Spongy degeneration of grey matter in 3 children

Neuropathological report

IVAN JANOTA

From the Department of Neuropathology, Institute of Psychiatry, De Crespigny Park, London

Janota, I. (1974). *Archives of Disease in Childhood*, 49, 571. **Spongy degeneration of grey matter in 3 children: neuropathological report.** Spongy degeneration of the cerebral grey matter is reported in 3 unrelated boys dying at the ages of 15 and 16 months and 3 years. Some of the neuropathological changes in the cases presented here and in other similar cases are like those in Creutzfeldt-Jakob disease and in kuru, conditions which have recently been transmitted to monkeys. The aetiology of spongy degeneration in children is not known, and it would be worth while to find out whether the disease is transmissible.

In some infants and children progressive neurological and mental deterioration may be associated with cerebral atrophy and spongy degeneration of the grey matter. The condition has occurred in isolated cases and in sibs. Progressive disease usually becomes apparent early in infancy and epileptic seizures occur in some cases; less frequently the onset is later, after apparently normal early development, and then seizures may be the predominant clinical feature. The outcome is always fatal. In this paper spongy degeneration of the grey matter in 3 unrelated boys, dying at 15 and 16 months and at 3 years, is reported.

Case reports

Case 1. A first child born on 9 January 1962 at term after normal pregnancy. There was no family history of mental retardation or epilepsy, and a sister born later was normal. At 9 months he was unable to lift his head or to sit unaided. He was lethargic, his eyes did not follow light, and the muscle tone in the left leg was increased. CSF contained white cells (mostly lymphocytes) 97/mm³, and protein 25 mg/100 ml. Extensive laboratory investigations showed no abnormality. A month later he began to have frequent brief seizures involving the left side of the face and the limbs. EEG showed a gross asymmetry between the two hemispheres with a lack of normal rhythms on the right. He became progressively more lethargic and developed frequent chest infections. He remained flaccid and hardly rousable. The pupils were equal and responded to light. Tendon jerks were absent. Fibrillation of the tongue was observed. He died at the age of 16 months.

The brain weighed 688 g (normal 971 g) (Fig. 1a). The cerebral cortex looked granular (Fig. 2). The corpus callosum was thin and the lateral ventricles were dilated. The right Ammon's horn was shrunken and

FIG. 1.—(a) Case 1. Loss of white matter and dilated lateral ventricles. The brain is small compared to that of a normal 16-month-old shown in (c). (b) Case 2. A shrunken brain with dilated ventricles. (a, b, c are coronal slices, reduced to about one-quarter the original size.)

Received 13 December 1973.

FIG. 2.—Case 1. Fragmentation of the cerebral cortex. ($\times 2.5$.)

sclerotic, and the thalamus was smaller than normal. The cerebellum was atrophied with hard white folia.

Case 2. Born on 16 February 1971 at term. There was no family history of any disease and a 5-year-old brother and 3-year-old sister were normal. He supported his head at the age of 3½ weeks and he followed objects with his eyes a week later. At 5 weeks his limbs began to twitch, and seizures continued until he died. He did not respond to visual stimuli or to sudden sounds. There were no localizing neurological signs. CSF contained 150 mg protein/100 ml and 46 white cells/mm³ (75% lymphocytes). Subdural tap and air encephalography showed no abnormality. EEG showed a severe generalized abnormality with prolonged paroxysmal features. Extensive laboratory investigations showed no abnormality. At the age of 3 months he was flabby, inert, not reacting to painful stimuli. His pupils did not react to light. Visually evoked responses from both retinae and the occipital cortex were of latency and form usual for his age. There was nystagmus and intermittent external strabismus. The limbs were hypertonic, tendon jerks were present, plantar responses were extensor, and abdominal reflexes were absent. At the age of 6 months he had long twitching attacks or he was just lethargic, probably unable to hear anything. He had repeated chest infections and he died of inhalation pneumonia at the age of 15 months.

The small brain weighed 493 g (normal 971 g). It was soft with mild opacity of leptomeninges. The sulci were widened, but of normal pattern. The cortex was granular and, particularly in the frontal and temporal lobes, it fragmented. The white matter was firm pale greyish brown (Fig. 1b). The corpus callosum was thin and the ventricles were dilated. The Ammon's horns were normal. In the brainstem there was no obvious abnormality, apart from the pyramids which were grey. The cerebellar folia were shrunken and the deep cerebellar white matter was greyish.

Case 3. Born on 25 July 1969 of term normal delivery after a normal pregnancy. At the age of 4 months he had osteomyelitis of the right index finger. At the age of 11 months he was alert and active. At the age of 2 years 11 months he had had two febrile convulsions, possibly associated with otitis media, followed by status epilepticus. He responded to painful stimuli only. His eyes deviated to the right, tone on the right side was increased, and both plantar responses were extensor. CSF contained 53 mg protein/100 ml and no cells. After treatment and a period on a respirator his condition improved. Skull x-rays, air encephalograms, and carotid angiograms were normal. 3 weeks later he had a right-sided seizure followed by status epilepticus with respiratory arrest, and he developed a right hemiplegia. CSF contained 104 mg protein/100 ml and 4 lymphocytes/mm³. EEGs at first showed the features of status epilepticus and no evidence of a localized lesion, but 3 months later they suggested a widespread lesion in the left hemisphere. He was blind and hypertonic with ataxia and athetotic movements. At the age of 3 years 2 months the seizures became frequent and difficult to control. He remained unresponsive, blind, and flaccid, with a right hemiparesis. He finally developed bronchopneumonia and died at the age of 3 years 5 months. Extensive laboratory investigations in life were negative.

