

Features of Creutzfeldt-Jakob Disease in Brains of Patients with Familial Dementia of Alzheimer Type

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SUMMARY: *Necropsy findings consistent with spongiform encephalopathy of the Creutzfeldt-Jakob type are described in the brain of a 48-year-old woman whose prolonged course and clinical features had suggested Alzheimer's presenile dementia. Six other members of her family in two generations have also died of progressive presenile dementing illnesses of Alzheimer*

type, lasting 5-10 years.

Autopsies showed a post-viral temporal lobe encephalopathy in one and spongiform (C-J) lesions in another. Neuropathological studies in this family add weight to the idea that Alzheimer's disease and Creutzfeldt-Jakob disease represent different manifestations of a genetic predisposition to "slow virus" encephalopathies.

RÉSUMÉ: *Nous décrivons, dans le cerveau d'une dame de 48 ans dont l'évolution clinique prolongée avait suggéré une démence présénile d'Alzheimer, l'évidence nécropsique d'une encéphalopathie de type Creutzfeldt-Jakob (CJ). Six autres membres de sa famille, sur deux générations, sont également décédés après une maladie démentielle progressive de type Alzheimer depuis 5-10 ans. Chez un de ces cas l'autopsie avait montré une*

encéphalopathie post-virale du lobe temporal, et chez un autre des lésions spongiformes compatibles avec le C.J. Les études neuropathologiques chez cette famille ajoutent donc du poids à l'hypothèse selon laquelle la maladie d'Alzheimer et celle de Creutzfeldt-Jakob représentent des manifestations différentes de la même prédisposition génétique aux encéphalopathies "à virus lents".

INTRODUCTION

The possibility that the pathogenetic mechanisms underlying spongiform encephalopathy of the Creutzfeldt-Jakob type, on the one hand, and Alzheimer's disease, on the other, may be significantly related is supported not only by occasional autopsy reports of both types of pathology in a single brain (Gaches et al., 1977; Hirano et al., 1972), but also by isolated examples of a greater than chance occurrence of both diseases in the same family. Cook et al (1978) have reported a family in which histologically proven Alzheimer's disease and spongiform encephalopathy (Creutzfeldt-Jakob) co-existed in one sibship. Kovanen and Haltia (1978) described a Finnish family with two neuropathologically and three clinically studied cases of Creutzfeldt-Jakob disease in two generations, in which three other members from earlier generations also had a history of presenile dementia. The age of onset varied from 46 to 62 years and electroencephalography showed only progressive slowing but none of the sharp-wave complexes typical of Creutzfeldt-Jakob disease. Diagnosis was confirmed in one patient by frontal brain biopsy and in a second by postmortem examination. In the latter, the pronounced spongiform changes were accentuated in both temporal lobes. The results of slow virus transmission experiments from material mentioned in these two papers are not available.

In the Bethesda laboratories, material from 35 patients with Alzheimer's disease has been inoculated into primates. One of these patients was a woman who began to dement at age 51. Her father had died at age 63 after progressive dementia and her sister, aged 50, required hospitalization for

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"nervous troubles". A left temporal lobe brain biopsy nine months after onset of her memory loss revealed neurofibrillary tangles and senile plaques interpreted (by Dr. N.B. Rewcastle) as Alzheimer's disease. The squirrel monkey recipient 29 months after inoculation showed spongiform encephalopathy (Traub et al., 1977).

This report documents the necropsy findings in a woman with a striking familial history of presenile dementing illnesses. Details of her clinical, genetic, and biopsy findings have already been described (Rice et al., 1979).

CLINICAL HISTORY

The probanda was a Caucasian woman who at age 38 years developed diminishing insight, compulsive eating, and inappropriate gregarious and affectionate behavior. Her memory worsened, comprehension failed, and within 3 years placement in an institution was required. At age 42 she was almost totally impoverished of speech, capable of echolalia only, demonstrated kleptomania, and was completely disoriented and incontinent of both urine and stool. Motor examination showed only stereotyped movements. At age 45 she could no

longer feed herself and could walk only with assistance.

