophilic neuronal inclusions, with a characteristic immunocytochemical profile, were found in brainstem nuclei, hypothalamus, and basal ganglia. Ultrastructurally, in 3 patients these inclusions showed hitherto undescribed abnormally assembled filaments. Glial cytoplasmic inclusions were widespread in white matter structures. Immunocytochemistry failed to demonstrate the protease-resistant prion protein. The pathology appears to be unique, involving various cortical and subcortical structures, and is consistent with the clinical findings of Klüver-Bucy–like syndrome, parkinsonism, and frontal lobe dementia. For this entity we suggest the term "chromosome 17–linked dementia."

We recently reported a family in which 13 members had varying degrees of disinhibition, parkinsonism, dementia, and in some members, amyotrophy. We suggested the name "disinhibition-dementia-parkinsonism-amyotrophy complex" [1]. In 6 members from this family who underwent autopsy, the onset of obvious disease occurred at a mean age of 44 years. Initially, the patients showed a range of personality and behavioral changes. Disinhibition, a predominant feature, manifested as a Klüver-Bucy–like syndrome with hyper/hyposexuality and oral tendency, alcoholism and aggressiveness. Social withdrawal, depression, and a schizophrenia-like picture occurred in some patients. These features were found in a variety of combinations and varied over time in individual patients. Memory was eventually affected in all, with relative preservation of orientation, speech, and calculation ability until late in the disease. Parkinsonism and cognitive deterioration led to a rigid, akinetic mute state. Amyotrophy

was obvious in 1 patient. The mean duration of the disorder to death was 14 years.

A genetic etiology was suspected because of the familial clustering of the disorder. Linkage analysis by typing of simple sequence repeat polymorphisms in 33 family members localized the disease locus to 17q21-22 [1–3], the same locus to which familial progressive subcortical gliosis recently was linked [4]. The disorder is transmitted as a highly penetrant autosomal dominant trait. As in other familial neurodegenerative disorders [5–9], there appear to be sporadic forms with clinical and pathological phenotypes similar to the chromosome 17–linked disease reported here [3]. However, the genetic etiologic relationship of sporadic disease with a similar pathology to the present disease is unknown.

We reviewed the pathological findings in all available members with familial disease to identify characteristic and consistent features that could be correlated with the clinical features of this disease [1].

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Materials and Methods

Clinical information obtained in the 6 affected family members reported here included results from neurological examination, neuropsychological tests, and detailed mental status assessments (memory, orientation, construction, naming, and other language functions). These findings have been reported elsewhere [1].

Neuropathology

The brains from the 6 members (III-33, III-35, III-37, III-39, III-53, and III-57 [1]) were inspected grossly at autopsy. In 1 member (III-35) the brain was hemidissected and one hemisphere was frozen. One patient (III-53) was described in a previous case report [10]. The brains were fixed in formalin. A total of 46 neuroanatomical sites variably available in the individuals (Table) were examined by light microscopy. Paraffin sections were stained with hematoxylin-eosin, cresyl violet–Luxol fast blue–eosin, phosphotungstic acid and hematoxylin, congo red, and Bielschowsky's silver impregnation. The severity of neuronal loss, gliosis, and spongiosis was scored on a scale from 0 to +++; (0 = normal, + = mild; ++ = moderate, and +++ = severe) by consensus (A. A. F. S., C. K., and C. D.'A.). The presence of neuronal tangle-like inclusions (considered either as Alzheimer's disease [AD] or non-AD tangles), neuritic plaques, ballooned neurons, and spheroids were noted as present (+) or absent (0).

Immunocytochemistry

Five-micrometer-thick sections from most sites were deparaffinized and immunostained by the avidin-biotin-peroxidase complex (ABC) method [11] with a Vectastain ABC kit (Vector, Burlingame, CA). The following primary antibodies were applied: polyclonal rabbit antitau (1:100) (Sigma Chemical, St. Louis, MO), polyclonal rabbit anti–human ubiquitin (1:100) (Dako, Carpenteria, CA), monoclonal anti–phosphorylated neurofilament (1:250) (Sternberger Monoclonals, Baltimore, MD), monoclonal mouse anti–human beta-amyloid (1:100) (Dako), and polyclonal rabbit anti–human glial fibrillary acidic protein (GFAP) (1:250) (Sigma). Nonspecific binding was blocked by pretreatment with a blocking kit (Vector). Negative control samples were provided by omitting the primary or secondary antibody. Sections were incubated with the required primary antibody followed by the secondary reagent, including biotinylated anti-rabbit or anti-mouse IgG, for 30 minutes, and then with ABC. The sections were then subjected to peroxidase reaction containing freshly prepared 0.02 M 3,3'-diaminobenzidine-tetrachloride and 0.05% hydrogen peroxide in 0.05 M Tris–hydrochloric acid buffer at pH 7.6 for 10 minutes at room temperature. The staining was performed with a Histostainer Ig instrument (Leica, Deerfield, IL).

