Creutzfeldt-Jakob disease: further similarities with kuru

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SYNOPSIS A typical case of Creutzfeldt-Jakob disease is described. Two unusual morphological features—namely, 'kuru-like' plaques in the cerebellum and coarsely vacuolated neurones in the striatum—are further similarities between Creutzfeldt-Jakob disease and kuru.

It is now well established that Creutzfeldt-Jakob disease and kuru have a number of neuropathological features in common which are regarded as typical for both diseases. This observation was first made by Klatzo *et al.* (1959) when, in their original neuropathological description of kuru, they likened this condition to Creutzfeldt-Jakob disease. They based their comparison on the widespread neuronal loss and degeneration, and the intense proliferation and hypertrophy of fibrous astrocytes within the grey matter which are both so characteristic of the two diseases. Status spongiosus of the grey matter, another typical pathological change in Creutzfeldt-Jakob disease, was first observed in kuru by Fowler and Robertson (1959) and later confirmed by Neumann *et al.* (1964) who once again drew attention to the similarities between kuru and Creutzfeldt-Jakob disease. Degeneration of the cerebellum, the most striking and constant feature in kuru (Beck *et al.*, 1969), is less frequent in Creutzfeldt-Jakob disease where it is found in only about 50% of all cases (Kirschbaum, 1968). However, when Brownell and Oppenheimer (1965) defined a corticostriatocerebellar variant of Creutzfeldt-Jakob disease as a nosological entity, still another similarity with kuru was established. Lastly, both conditions are experimentally transmissible to primates after a similarly long latent period (Gajdusek *et al.*, 1966; Gibbs *et al.*, 1968; Gajdusek, 1972; Gibbs and Gajdusek, 1972).

The present report describes two further morphological features, both rare in other neuro-

logical conditions, which can be found in Creutzfeldt-Jakob disease as well as in kuru—that is, coarse intracytoplasmic vacuolation within many of the large neurones of the striatum, and Schiff (PAS) positive plaques in the cerebellum.

CASE REPORT

CLINICAL HISTORY In September 1969, A.S., a woman aged 46 years, noticed that her gait was becoming a little unsteady. Before this time she had enjoyed excellent health and had been well-known for her organizing ability both in business and social spheres. By December 1969 her activities were becoming restricted because of unsteadiness and lack of confidence. By July 1970 her mental confusion was becoming much worse, and she was referred to a consultant psychiatrist.

When admitted to hospital in September 1970, she had severe cerebellar ataxia, and an established organic dementia with disorientation in time and a severe memory disturbance, especially for recent events. The electroencephalogram showed a generalized abnormality with evidence of a structural lesion in the left frontotemporal area. Bilateral carotid angiograms were normal. A pneumoventriculogram showed slight enlargement of the body of the left lateral ventricle. A Tc. 99m scan of the brain was within normal limits.

A provisional diagnosis of cerebellar atrophy was made at this time—possibly subacute cerebellar degeneration due to a latent carcinoma. Further investigations failed to reveal any primary tumour.

The patient's clinical deterioration became more rapid, and by November 1970 she was incontinent.

FIG. 1. *Status spongiosus of the cingulate cortex. Note also the reduction in the number of nerve cells. Haematoxylin and eosin, $\times 190$.*

FIG. 2. *Putamen. Multiple intracytoplasmic vacuoles within a large neurone. Note the eccentric nucleus with large, well-preserved nucleolus. Cresyl violet $\times 770$.*

Early in December she began to show signs of a left upper motor neurone lesion. In late December a pneumoencephalogram showed appearances suggestive of cerebellar as well as cerebral atrophy. The patient died on 13 January 1971 as a result of a massive pulmonary embolism, 16 months after the onset of neurological symptoms.

NECROPSY FINDINGS The only significant abnormality outside the central nervous system was massive pulmonary embolism.