Apart from severe emaciation, physical examination at age 47 showed no other general findings. Neurologically, she was unresponsive to verbal command, uttering only occasional monosyllabic sounds. Grasp, glabellar, palmomental, and sucking reflexes were easily demonstrated. Fasciculations of the tongue were seen. Rigidity was diffuse, with a preferred flexion posture. Tendon reflexes were brisk and both toes were upgoing. Myoclonus was never seen and there was no startle response.

Skull films were not remarkable and CAT scan showed profound atrophy of grey matter. EEG showed a grade I dysrhythmia.

Biopsy of right frontal lobe in May, 1978, showed no neurofibrillary tangles of Alzheimer, no senile plaques, but a definite, patchy neuronal dropout, especially in layers III and IV, as well as a moderately severe gliosis, especially of fibrous astrocytes. Electron microscopy (Fig. 1) showed many scattered neuritic processes, both pre-synaptic and post-synaptic, exhibiting marked vacuolation. Within the distended neurites fragments of membranous material were seen (Figs. 1b and c) and occasionally clusters of membranous, multivesicular structures (Figs. 1d and e).

FAMILIAL HISTORY

The clinical fascination with this case arose because of the unique family tree (Fig. 2). The proband's mother (II-2) died at age 48 in a mental hospital following several years' deterioration of personality and memory. The clinical diagnosis was Alzheimer's disease. A maternal aunt of our patient (II-1) died at 47 years of age, after a 7-year gradual deterioration in cognition with profound behavioral aberrations. One of the proband's maternal first cousins (III-1) gradually lost memory at age 41, exhibiting progressive apathy and uninhibited personality with vulgarity and inappropriate behavior. Within three years she required institutionalization and in the next five years demonstrated progressive flattening of affect, double incontinence, restriction of language, and loss of all cognition. In her terminal year she was