Electron Microscopy

One-millimeter tissue cubes were cut from paraffin blocks from 3 family members (III-37, III-39, and III-53) containing intracytoplasmic inclusions on light microscopic examination. These were then deparaffinized, postfixed in 2.5% buffered glutaraldehyde followed by 1% buffered osmium tetroxide, dehydrated, and embedded in epoxy resin (Epon) and examined with an electron microscope.

Immunoblot Analysis of Brain Extracts

Previously frozen tissue from 1 patient (III-35) was homogenized in nine volumes of lysis buffer (100 mM sodium chloride, 10 mM ethylenediaminetetraacetic acid, 0.5% NP40, 0.5% sodium deoxycholate, 10 mM Tris, pH 7.4) and aliquot was digested with proteinase K (100 µg/ml) for 1 hour at 37°C. Digestion was terminated by the addition of PMSF (2 mM final concentration) and boiling in electrophoresis sample buffer (3% sodium dodecyl sulfate in 62.5 mM Tris, pH 6.8). Sample was resolved on 12% polyacrylamide gels, immunoblotted with the monoclonal antibody 3F4, which recognizes the prion protein (PrP) residues 109 to 112, and developed as previously described [12].

Prion Protein Immunocytochemistry

Paraffin sections from frontal, temporal, and parietal cortices, hippocampus, and cerebellum from all 6 family members were treated with 98% formic acid and hydrolytic autoclaving to enhance PrP immunoreactivity [13]. Sections were then incubated with monoclonal antibody 3F4 raised against hamster PrP. The peroxidase-antiperoxidase method was used.

Results

Clinical Characterization

The clinical histories of the 6 members reported here have been summarized [1, 2]. The clinical findings in a typical index patient (III-37) are briefly presented.

A 52-year-old woman (III-37) presented with progressive personality change and dementia. She complained of losing things around the house and forgetting names and recent events. She had received a high school education and had worked as a phone receptionist. Past medical history was noncontributory. Her father (II-8), paternal grandmother (I-15), paternal aunt (II-6), paternal uncle (II-10) [1], and a brother (III-39) died of dementing illnesses with parkinsonian features. A similar dementing-parkinsonian illness has since developed in another brother (III-45) and sister (III-41). Four other siblings and 7 children have no neurological disease to date.

Her family noted behavioral changes, initially seen at her mother's funeral where she was unfriendly to other family members and tended to "shy away." She acted in a "childish but affable" manner and compulsively walked the same route daily. She had a decreased libido and a craving for sweets, gaining 90 pounds over 4 years.

At age 53 she was oriented to person, place, and time; was slow in calculations; and was able to recall only one out of three objects at 5 minutes. On the Wechsler Adult Intelligence Scale-Revised (WAIS-R) she scored an IQ of 72, with a verbal score of 72 and a performance score of 67. Speech was normal and her motor findings were normal without evidence of extrapyramidal dysfunction.

At age 54 she was alert, attentive, and oriented to person, place, and time. She repeated nine digits forward and four backward. She named 1 out of 10 pictured objects and body

Neuropathological Findings in Patients with Chromosome 17–Linked Dementia[a]

| Anatomical Site | Neuronal Loss | Gliosis | Spongiosis | Intraneuronal Inclusions[b] | | Ballooned Neurons[b] | Spheroids[b] |
				AD Tangles[c]	Non-AD Tangles		
Cortices							
Entorhinal cortex	+ +	+ + +	+ +	+	0	+	0
Anterior temporal cortex	+ +	+ + +	+ +	+	0	+	+
Prefrontal cortex	+	+ +	+ +	+	0	+	0
Anterior cingulate	+ +	+ +	+ +	+	+	+	+
Posterior cingulate [3]	0	+	+	+	0	+	0
Insular cortex	+	+ +	+ +	+	0	+	0
Prepiriform cortex [4]	+ +	+ + +	+	+	0	0	+
Occipital cortex [5] (area 17)	0	0	0	+	0	0	0
Occipital cortex [3] (area 18)	+ +	+ + +	+ +	0	0	+	0
Parietal cortex [3]	0	0	0	0	0	0	0
Motor cortex [1]	0	0	+ +	0	0	0	0
Hippocampus [5][d]						0	0
CA1–CA3	+	+	+	+	0	0	0
CA4	+ +	+ +	0	0	0	0	+
Perforant tract	−	+ + +	+	−	−	0	+
Dentate fascia [5]	+	+ +	0	0	0	0	+
Molecular layer of dentate	+ +	+ + +	0	0	0	0	+
Subiculum [5][d]	0	+	0	+	0	0	0
Prosubiculum	0	+	0	+	0	+	+
Subcortical nuclei						+	0
Putamen	+ +	+ +	+	0	+	0	0
Caudate	+ +	+ + +	+	0	+	+	0
Accumbens [5]	+ +	+ +	+	0	+	+	+
Globus pallidus							
Medial	+ +	+ + +	+	0	+	+	0
Lateral	+	+	+	0	+	+	0
Claustrum [5]	+	+ +	0	0	+	+	+
Amygdala [4]	+ + +	+ + +	+	+	+	+	0
Mamillary body [3]	0	+	0	0	+	+	+
Ventral hypothalamus [4]	+ +	+ + +	0	0	+	0	0
Subthalamic nucleus [4]	+	+ +	0	0	+	0	+
Thalamus [4]							
Anterior	+	+ +	0	0	+	0	+
Dorsomedial	0	+	0	0	+	0	+
Ventrolateral	+	+	0	0	0	0	0
Substantia nigra [5]							
Pars compacta	+ +	+ + +	0	0	+	+	+
Pars reticularis	+ +	+ + +	+	0	+	0	+
Red nucleus [5]	+	+ +	0	0	+	0	+
Locus ceruleus [4]	+	+ +	+	0	+	0	+
Pontine nuclei [5]	0	0	0	0	0	0	0
Substantia innominata [5]	+	+	0	+	+	+	0
Periaqueductal gray	+ +	+ + +	+	0	+	0	+
Third nucleus	0	0	0	0	+	0	0
Inferior olivary nucleus [4]	+	+	0	0	0	0	0
Cerebellar cortex [4][d]	0	0	0	0	0	0	0
Cerebellar dentate nucleus [4][d]	0	+	0	0	0	0	+
Spinal cord [3]							
Anterior horn	+ +	+ +	0	0	0	0	+
Intermediolateral column	+	+	0	0	0	0	0

