

Neuropathology Education

A 62-year-old man with a family history of dementia, showing dementia and parkinsonism, presented with personality change and behavioral abnormality

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CLINICAL HISTORY

The patient was a 62-year-old man. His mother, maternal uncle and grandfather had suffered from dementia. At the age of 57, the patient developed hypobulia, apathy and mental irritability, and showed disinhibited and stereotypical behaviors. At the age of 58, he showed personality change, poor understanding, restless and aimless walking, perseveration and echolalia as well as memory disturbance and disorientation. There was amnesic aphasia but no apraxia or agnosia. A CT scan and MRI disclosed localized symmetrical atrophy of the frontal and temporal lobes. Thereafter, he became mutistic and developed bradykinesia, rigidity of the extremities and impairment of vertical ocular pursuit movement. Sucking and grasp reflexes were positive with forced crying. He also revealed increased deep tendon reflexes in the extremities and bilateral Babinski signs. At the age of 59, he showed an oral tendency and could no longer walk. At the age of 60, he became bedridden, and tube feeding was started because of pseudobulbar palsy. At the terminal stage, he had repeated episodes of bronchopneumonia and died with akinetic mutism after a disease duration of about 5 years.

NEUROPATHOLOGICAL EXAMINATION

Macroscopic findings

The brain weighed 960 g. The cerebrum showed symmetrical localized frontotemporal lobe atrophy including the

precentral gyrus (Fig. 1). Cerebral slices revealed narrowing of the frontal and temporal cortices, and atrophy of the subcortical white matter. The hippocampus, amygdala, caudate nucleus and medial thalamus were also atrophic. The brainstem showed discoloration of the substantia nigra and locus ceruleus and atrophy of the cerebral peduncle and pyramis.

Light microscopic findings

Severe neuronal loss and protoplasmic astrogliosis with spongy change in the superficial layers were found in the frontal, temporal and precentral cortices (Fig. 2a). Some ballooned neurons were scattered in the deep cortical layers. There was destruction of the myelin and axons with astrogliosis in the subcortical white matter, in which numerous Gallyas-Braak-positive (GB-positive) coiled bodies and argyrophilic threads were noted (Fig. 2b). Severe neuronal loss with astrogliosis was also found in the hippocampus and amygdala. In the brainstem, the substantia nigra showed moderate neuronal loss and astrogliosis (Fig. 2c). Severe degeneration of the bilateral corticospinal tracts was detected.

Immunohistochemical findings

In the cerebral cortex, many protoplasmic astroglia showed granular-positive staining in the cytoplasm and processes with antiphosphorylated tau antibodies (Fig. 2d). The ballooned neurons showed granular-positive staining at the periphery of the cytoplasm with these antibodies. In the subcortical white matter, numerous coiled bodies and mesh-like structures were positive to these antibodies (Fig. 2e). In the subcortical nuclei, many pretangle neurons showed granular-positive staining with these antibodies in

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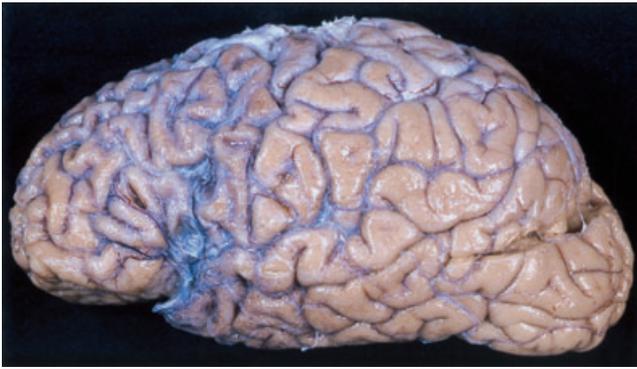


Fig. 1 The cerebrum shows localized atrophy of the fronto-temporal lobes including the precentral gyrus.

the amygdala, hypothalamus, substantia nigra, locus ceruleus and raphe nucleus (Fig. 2f).