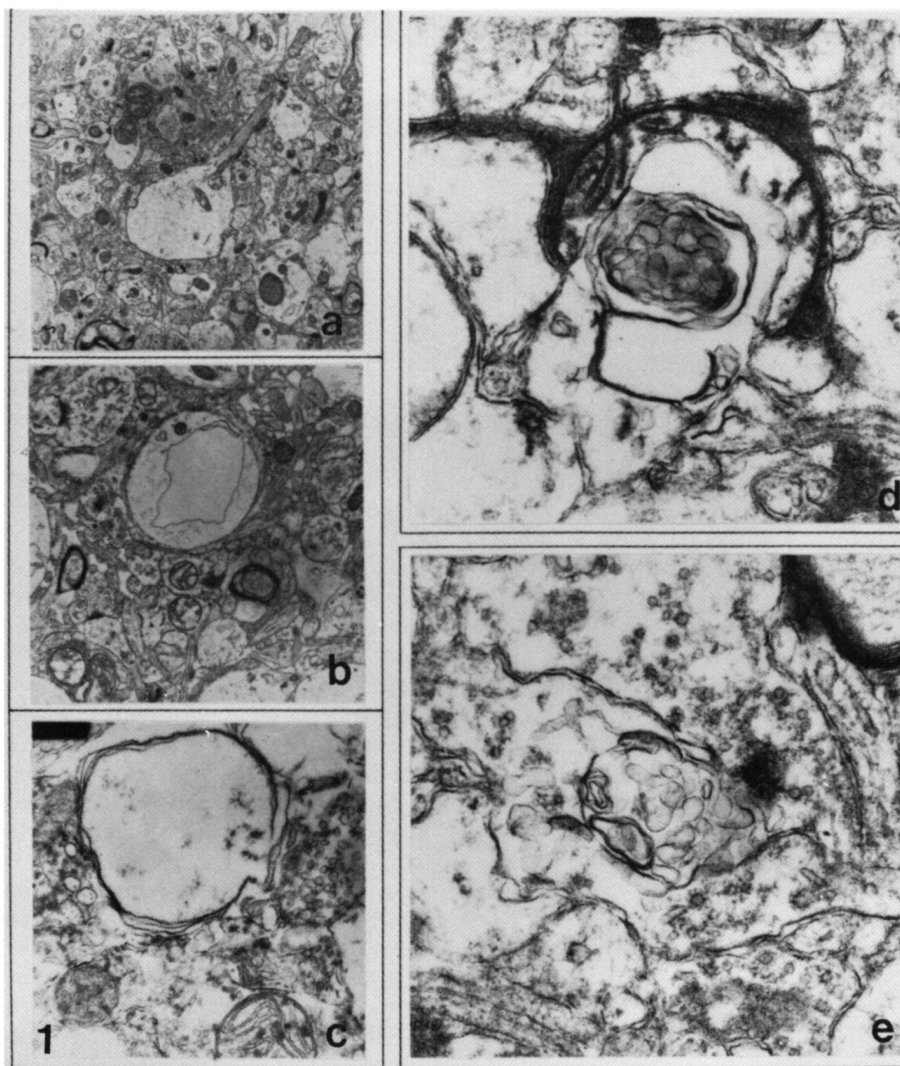


Figure 1 — Electron-micrograph of frontal biopsy of probanda. Distended neurites exhibit marked spongiform vacuolation, often focally (1a). Fragments of proliferating membranous material are noted (1b, c), occasionally in multivesicular clusters (1d, e). Uranyl acetate, Pb citrate, x 4200 and x 28,000.

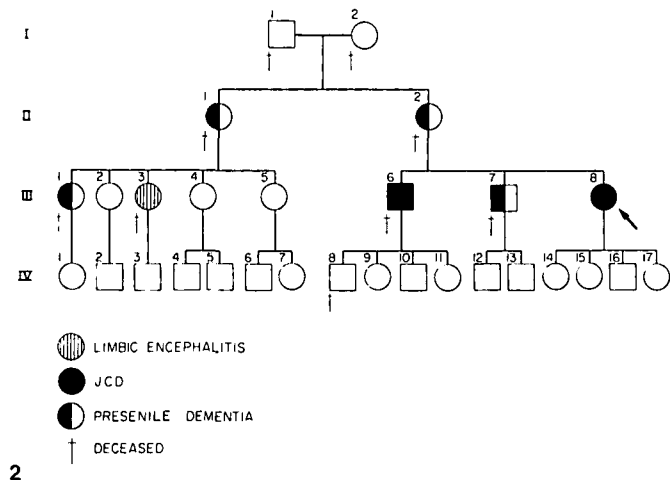


Figure 2 — Pedigree of familial presenile dementia, clinically of the Alzheimer type, afflicting 7 members of 2 generations. Proband (arrow, III-8) and one brother (III-6) show subacute spongiform lesions of C-J disease at autopsy.

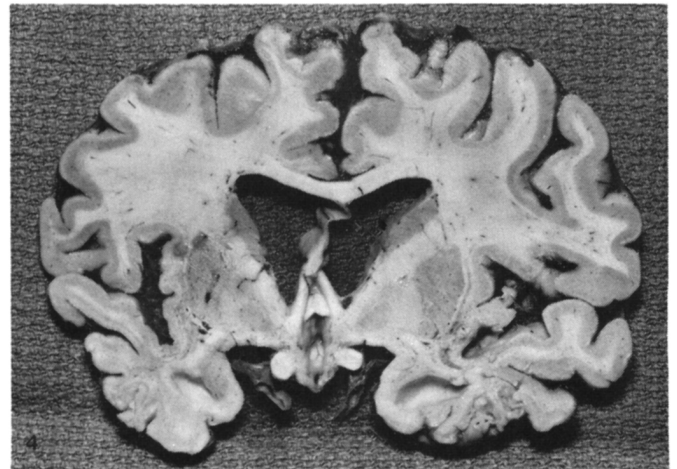


Figure 4 — Coronal section of proband's brain, showing hydrocephalus and prominent cortical atrophy worse in mesial temporal lobes.

bedridden, requiring feeding, and had great difficulty swallowing. Electroencephalogram was normal.