NEUROPATHOLOGY The brain was suspended in 10% formol saline for three weeks before dissection. Large bilateral blocks from the frontal, parietal,

FIG. 3. *Putamen. Intense proliferation and hypertrophy of fibrous astrocytes within grey matter. Note the absence of astrocytes from a small myelinated striopallidal fascicle. Cajal gold sublimate impregnation, $\times 300$.*

FIG. 4. *Thalamus.* Fibrillary gliosis is particularly dense within the medial and dorsal portions which contain the association nuclei dorsalis medialis and lateralis posterior. The sensory relay nuclei, situated within the ventrolateral portions are considerably less affected. (The lateral edge of the thalamus has been marked by a dotted line.) Holzer, $\times 1.2$.

occipital, and temporal lobes (three levels, including the basal ganglia), cerebellum, and brain-stem were embedded in celloidin, and some other representa-

tive blocks in paraffin wax. Frozen sections were prepared from cerebral cortex, striatum and cerebellum. A variety of routine and special staining methods, including the periodic-acid Schiff reaction (PAS), with and without pretreatment with diastase, and some impregnation techniques, was applied.

For the reconstruction of plaques, 20 consecutive serial sections, $7\ \mu$ thick, were cut from the cerebellar cortex and stained with PAS.

MACROSCOPIC FINDINGS The brain (fixed weight 1,340 g) was of normal external appearance. In 1 cm coronal slices of the cerebral hemispheres there was slight enlargement of the ventricles, and each thalamus was slightly smaller and firmer than normal. No other macroscopic abnormalities were seen in the cerebral hemispheres. The cerebellum and brain-stem were normal on section. The spinal cord was not available for examination.

MICROSCOPIC FINDINGS *Cerebral hemispheres* In the cortex, abnormalities were most conspicuous on the medial aspects of the hemispheres, particularly in the occipital lobes and in the cingulate and parahippocampal gyri where there was marked status spongiosus (Fig. 1) and a moderate proliferation of fibrous astrocytes: there was, however, no microglial reaction. Swollen, chromatolytic neurones were not found, but several examples of neuronophagia were present at the corticomedullary junction. There was a marked fall-out of Betz cells. The

MOLECULAR LAYER

FIG. 5. *Projection drawing of plaques from 20 consecutive $7\ \mu$ thick serial sections through the cerebellum stained by the periodic acid Schiff reaction. The numerals by the side of each plaque denote the number of sections through which the same plaque could be followed. Note not only the different size of individual plaques but also that some of them form an intricately branching pattern. PC=Purkinje cell. $\times 230$.*

FIG. 6. *Cerebellum. Plaque at the junction of the granular and Purkinje cell layers. Note the dense central core surrounded by a halo of delicate, radially arranged fibrils. Periodic acid Schiff, $\times 480$.*

cerebral white matter showed a slight increase of glial nuclei but was otherwise unremarkable.

In each striatum there was a considerable loss of large and small neurones. Coarse intracytoplasmic vacuolation was conspicuous in many of the residual large neurones (Fig. 2). There was intense proliferation of fibrous astrocytes (Fig. 3) and of microglial cells, many of which contained fat stainable with oil red O. These reactive changes were confined to grey matter, and did not extend into the myelinated bundles of the internal capsule or the striopallidal fascicles (Fig. 3). There was a mild status spongiosus in the dorsal part of each putamen.

In each thalamus there was severe neuronal loss, intense glial proliferation, and dense fibrous gliosis most marked within the association nuclei (Fig. 4). The relay nuclei, particularly the sensory nuclei and the lateral geniculate bodies, were better preserved.

Other abnormalities were severe neuronal loss and gliosis in the mamillary bodies, gliosis in the anterior columns of the fornix and moderate gliosis in globus pallidus and nucleus subthalamicus on either side.