In tau-immunoelectron microscopy, the cytoplasm and processes of tau-positive protoplasmic astroglia were occupied by bundles of nanogold-decorated glial filaments measuring 7–8 nm in diameter (Fig. 3a). Tau-positive coiled bodies contained nanogold-decorated parallel arranged straight tubules measuring about 15 nm in diameter (Fig. 3b). Tau-positive pretangle neurons contained nanogold-decorated numerous free ribosomes in the cytoplasm (Fig. 3c).

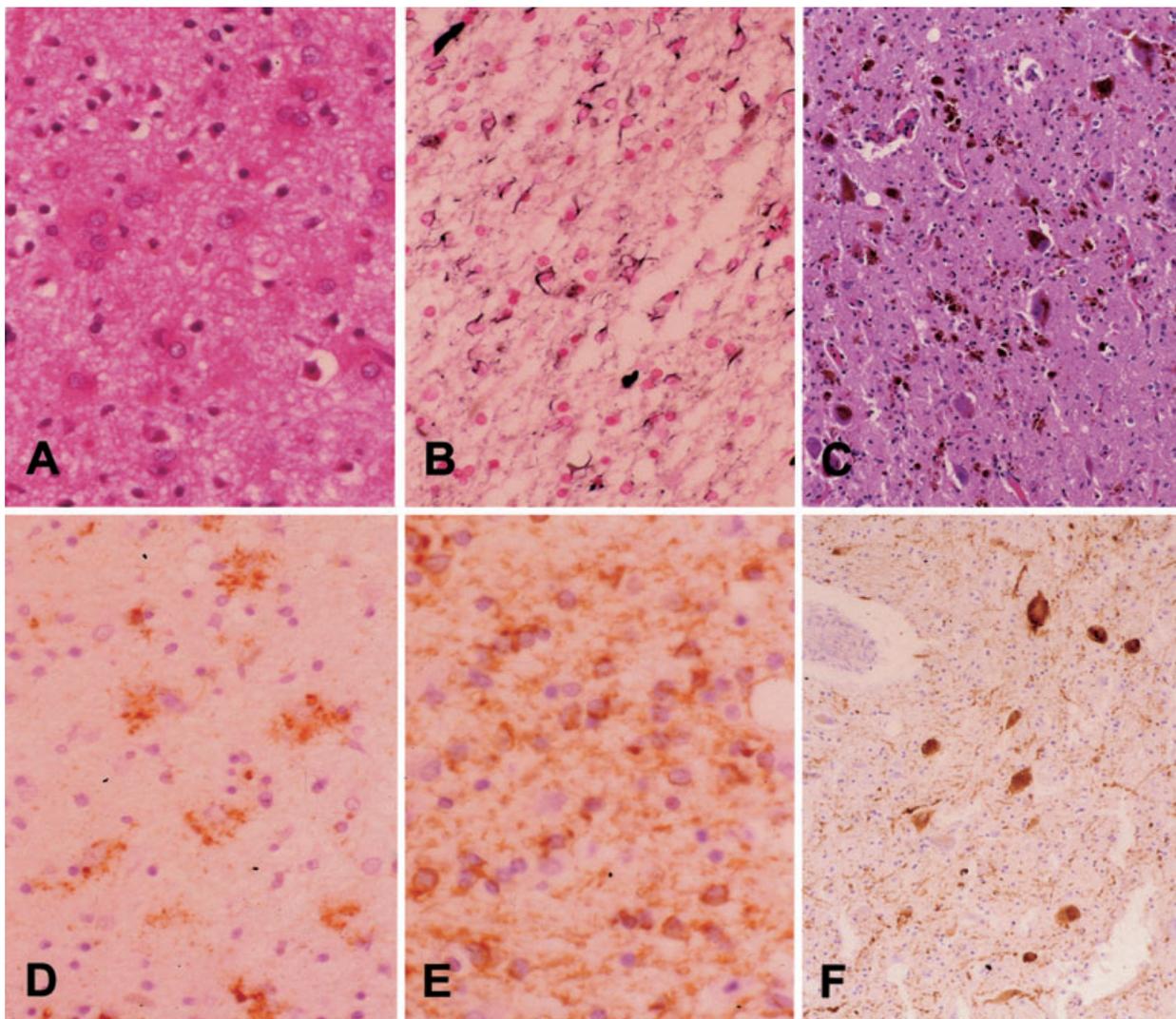


Fig. 2 (A) Proliferation of protoplasmic astroglia in the inferior temporal cortex (HE stain). (B) GB-positive coiled bodies and argyrophilic threads in the subcortical white matter. The middle temporal gyrus (GB stain). (C) Moderate neuronal loss and astrogliosis with many free melanins. The substantia nigra (HE stain). (D) Protoplasmic astroglia show granular-positive staining with antiphosphorylated tau antibody. The inferior temporal cortex (Tau-immunostaining). (E) Many tau-positive coiled bodies and mesh-like structures in the subcortical white matter. The middle temporal gyrus (Tau-immunostaining). (F) Pretangle neurons show diffusely cytoplasmic granular-staining with antiphosphorylated tau antibody. The raphe nucleus (Tau-immunostaining).