A sister of this maternal cousin (III-3) developed an insidious loss of higher cortical functions at 46 years of age,

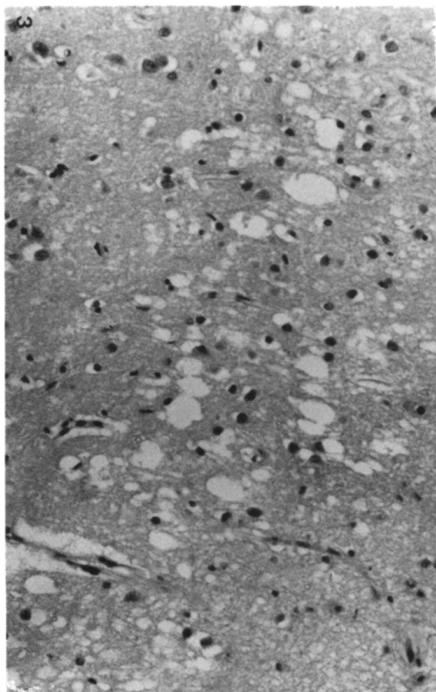


Figure 3 — Light micrograph of spongiform state in middle cortical laminae of brain of proband's brother (III-6). This type of vacuolation is consistent with C-J disease. H and E, x 50.

with loss of motivation. Pneumoencephalography revealed frontal atrophy. EEG and skull films were normal. She expired at age 56 with a clinical diagnosis of presenile Alzheimer's disease. Paraffin sections from a state mental hospital showed severe neuronal loss, intense astrogliosis, and extremely atrophic temporal gyri surrounding markedly dilated lateral ventricles. Sub-ependymal veins were surrounded by thick cuffs of lymphocytes. The neuronal drop-out and gliosis were most severe in the anterior portions of temporal lobe. Relatively well-preserved posterior hippocampus showed no senile plaques, neurofibrillary tangles, granulovacuoles, Hirano bodies, or Pick inclusions. Other samples of cerebral cortex, including pre-central motor strip and orbital frontal lobe, showed no lesions. Tiny perivascular lymphocytic cuffs were also noted in thalamus and one cerebral peduncle.

Changes were considered typical of an end-stage encephalitis, which in its earlier phase had apparently had its major effect on the temporal lobes, especially anterior portions. The likeliest etiological agent for this so-called "limbic encephalitis" was a Herpes virus, although no classical microglial "shrubs" were seen, nor were there any inclusions in material available. (An identical impression — end-stage of a necrotizing viral encephalitis of Her-

pes type — was held by Dr. E.P. Richardson, Jr., who also reviewed these slides.)

One brother of the proposita (III-7), a successful lawyer, developed a gradually dementing illness at age 43. Earlier he was hospitalized for frequent severe depressions, but later lost higher cognitive functions, requiring institutionalization within two years of onset. Compulsive eating was a major problem. Detailed neurological assessments showed no other abnormality. Pneumo-encephalography showed moderate frontal atrophy and skull x-rays and electro-encephalography were normal. He expired five years later at age 48.

Our proband's other brother (III-6) first developed memory loss, inappropriate behavior and speech and recurring depression at age 38. Physical examination showed no other findings. Pneumo-encephalography showed severe atrophy, most prominent in the left temporal horn. Skull x-rays, isotope brain scan, and EEG were normal. From age 45 he required institutional care. Compulsive eating and craving for sweets were transiently noted, but with progressive dementia he became apathetic. Terminally, he developed difficulty chewing and swallowing and died of aspiration at 48 years of age. Paraffin sections from some brain material were still available from a regional hospital. Parietal

cortex showed severe neuronal loss and astrogliosis, with lesser degrees of microglial hyperplasia, as well as a moderate spongiform change throughout the middle cortical laminae (Fig. 3). Temporal lobe sections showed an even more severe degree of neuronal drop-out, astrocytic and microglial hyperplasia of cortex, and white matter gliosis. A milder degree of spongiform degeneration was seen in the temporal cortex. One small intracortical vein showed a perivascular lymphocytic cuff. Laminar destruction of cortex was especially prominent in layers II, III and VI. Similar features were seen in cingulate frontal cortex, and another tiny lymphocytic cuff around an arteriole in corpus callosum. Despite Bodian stains, no plaques or tangles could be shown in any of the 31 sections available, nor were there any granulovacuolar changes or Hirano or Pick bodies. Samples of brainstem and cervical cord showed demyelination and gliosis of cortico-spinal pathways in basis pontis, more prominently in medullary pyramids and especially in lateral and ventral corticospinal tracts of cord. Both anterior horns showed mild neuronal loss and gliosis, with a small microglial nodule in one lateral column. Cerebellum was not remarkable. The striking degree of spongiform vacuolation affecting parietal and temporal cortex was highly suggestive of Creutzfeldt-Jakob disease and the pyramidal tract

degeneration was not dissimilar to that described in 3 family members with C-J disease having "spastic pseudosclerosis" (cortico-pallido-spinal degeneration) by Davison and Rabiner (1940). Unfortunately, wet tissue was no longer available from this CNS and electron-microscopy on paraffin material was inadequate technically. Nevertheless, these autopsy findings were considered to represent a spongiform encephalopathy.