[a]Scoring of the severity of neuronal loss, gliosis and spongiosis: 0 = normal; + = mild; + + = moderate; + + + = severe change. The numbers within brackets after the anatomical site indicate the number of cases available.
[b]The presence of AD tangles, non-AD tangles, ballooned neurons, and spheroids is indicated with "+" and their absence with "0."
[c]Very occasional AD tangles were found in 4 cases (III-33, III-35, III-37, and III-53).
[d]Case III-39 showed extensive remote hypoxic/ischemic changes of the hippocampus and cerebellum and is not included in the scores.

parts. Repetition was normal. Constructions were poor. At 5 minutes she recalled none of three objects. On the WAIS-R she produced a verbal IQ of 74 and a performance IQ of 65. She scored poorly on fund of general information and verbal abstract reasoning. Her behavior was childish and impulsive and she had difficulty following instructions. Cranial nerve findings were normal. A decreased arm swing, difficulty with rapid alternating movements, a positive glabellar tap, and bilateral palmomental responses were noted.

The following were normal: complete blood cell count, erythrocyte sedimentation rate, electrolytes, creatinine level, liver and thyroid function, electrocardiogram, coagulation screen, urinalysis, and cerebrospinal fluid (CSF), with a protein concentration of 45 mg/dl, glucose level of 59 mg/dl, 0 white blood cells, 1 red blood cell, and a CSF opening pressure of 150 mm H_2O. The electroencephalogram was normal.

Computed tomography at the age of 58 years showed diffuse cerebral atrophy, especially prominent in the frontal and temporal lobes. Sequential regional cerebral blood flow studies performed at ages 55, 56, and 57 revealed an initial decrement in cerebral blood flow affecting the frontal lobes, with later development of hypoperfusion of the posterior lobes.

Dementia progressed and was accompanied by slowing of movements with a stiff, shuffling gait. Eventually swallowing difficulties with drooling and muteness developed. By 59 years, she was bed bound and incontinent. Contractures of the elbows, knees, and hips had developed. Full extraocular movements were present. Reflexes were symmetrical and plantar reflexes were flexor. She followed no commands and remained mute, apart from groaning and grimacing in response to painful stimuli. She died at age 60.

Neuropathology

GROSS FINDINGS. Brain weights of the 6 patients ranged from 970 to 1,350 gm. Gyral atrophy was usually evident in anterior and inferior regions of the temporal lobes, the prefrontal areas, and the anterior cingulate gyrus, whereas the posterior frontal, parietal, and occipital areas appeared normal. The hippocampus appeared unremarkable. In the most severely affected members, the basal ganglia exhibited atrophy and mild brownish discoloration. The brainstem appeared normal, except for severe pallor of the substantia nigra in all members. The cerebellum was not remarkable.