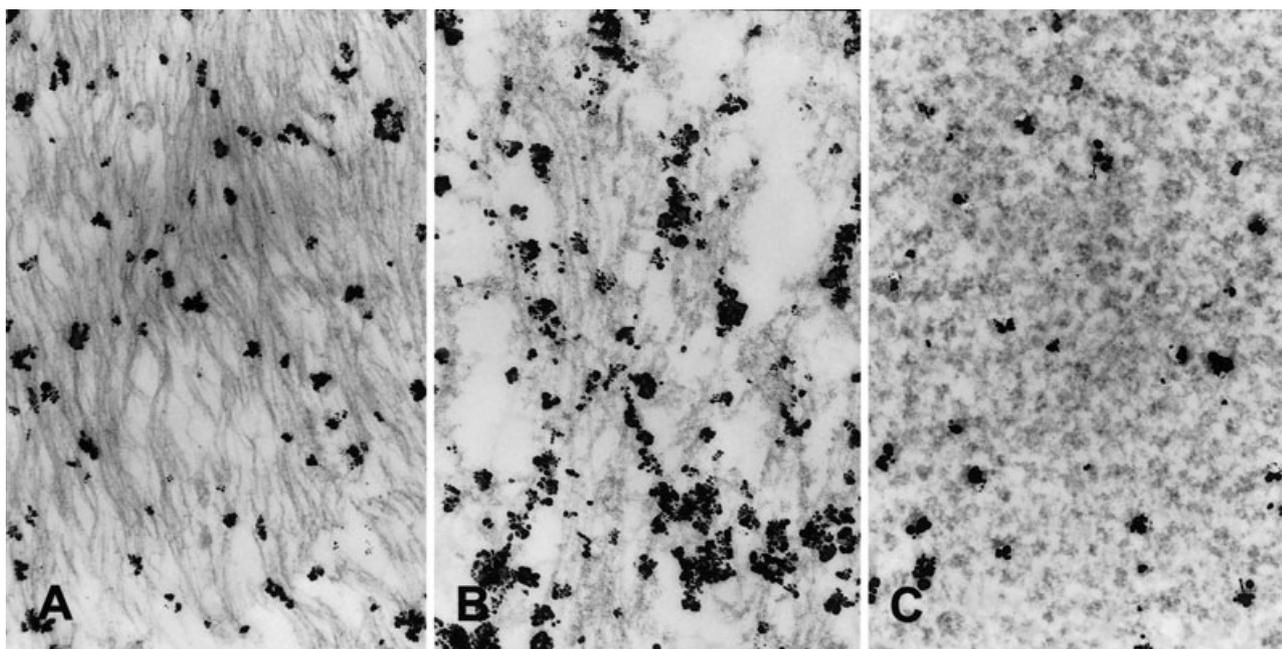


Fig. 3 (A) The bundles of tau-positive protoplasmic astroglia in the cerebral cortex are composed of nanogold-decorated glial filaments measuring 7–8 nm in diameter. Tau-immunoelectron microscopy ($\times 41,000$). (B) The bundle of tau-positive coiled bodies in the cerebral white matter is composed of nanogold-decorated parallel arranged straight tubules measuring about 15 nm in diameter. Tau-immunoelectron microscopy ($\times 56,000$). (C) The cytoplasm of tau-positive pretangle neurons in the raphe nucleus contains nanogold-decorated free ribosomes. Tau-immunoelectron microscopy ($\times 36,000$).

Mutation detection of the tau gene

Sequence analysis of exon 10 of the tau gene revealed an A to C transition at codon 296, leading to an amino acid substitution, asparagine to histidine (N296H), in the microtubule-binding domain of the tau protein.

Immunoblotting of the insoluble tau

Immunoblotting of sarkosyl-insoluble tau appeared as two major bands and a minor band that aligned with the recombinant four-repeat tau isoforms.

DIAGNOSIS

Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17).

DISCUSSION

Although there is clinicopathological heterogeneity among and within families, the majority of FTDP-17 cases clinically share frontotemporal signs and parkinsonism without resting tremor, and neuropathological atrophy of the frontotemporal lobes as well as the basal ganglia and substantia nigra, which is accompanied by neuronal loss, gliosis, spon-

giosis and tau accumulation in both neurons and glial cells.^{1,2} The tau accumulation represents different kinds of filaments such as twisted ribbons, paired helical filaments and straight tubules according to the case.^{2,3} These filaments consist of different insoluble isoforms of tau among the cases, four-repeat isoforms or all six isoforms.⁴ Several exonic and intronic mutations have been identified in the tau gene in FTDP-17.^{2,3}