AUTOPSY FINDINGS

The probanda (III-8 of Fig. 2) expired of respiratory complications in March, 1979. Only the brain and upper cervical cord were available. The body showed extreme emaciation. The fresh brain weighed 890 grams. There was severe generalized convolutional atrophy diffusely, most prominent in frontal and temporal lobes and least obvious in occipital lobes. Leptomeninges were not remarkable, except for a small cortical scar in the right second frontal gyrus at the site of previous biopsy. The arteries of the Circle of Willis showed no atheroma. The severe cortical atrophy in both temporal lobes appeared somewhat worse on the left.

Serial coronal sections of the formalin-fixed brain showed marked dilatation of the symmetrical ventricular system, with severe blunting particularly of the frontal angles, as well as severe enlargement of the third ventricle. This

was accompanied by marked thinning of the cortical ribbon in all lobes, but especially (a) in the frontal region bilaterally and (b) in both temporal lobes (Fig. 4). Only a tiny ribbon of shrunken cortex remained in the hippocampi, especially their anterior portions at the level of the mammillary bodies, where the mantle was reduced to 1 mm. thickness. An unusual, somewhat friable gross appearance extended laterally to involve the inferior temporal gyri as well, although relatively less prominently in the middle and superior temporal gyri (Fig. 4). The hippocampal atrophy appeared worse in the pes hippocampi rather than in their mid- and posterior portions. Thalamic and hypothalamic areas were also small, in keeping with the enlarged third ventricle. The other basal ganglia were not remarkable, except for mild atrophy of the head of both caudate nuclei whose ventricular borders were slightly concave to straight, rather than convex, in their anterior portions.

Transverse sections of brainstem and cerebellum showed adequate pigmentation of substantia nigrae and loci cerulei grossly but reduction in cross-sectional areas of all three portions of the bulb, with shrunken yellow discoloration of the medial half of each cerebral peduncle. The Sylvian aqueduct and fourth ventricle, however, were normal. The cerebellar hemispheres were small but not

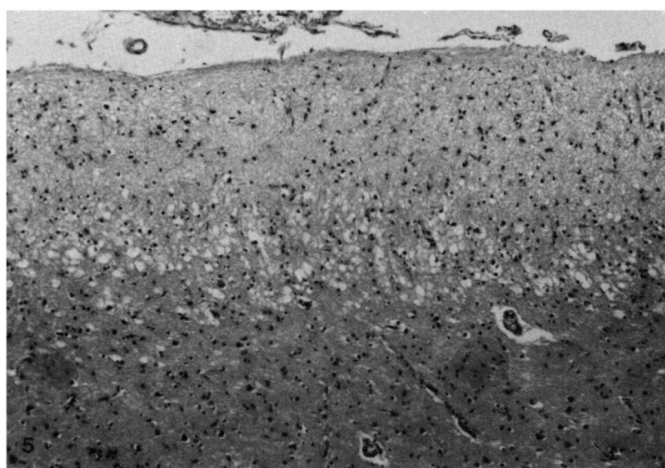


Figure 5 — Light micrograph of spongy degeneration in second cortical layer of inferior temporal gyrus of proband's brain (autopsy). H and E, x 25.