MICROSCOPIC FINDINGS. Although the severity of histopathological changes varied from brain to brain, their distribution appeared uniform. In the most severely affected cortical areas, neuronal loss and gliosis were seen throughout the thickness of the cortex (Fig 1). In less severely affected areas of cerebral cortex, the second, third, and sixth layers appeared to be primarily involved, with relative sparing of the fourth and fifth layers (Fig 2). Generally, the astrogliosis seemed to exceed the severity of neuronal loss (see Table). The atrophy of the superficial cortical layers was associated with laminar spongiosis commonly confined to the contigu-
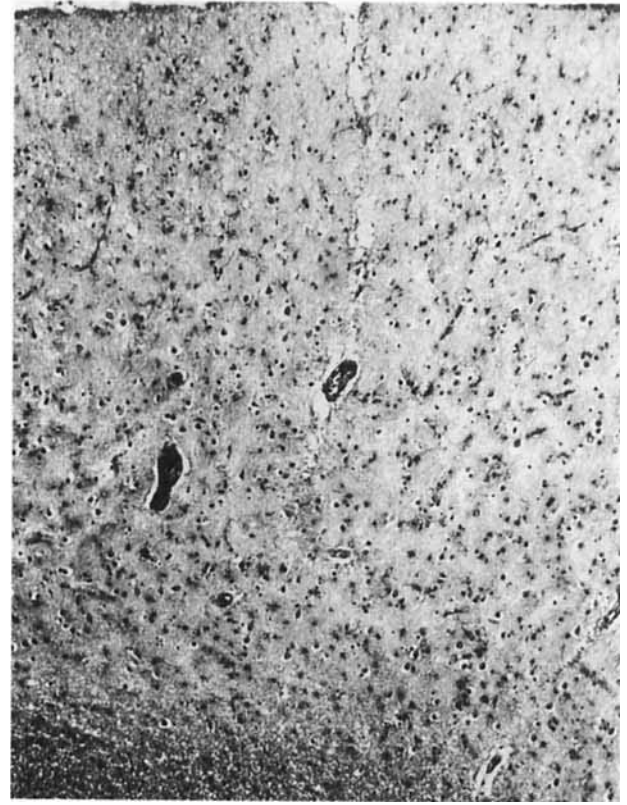

Fig 1. Entorhinal cortex from Case III-35 showing marked neuronal loss and dense gliosis throughout the thickness of the cortex. In the superficial layers 1 and 2 there is mild spongiosis. (Phosphotungstic acid and hematoxylin, × 56 before 11% reduction.)

ous deep and superficial parts of the first and second layers (see Fig 1). The most severely affected areas of the cerebral cortex were, in descending order, the prepiriform, anterior temporal, entorhinal, visual association (area 18), anterior cingulate, prefrontal, and insular regions (see Table). The white matter underlying the most severely affected cortices showed axonal loss, myelin pallor, and mild isomorphic astrogliosis with relative sparing of the U fibers. Clustering of astroglial elements was not seen in subcortical areas (see Fig 2). The posterior cingulate gyrus, parietal cortex (available from 3 members), and visual cortex (area 17) (available from 5 members) did not show neuronal loss or significant gliosis. The motor cortex, available from only one of the most severely affected patients (III-35), showed no neuronal loss or gliosis. In all specimens, a striking feature was the sharp demarcation between severely affected cortices and seemingly normal cortex. This was most pronounced between the anterior cingulate gyrus and the medial frontal cortex (Fig 3), and between areas 18 and 17 of the occipital cortex. Affected areas showed occasional ballooned neurons and
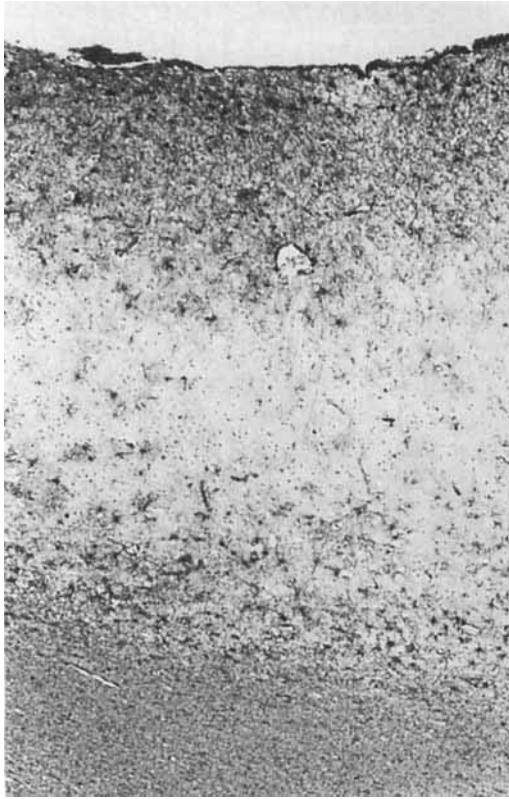
Fig 2. Anterior temporal cortex from Case III-31 showing fibrillary gliosis of layers 1 to 3 and 6, whereas layers 4 and 5 are relatively spared. Subcortical white matter shows no gliosis. (Glial fibrillary acidic protein immunostaining, × 48.)

Fig 3. Case III-35. There is moderate degeneration and atrophy of the anterior cingulate gyrus. The neighboring superior frontal gryrus appears virtually normal, demonstrating the sharp demarcation of involved cortices. (Cresyl violet–phosphotungstic acid and hematoxylin, × 10 before 28% reduction.)