The present case presented with frontal signs followed by temporal signs,⁵ and revealed localized atrophy of the frontotemporal lobes, corresponding to the clinical characteristics of Pick-type frontotemporal dementia. In addition, this case showed probably autosomal-dominant inheritance, with parkinsonism during the clinical course, suggesting that this case involved FTDP-17.

Neuropathologically, this case showed severe degeneration in the frontotemporal cortex with spongiosis in the superficial layers and ballooned neurons in the deep layers, severe degeneration in the subcortical white matter with many coiled bodies and argyrophilic threads, neuronal loss with pretangle neurons in the subcortical nuclei including the substantia nigra, and secondary degeneration of the pyramidal tracts due to involvement of the precentral gyrus, resembling the pathology of corticobasal degeneration. With tau-immunohistochemistry, this case characteristically showed proliferation of tau-positive pro-

toplasmic astroglia without neurofibrillary tangles (NFT) in the cerebral cortex, although there were tau-positive coiled bodies and threads in the subcortical white matter and tau-positive pretangle neurons in the subcortical nuclei.

On tau-immunoelectron microscopy, phosphorylated tau accumulated in glial cells and neurons in different modalities such as straight tubules in coiled bodies, free ribosomes in pretangle neurons and glial filaments in protoplasmic astroglia. In FTDP-17 cases showing mutations in exon 10, there were tau-positive twisted ribbons or straight tubules in NFT and coiled bodies.^{2,3} These findings suggest that tau proteins can be phosphorylated on free ribosomes in pretangle neurons, and that phosphorylated tau proteins can accumulate in glial filaments in reactive astroglia.

The N296H mutation in the microtubule-binding domain of exon 10 of the tau gene may interfere with the ability of mutated tau to bind with microtubules and lead to tau aggregation. In this case, the four-repeat tau accumulated in both neurons and glial cells, although predominantly in glial cells.

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