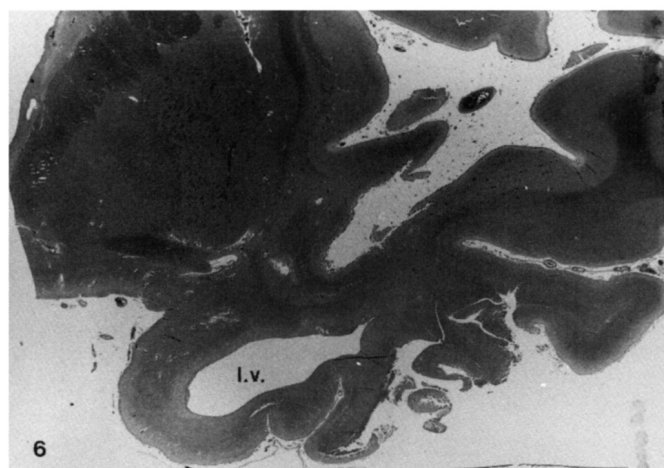


Figure 6 — Light micrograph of severely atrophic cerebral mantle of pes hippocampus surrounding dilated temporal horn of lateral ventricle (l.v.). H and E, orig. x 20.

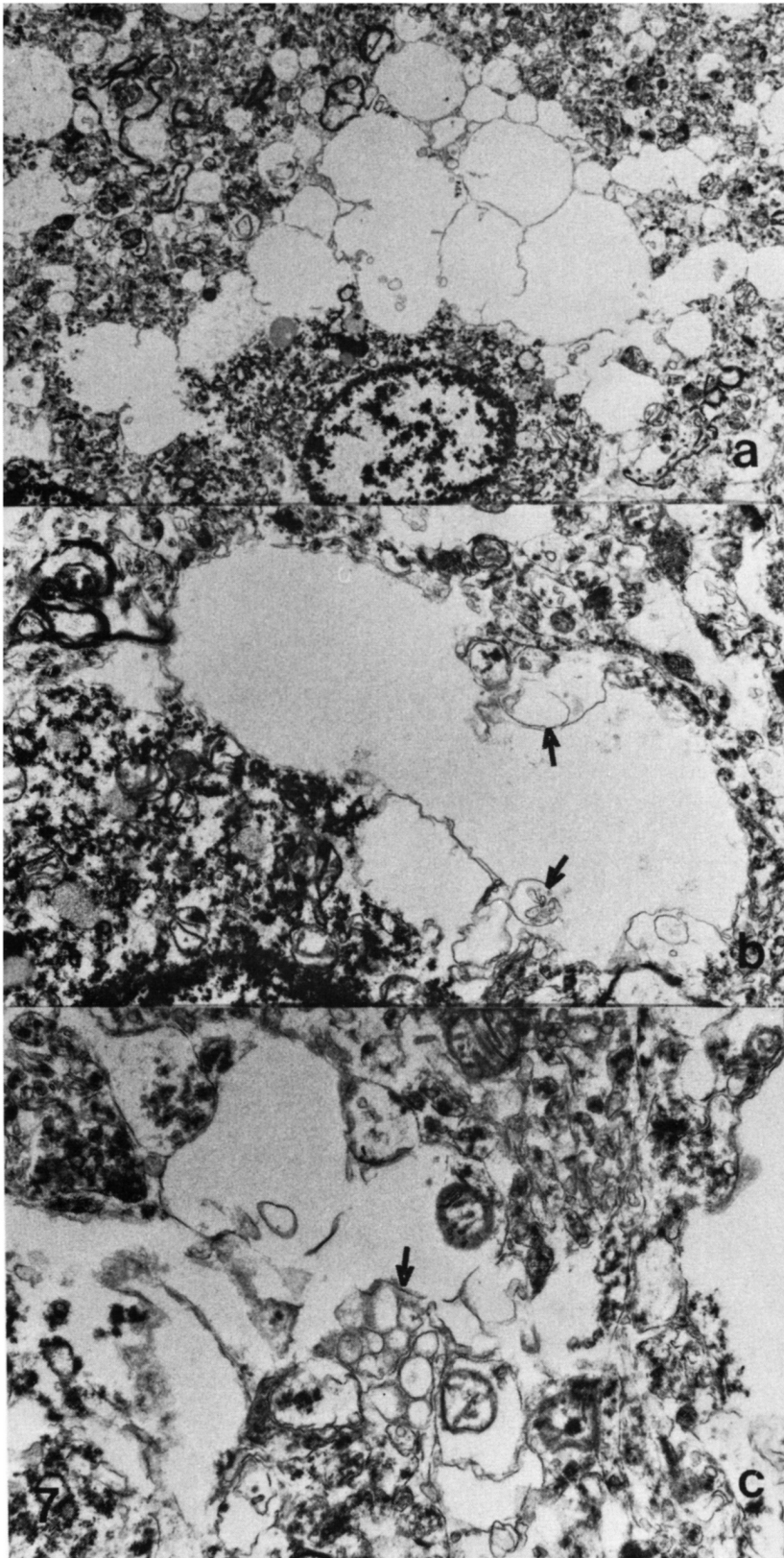


Figure 7 — Electron-micrographs of temporal cortex from proband's brain at autopsy. Spongiform vacuoles within neuronal cytoplasm (a), sometimes containing membrane fragments (b), and occasionally multivesicle structures (c). Uranyl acetate-Pb citrate, x 1800 and x 3000.

otherwise remarkable.

(a) Light Microscopy

Paraffin sections were stained with hematoxylin-eosin/Luxol fast blue, periodic acid-Schiff, phosphotungstic acid-hematoxylin, Holzer, cresyl violet, Kluver-Barrera, and Bodian silver techniques.

Despite extensive searching and serial sectioning of the hippocampi, not a single senile (neuritic) plaque, neurofibrillary tangle of Alzheimer, Hirano body, or nerve cell with granulo vacuolar degeneration could be found. Diagnosis of Alzheimer's disease was therefore clearly ruled out. Similarly, no argentophilic Pick inclusion bodies or swollen nerve cells with cytoplasmic "ballooning" were ever found, so that Pick's disease was also eliminated. The striking microscopic features were a spongiform vacuolation of the superficial cerebral cortical laminae; a patchy neuronal loss and gliosis; and evidence of motor neuron system degeneration.

The spongiform degeneration of the neuropil chiefly affected the second neocortical layer, severely in the inferior temporal and moderately in the middle and superior temporal gyri (Fig. 5). This extensive spongiform state, the vacuoles of which occasionally indented adjacent neuronal cytoplasm, was also present to a severe degree in the middle frontal gyri and in the prefrontal cortex. A milder degree of the same vacuolation was present in the pre-central motor strip, in Rose's H₂ zone of each hippocampus, and in the head of the caudate nuclei. The neuronal depletion was extremely severe in all layers of the temporal and frontal cortex, increasing