Fig 4. Phosphotungstic acid and hematoxylin–stained section of the subiculum in Case III-53 demonstrating marked gliosis of the crossing perforant tract (arrowheads) and adjacent molecular layer of the dentate fascia (arrows). (Glial fibrillary acidic protein immunostain, × 54 before 30% reduction.)

spheroids. The latter appeared to correlate with the severity of the cortical changes. The hippocampal formation showed relative sparing with no or only mild neuronal loss in cornu ammonis CA1 to CA3, subiculum, and prosubiculum. Severe gliosis and axonal loss affected the perforant tract (Fig 4) and the molecular layer of the dentate fascia. There was mild neuronal loss and gliosis of the dentate fascia also involving the adjacent areas of CA4. In 1 patient (III-39), abnormalities in the hippocampus were confounded by extensive remote hypoxic/ischemic loss of pyramidal neurons (see Table).

The most severely affected subcortical structures were, in descending order, the amygdala, substantia nigra (Fig 5), ventral globus pallidus, periaqueductal gray, ventral putamen, ventral hypothalamus, and caudate nucleus (see Table). The locus ceruleus, available from 4 members, showed mild neuronal loss and gliosis. The pontine nuclei were unremarkable, the red nucleus was only mildly affected, and the thalamic nuclei and substantia innominata were minimally involved. In all specimens, the basal ganglia showed a gradient in the severity of neuronal loss and gliosis. The rostral and ventral parts of the caudate nucleus, nucleus accumbens, putamen, medial pallidum, and claustrum were most severely affected by neuronal loss and gliosis, whereas the caudal and dorsal parts of the basal ganglia appeared virtually normal.

Mild neuronal loss was found in the inferior olivary nucleus and dorsal vagus nucleus. The cerebellar dentate nucleus and cortex appeared normal (see Table). Mild to moderate loss of motor neurons and gliosis was found in 2 (III-39 and III-53) of 3 members from
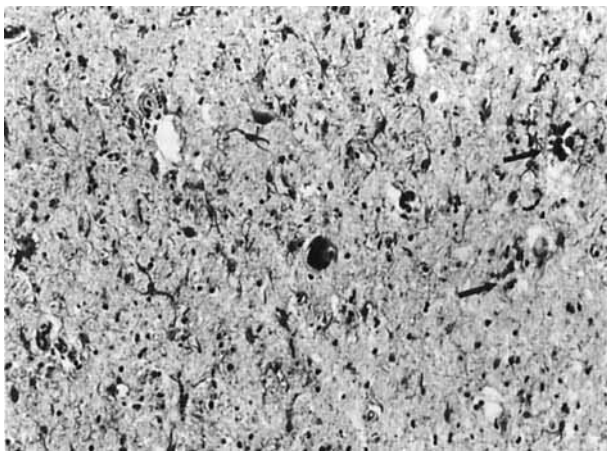
Fig 5. Case III-39. Photomicrograph of substantia nigra pars compacta, showing an occasional pigmented neuron, intense gliosis, and free melanin pigment (arrows). (Phosphotungstic acid and hematoxylin, × 230 before 20% reduction.)

whom the spinal cord was available. One of these (III-39) also showed mild neuronal loss of the intermediolateral column.

The hippocampus and cerebral cortex showed insignificant numbers of neurofibrillary tangles or neuritic plaques of the Alzheimer type (see Table). No Lewy bodies were demonstrated in any of the samples.

In all 6 family members, argyrophilic neuronal cytoplasmic inclusions were seen in several subcortical structures, most commonly in the third nerve nucleus (Fig 6), followed by the dorsal raphe nucleus, ventral hypothalamus, subthalamic nucleus, periaqueductal gray, pars compacta of the substantia nigra, red nucleus, and globus pallidus, The inclusions stained intensely with Bielschowsky's silver impregnation and appeared by light microscopy to be composed of haphazardly arranged spicules (see Fig 6).

In addition, oligodendroglial argyrophilic tangle-like inclusions were seen in the white matter, the external capsule, ansa lenticularis, corpus callosum, and brainstem.

Mild congophilic angiopathy was found in meningeal vessels of the occipital and parietal lobes in 1 brain (III-35).