CEREBELLUM The most conspicuous abnormality in the cerebellum was the presence of numerous plaques:

the great majority of these lay within the granule cell layer of the cerebellar cortex, but they were also seen in the molecular and Purkinje cell layers and in the subcortical white matter. In serial sections the plaques were found to vary greatly in size and shape. The majority lay singly and were spherical with an average diameter of about $35\ \mu$. Sometimes, however, they were grouped in small clusters which in serial sections were shown to form an intricately branching pattern (Fig. 5). Each plaque was composed of a solid, homogeneous core surrounded by a halo of delicate radially arranged fibrils (Fig. 6). They were strongly PAS positive, even after pre-treatment with diastase, moderately argentophilic, and slightly metachromatic with basic aniline dyes. They were also stained selectively with Congo red, when they were birefringent in polarized light (Fig. 7).

The granule cells were preserved, but there was a mild patchy loss of Purkinje cells. The number of axonal torpedoes was greater than one would normally expect to find in a patient of this age. There was slight hypertrophy of the Bergmann glia and a mild increase of glial nuclei in the white matter. Each dentate nucleus was severely degenerated, showing an intense cellular and fibrous gliosis throughout

FIG. 7. *Cerebellum. Two plaques at the junction of the granular and Purkinje cell layers. All plaques appear birefringent under polarized light after staining with Congo red. $\times 770$.*

FIG. 8. *Cerebellum: dentate nucleus. Note large numbers of degenerated (swollen and argentophilic) boutons terminaux (arrows) which outline the remnants of a degenerated nerve cell. Gros-Bielschowsky, $\times 770$.*

Its neurones were filled to capacity with lipochrome and the grey band of the nucleus contained innumerable degenerating boutons terminaux (Fig. 8).

BRAIN-STEM In each substantia nigra there was some neuronal loss associated with 'free' pigment and gliosis. Elsewhere there was no more than a mild diffuse fibrillary gliosis which was accentuated in both inferior olivary nuclei.

DISCUSSION

The most generally accepted neuropathological abnormalities common to Creutzfeldt-Jakob disease and kuru, both of which appear to be primary degenerations of the grey matter that can be transmitted to experimental animals, are widespread degeneration of neurones associated with status spongiosus and a proliferation of fibrous astrocytes; furthermore there is no primary white matter lesion in either disease nor is

there an inflammatory response. The distribution of the basic abnormalities is relatively constant in kuru—that is, the cortex of the limbic system, the striatum, the medial thalamus, the cerebellum, and the brain-stem—but varies greatly from case to case in Creutzfeldt-Jakob disease. This is well seen in the various types described—namely, the cortical, corticostriatal, corticospinal, and corticostriatospinal variants (Siedler and Malamud, 1963; see also Daniel, 1972) to which the corticostriatocerebellar form defined by Brownell and Oppenheimer (1965) should be added.

Two further features characteristic of kuru—namely, plaques in the cerebellum, and coarse intracytoplasmic vacuolation within many of the large neurones of the striatum—were found in the present case which, in other respects, showed all the conventional neuropathological features of Creutzfeldt-Jakob disease. The plaques were numerous, and identical in every respect with those found in kuru. They were, however, restricted to the cerebellum, whereas in kuru they are sometimes more widely distributed throughout the brain. They have, to the best of our knowledge, been reported only once previously in a case of Creutzfeldt-Jakob disease (Chou and Martin, 1971). The interesting observation revealed by consecutive serial sections that some of the plaques are not spherical but form intricate branching structures, may in time reflect upon their morphogenesis. Regarding the occurrence of vacuolated neurones within the striatum, these were originally described and illustrated by Jakob (1923) and subsequently by other investigators of the corticostriatal variant of Creutzfeldt-Jakob disease. However, as far as we can ascertain, attention has not hitherto been drawn to their being another similarity between kuru and Creutzfeldt-Jakob disease.

It would appear, therefore, that every one of the characteristic neuropathological features found in almost every case of kuru may also occur in Creutzfeldt-Jakob disease, although some of these features such as plaques in the cerebellum and coarsely vacuolated neurones in the striatum are clearly rare in the latter disease. In addition, kuru and Creutzfeldt-Jakob disease are the only two naturally occurring subacute degenerative neurological diseases of man that can consistently be transmitted to experimental animals.

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