in degree from middle through inferior temporal through hippocampal gyri. Nerve cell loss and gliosis were moderate in the parietal cortex and mild in occipital cortex and head of caudate nuclei. There were severe focal neuronal dropout and astrogliosis in the H₁ zone and subiculum of the hippocampal formations; and a moderate neuronal loss and gliosis in both substantiae nigrae. In many neocortical samples the old astrogliosis was not limited to the regions of the spongiform change. In some foci the neuronal depletion and glial scarring had reduced the cortical

mantle to a thickness less than 1 mm., such as in the pes hippocampus surrounding the severely dilated temporal horn (Fig. 6).

Leptomeninges and ventricular ependyma in all samples were not remarkable, and all vessels seen were normal.

The depletion of the Betz cell population from the motor cortex was accompanied by marked demyelination and gliosis of the corticospinal portions of the cerebral peduncles, the longitudinal fibers of the basis pontis, and both medullary pyramids. The same loss of myelin and astrogliosis were noted in both lateral and both ventral corticospinal tracts of the cervical cord.

A very occasional neuron showing central chromatolysis could be found in frontal and temporal cortex, mammillary nucleus, subthalamic nucleus, periaqueductal gray, hypoglossal nucleus, and one anterior horn of cervical cord. A rare microglial nodule could be found in the left cerebellar dentate; and an occasional arteriole with perivascular lymphocytic cuffing was noted in one cerebral peduncle and in the spinal cord white matter.

A few large neurons in the temporal cortex contained unusual "inclusions" in their cytoplasm, sickle-to-cigar-shaped, homogeneous, basophilic structures filling most of the cytoplasm. These were not argentophilic and were PAS-negative. Their nature is unclear. No Lewy bodies were found in any residual neurons of the substantia nigrae. Cerebellar cortex and white matter were not remarkable, with no spongy changes in the molecular layer.