IMMUNOCYTOCHEMICAL FINDINGS. The subcortical neuronal inclusions stained positive for phosphorylated neurofilament (see Fig 6) and ubiquitin, whereas they were negative for beta-amyloid and tau and were therefore considered non-AD tangles. Occasional tau- and beta-amyloid–positive tangles were considered AD tangles (see Table). Ballooned neurons stained positive for phosphorylated neurofilaments and variably positive for ubiquitin and tau. In areas of cortical neuronal loss
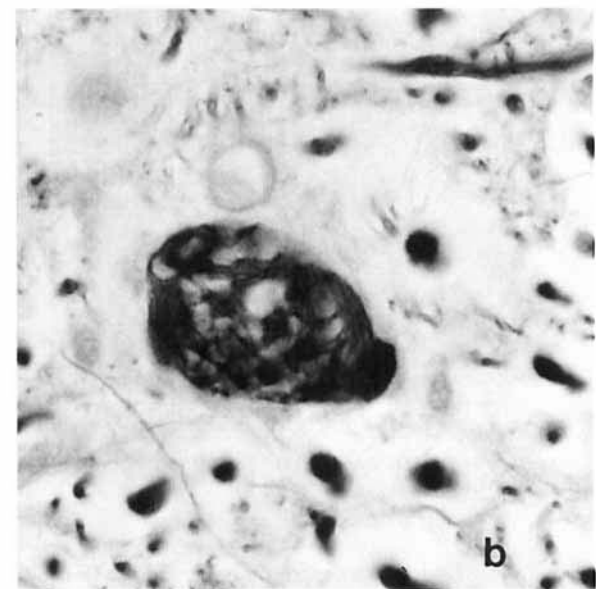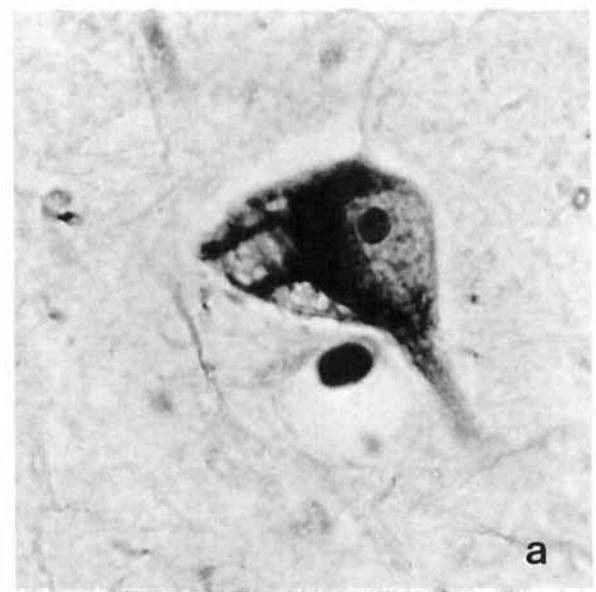

Fig 6. (a) Motor neuron of the third nucleus from Case III-35 showing spicule-like argyrophilic inclusion. (b) Similar inclusions staining positive for phosphorylated neurofilament in a dorsal raphe neuron. (Bielschowsky silver impregnation and antiphosphorylated neurofilament immunostain, respectively; × 980.)

and gliosis, numerous ubiquitin-positive and to a lesser degree, tau-positive granules and spheroids were seen.

The oligodendroglial argyrophilic inclusions stained positive for ubiquitin and tau (Fig 7), whereas they were negative for beta-amyloid, phosphorylated neurofilament, and GFAP.

ELECTRON MICROSCOPY. Intraneuronal inclusions were identified ultrastructurally in 3 brains and consisted of 10- to 14-nm filaments showing a three-
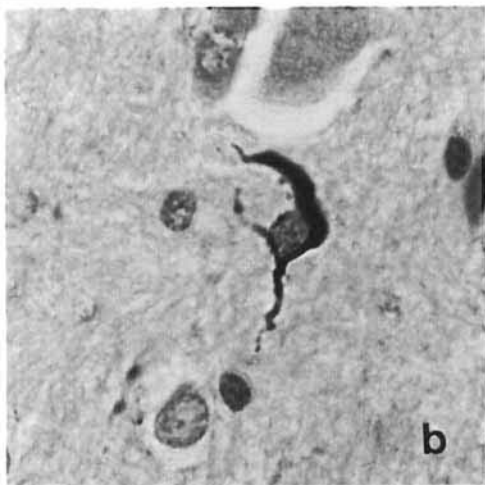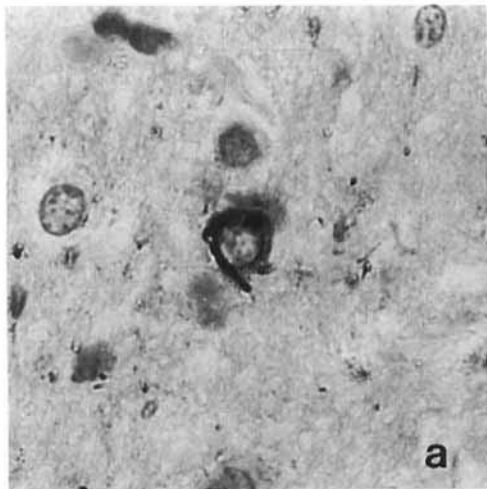
Fig 7. Oligodendroglial fibrillary inclusions in Case III-33. (a) The inclusion is stained with (a) antiubiquitin and (b) with antitau immunostains. (× 980.)
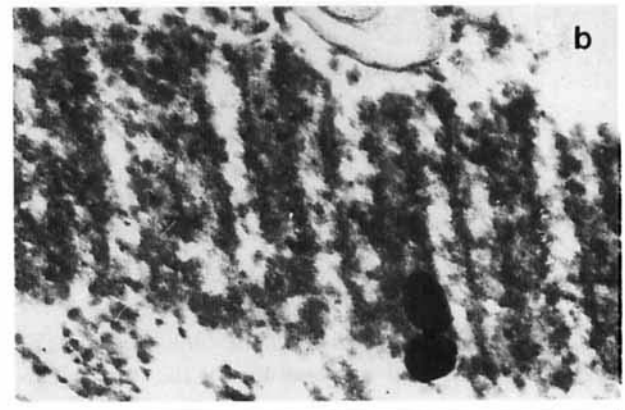

Fig 8. Electron micrograph of intraneuronal inclusions in the third nucleus from Case III-33 demonstrating periodically arranged neurofilaments (a). (b) Higher magnification demonstrating a three-dimensional arrangement of filaments measuring between 10 and 14 nm. (a: × 28,500; b: × 90,800 before 22% reduction.)
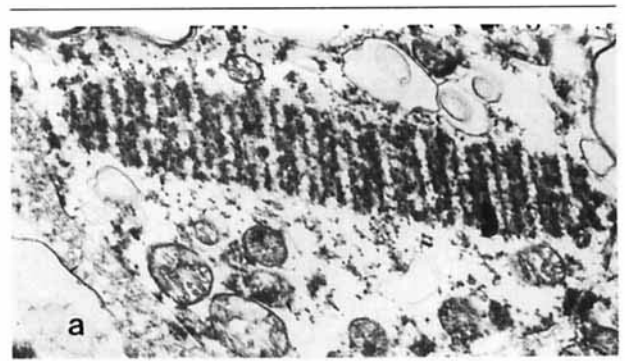
dimensional lattice-like arrangement with a variable periodicity (Fig 8). The inclusions demonstrated in oligodendroglial cells showed parallel tubular structures measuring approximately 14 to 17 nm in diameter.

IMMUNOBLOT ANALYSIS. Western blot analysis of brain extracts from the cerebellum of 1 member (III-35) failed to detect protease-resistant PrP (Fig 9).

PRION PROTEIN. No immunoreactive deposits of PrP were detected in any of the sections from the 6 brains.

Discussion

The degree of cerebral atrophy varied among family members. The prefrontal and anterior temporal lobes were severely and consistently affected, with a striking preservation of the hippocampal formation. The atrophy was symmetrical and showed a knife edge–like pattern in severely affected areas.

The characteristic pathological changes were neuronal loss, astrogliosis, and laminar spongiosis of the limbic and association cortices, often in a sharply circumscribed fashion. Similar changes also involved various subcortical structures.

The most striking finding consisted of neuronal intracytoplasmic inclusions consisting of hitherto undescribed phosphorylated neurofilaments arranged in lattice-like formations. They were common in brainstem nuclei, hypothalamus, and basal ganglia. Their distribution was similar to that of tangles in progressive supranuclear palsy (PSP) [14, 15], although their fine structural features appeared unique and different from the straight tubular structures characterizing PSP tangles [16, 17]. Immunocytochemically they were positive for phosphorylated neurofilament and ubiquitin but negative for tau and beta-amyloid. Since similar microfilamentous inclusions have not been described previously, they may serve as a histopathological marker for chromosome 17–linked dementia (Ch-17D). An unexpected finding was oligodendroglial cytoplasmic inclusions, so-called glial cytoplasmic inclusions (GCIs), with an immunocytochemical profile
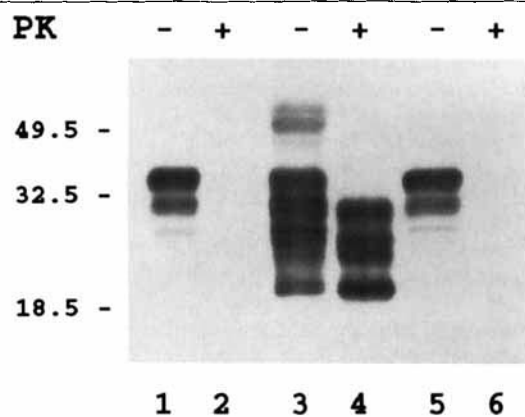
Fig 9. Western blot immunodetection of prion protein before (lanes 1, 3, and 5) and after proteinase K (PK) digestion (lanes 2, 4, and 6). Lanes 1 and 2: cerebellum from a normal age-matched human brain; lanes 3 and 4: cerebellum from a subject with a sporadic Creutzfeldt-Jakob disease; lanes 5 and 6: cerebellum from Case III-35 with chromosome 17–linked dementia. In this subject, as in the control, protease-resistant prion protein was not detected. In this experiment a volume equivalent to 0.3 mg of wet tissue was loaded in each lane. The same result was obtained loading a volume equivalent to 2 mg of wet tissue.

identical to those described in multiple-system atrophy (MSA) [18–20]. This observation suggests that GCIs are not specific for MSA [18]. They have also been observed in cortico–basal ganglionic degeneration (CBD) [21], PSP [22–23], and spinocerebellar atrophy type 1 (SCA1) with multiple-system degeneration [24].

The distribution of the present changes suggests involvement of cortical and subcortical structures encompassing cortico–basal ganglionic circuits such as the entorhinal, anterior temporal, and cingulate projections to the ventral striatum [25, 26], as well as projections from the piriform cortex and amygdala to the ventral hypothalamus, entorhinal cortex, and temporal association cortex [25, 26]. Furthermore, involvement of the mesolimbic system may be postulated, involving projections from the ventral tegmental area of the substantia nigra to the anterior cingulate, entorhinal, and insular cortices [27–29].