(b) Electron Microscopy

Neocortical samples were fixed in glutaraldehyde and processed in Spurr, cut and stained with uranyl acetate and lead citrate, and examined with a Zeiss #9 electron-microscope. The spongiform lesions proved to be many large vacuoles, single membrane bound, located next to and often within neuronal cytoplasm (Fig. 7a). Some of these were clearly within swollen neuritic endings, both pre- and post-synaptic in type. As in the biopsy material, the occasional normal dendrite could be seen ballooning suddenly into such a vacuolated enlargement.

Proliferating bits of membranous fragments were seen in small numbers within the 'lumina' of several such vacuoles (Fig. 7b); a few also contained more tightly packed clusters of small multivesicular bodies having the configuration of a "clump of grapes" (Fig. 7c). All these features are similar to the spongy degeneration documented ultra-structurally in classical cases of Creutzfeldt-Jakob disease. (Kidd, 1967; Bignami and Forno, 1970; Bubis et al., 1972; Gonatas et al., 1977).

DISCUSSION

None of the histological stigmata either of Alzheimer's disease or of Pick's disease was present in this case. On the other hand, the spongiform changes in cortex, associated with significant neuronal loss and fibrillary gliosis, are in keeping with a diagnosis of spongiform encephalopathy, possibly the amyotrophic form of Creutzfeldt-Jakob disease. In the experimental primate model of Creutzfeldt-Jakob dementia, Masters et al. (1976) observed that the gliosis and the neuronal loss occur later in the temporal evolution of the process than the third member of the pathological triad, neuronal vacuolation. The spongiform degeneration in our case is more restricted (to superficial laminae) than in a typical Creutzfeldt-Jakob brain, but Daniel (1972) has observed that the spongy change may be very difficult to see with the light microscope "especially in very advanced cases" of C-J disease. Similarly, Masters and Richardson (1978) have remarked that the greater sponginess of the deeper cortical laminae in some brains is not as obvious in the longer surviving cases. Finally, despite some artifact in both biopsy and autopsy material, the ultrastructural features observed in our *proposita's* cortex also support the impression of a genuine spongiform phenomenon, rather than merely status spongiosus associated with gliotic rarefaction.

The very occasional microglial shrunken and perivascular lymphocytic cuffs in this patient are of more than usual interest in the light of the pathology in two of her autopsied relatives; the post-encephalitic temporal lobe destruction in the maternal

first cousin and the more typical, fulminant spongiform encephalopathy in her deceased brother. A theme of this family genetically predisposed to slow virus encephalopathies emerges from their pedigree.

The diagnosis of spongiform encephalopathy in affected members of the present family can be reconciled with their clinical features, although certain aspects are clearly unusual. Sporadic cases of Creutzfeldt-Jakob disease of such long duration have been described on occasion (Kirschbaum, 1968), but such long duration has not been a special feature in some familial examples of Creutzfeldt-Jakob dementia (May et al., 1968). As well, certain characteristic clinical features (e.g. myoclonus) and electroencephalographic changes are under-represented in this particular family tree. On the other hand, it may not be merely coincidental that the 9 cases of Creutzfeldt-Jakob presenile dementia being reported in one family by Haltia and co-workers (1979) did show a mean duration of disease (21 months; range 11-36) longer than in the sporadic form; and an absence of repetitive high-voltage EEG complexes at any stage of their disease.

Geographic clustering of some cases of Alzheimer's disease and Creutzfeldt-Jakob dementia has heightened speculation that exposure to a common factor may be important (Bubis et al., 1972). Rosenthal et al (1976) described a single large genealogy with increased incidence of neurological illnesses. One member developed Creutzfeldt-Jakob disease, three others suffered from chronic dementia, and fourteen others displayed various motor system abnormalities. This apparently autosomal dominant inheritance pattern suggests that the susceptibility to "degenerative" neurological disease may be a genetic trait, although some form of vertical transmission of an infectious agent must also be considered (Masters et al., 1979).

The ultimate proof of the transmissible nature of the agent in the present proband must await the results of the inoculation experiments in progress. Meanwhile, more neuropathological attention should be paid both to any Alzheimer type of lesion in the brains

of unaffected members of familial Creutzfeldt-Jakob disease, as well as to the more subtle degrees of spongiform lesions being noted with increasing frequency in otherwise classical, sporadic examples of Alzheimer's dementia, particularly the presenile form. (Flament-Durand and Couck, 1979).

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