The severe involvement of the anterior temporal cortex, including the amygdala, is likely to correlate with the personality changes characterized by hyperorality and hypo/hypersexuality consistent with the Klüver-Bucy syndrome [30, 31]. The changes of prefrontal cortex and apparent deafferentation of the hippocampal formation are most likely responsible for the frontal lobe release signs, frontal lobe dementia, and eventually global dementia. The profound degeneration of the substantia nigra corresponds to the parkinsonian signs exhibited early in the course of the disease. The prefer-

ential involvement of the ventral striatum is most likely associated with the pathology in the association cortices and neocortical limbic structures [25, 26].

The present disease is sufficiently different from AD, Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) that they need not be considered in the differential diagnosis. Ch-17D shares clinical features with Pick's disease [32–35], hereditary dysphasic dementia (HDD) [32], lobar atrophy [36, 37], pallidopontonigral degeneration (PPND) [38], progressive subcortical gliosis (PSG) [9, 39–42], frontal lobe degeneration (FLD) [43, 44], CBD [45, 46], mesolimbocortical dementia [47], diffuse Lewy body disease (DLBD) [48–50], and parkinsonism-ALS and related disorders [51–53]. Ch-17D [1] and familial PSG [4] are the first frontal lobe dementia syndromes that have been linked to chromosome 17, and differ from known genetic loci for other dementing disorders, parkinsonism, or motor neuron disease [54–57].

The disorders that demonstrate similarities with Ch-17D, and therefore should be considered in the differential diagnosis, include PSG, CBD and FLD and its subtypes [44]. Sporadic and familial PSG shows preferential involvement of white matter, usually most severe in the frontal lobe [9, 40], variably asymmetrical [9, 58], and without sharp demarcation between affected and unaffected cortices [9]. PSG shares with the present disease severe involvement of the substantia nigra, and sparing of the hippocampus and cortical astrogliosis exceeding that expected from the degree of neuronal loss [4, 9]. However, in the brains studied here, subcortical gliosis, the hallmark of PSG, was absent. In contrast to the familial PSG patients reported by Lanska and colleagues [9], the present family members showed uniformly moderate to severe involvement of the rostroventral basal ganglia, including ventromedial pallidum and amygdala. Perhaps the most striking pathological differences between Ch-17D and PSG were the presence of intraneuronal inclusions and GCIs in Ch-17D. Petersen and coauthors [4] reported that the two kindreds of PSG originally described by Lanska and colleagues [9] showed the presence of proteinase K–resistant PrP and appear to be allelic to chromosome 17. This finding raises the possibility that a gene on chromosome 17 may be involved in prion metabolism. The present study failed to demonstrate proteinase K–resistant PrP by immunocytochemistry. This, however, does not exclude a possible genetic overlap between PSG and Ch-17D [4].

CBD is a discrete clinicopathological entity. The neuropathological abnormalities include frontoparietal atrophy with relative sparing of the temporal lobe, ballooned neurons within the cerebral cortex, and variable degeneration of subcortical structures, most consistently affecting the substantia nigra [21, 46, 59]. Three brains affected with CBD reported by Wakabayashi

and associates (21) also demonstrated involvement of the rostral internal and external segments of the globus pallidus, putamen, and caudate nucleus, similar to the pathology reported here. The same authors demonstrated GCIs and subcortical neurofibrillary tangles of the PSP type, and hence different from those reported here [17]. The present entity therefore shows considerable overlap with CBD, although differences exist in the involvement of the parietal and temporal lobes, and the asymmetrical involvement of the pathology in CBD [21]. Whether the two entities are genetically linked remains to be investigated, although substantial clinical differences exist. CBD starts at a later age and has a more rapid course [21, 46].

The cortical changes in Ch-17D are similar to those in FLD, although the parietal lobe and the hippocampus are commonly involved in the latter [43, 44], and FLD lacks the neuronal and glial inclusions described here.

Despite substantial overlap in pathology with several degenerative dementing disorders, we conclude that the present disease shows several distinguishing features, such as sharply circumscribed cortical atrophy involving limbic structures and association cortices, unique intraneuronal inclusions, and lack of subcortical gliosis, to regard it, for now, as a separate pathological entity. Further genetic analyses of patients with CBD, FLD, PPND, or classic Pick's disease will be of interest in determining whether these diseases are genetically distinct or whether they are linked to chromosome 17 as are the present disease and PSG [4].

In summary, we described the pathology in a familial progressive dementing disorder, clinically characterized as disinhibition-dementia-parkinsonism-amyotrophy complex [1]. Study of 6 available brains showed a uniform distribution of neuropathological changes. The clinical and pathological distinctions between multisystem degenerations may at times be difficult, and overlapping syndromes may be etiologically related [4, 32, 38]. Their etiological relationship will require determination of the molecular basis for these conditions. For simplicity and in keeping with the genetic characterization of the present disorder, we suggest that the clinical and pathologic entity be called "chromosome 17–linked dementia."

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