At necropsy the body was 91 cm long (normal average 100 cm). General examination showed congestion and patchy consolidation of the lungs, and acute congestion of the liver. Both middle ears were normal.

The brain weighed 1025 g (normal 1179 g). There was mild atrophy of convolutions, but no abnormality of the pattern of the gyri. The basal leptomeninges were slightly thickened. The optic nerves looked normal. The cortical ribbon was a little narrowed. The white matter was reduced in amount and firm. The ventricles were dilated. Both Ammon's horns were shrunken with a loss of normal pattern. The cerebellar folia were atrophied and the white matter was abnormally firm. In the brainstem the inferior olives were firm and white and the pyramids were greyish and small. The spinal cord showed no obvious abnormality.

Methods

Sections of brain in all cases, spinal cord and posterior root ganglia in Cases 1 and 3, and viscera in Case 3 were examined. The material was embedded in paraffin wax, and in Case 1 also in celloidin, and frozen sections were prepared. A variety of histological staining techniques

was employed. In Cases 2 and 3 small blocks of brain fixed in formol saline were post fixed in glutaraldehyde, stained with uranyl acetate, and embedded in epon for electron microscopy.

Microscopical findings.

Case 1. There was a generalized spongy change (Fig. 3) in the cerebral cortex associated with astrocytic

FIG. 3.—Case 1. Spongy change and a loss of nerve cells in the cerebral cortex. (Haematoxylin and eosin. $\times 152$.)

proliferation and an increase in microglia with neutral fat. Though there was a loss of nerve cells, the architecture of the cortical layers was preserved. The occipital regions were least affected. In the white matter of the cerebral hemispheres there was severe fibrillary gliosis with paucity of myelin and a moderate amount of neutral lipid, but the myelination of some tracts, like the internal capsule, was normal. In the thalamus there was spongy change with much nerve cell loss and gliosis (Fig. 4). In the left hippocampus there was a severe loss of pyramidal cells and gliosis in the Sommer sector, while the right hippocampus was normal. In the cerebellum there was moderate gliosis in the molecular layer, proliferation of Bergmann glia, and loss of granule cells and of Purkinje cells with occasional 'torpedo' swellings of their axons. In the dentate nucleus there was nerve cell loss and gliosis. In the brainstem the corticospinal tracts were poorly myelinated. There was gliosis in the superior cerebellar peduncles, tectum, and inferior olives. In the spinal cord the corticospinal tracts were pale and there was chromatolysis and loss of nerve cells in the anterior horns. The anterior nerve roots were small and there

FIG. 4.—Case 1. Gliosis in the white matter and thalamus. (Holzer stain for fibrillary glia. $\times 2$.)

was a denervation atrophy of the skeletal muscles, more severe in the distal than in the proximal muscles.

Case 2. The cortical atrophy was more severe than in Case 1, but the changes in the cerebral hemispheres were similar. The cortical spongy change was widespread and it involved also the occipital region. There was a marked astrocytic proliferation (Fig. 5). In the white matter there was a severe fibrillary gliosis with lack of myelin (Fig. 6) and some neutral lipid. The Ammon's horns were preserved. The changes in the cerebellum and the brainstem resembled those in Case 1. The spinal cord, peripheral nerves, and skeletal muscles were not examined.

Case 3. Spongy change with astrocytic proliferation was present in all cortical regions, in the thalamus (Fig. 7), and in the subthalamic and red nuclei. There was a fibrillary gliosis in the white matter of the cerebral hemispheres with some gemistocytic astrocytes. Myelin was deficient but only a moderate amount of neutral lipid was found. In the hippocampus there was a loss of nerve cells in the Sommer sector, fascia dentata, and endfolium. In the cerebellum there was a patchy cortical atrophy with loss of Purkinje cells and granule cells and gliosis in the cerebellar cortex and white matter. There was a fibrillary gliosis, spongy change, nerve cell loss, and gliosis in the dentate nucleus. In the brainstem there was fibrillary gliosis in the superior colliculi and in the inferior olives where there was some loss of nerve cells. The corticospinal tracts and the middle cerebellar peduncles were pale. In the spinal cord the corticospinal tracts were pale and there was gliosis in the

FIG. 5.—Case 2. *Astrocytes in the cerebral cortex.* (Cajal. $\times 320$.)

grey matter. The Gasserian and spinal posterior root ganglia, the spinal nerve roots, peripheral nerves, and muscles were normal.

Electron microscopy in Cases 2 and 3 was of little value since the material was obtained at necropsy. Membrane-bound dilated processes not related to capillaries could rarely be recognized with certainty as glial or neuronal. Some contained membranous clumps. No virus particles or abnormal storage material were found.

FIG. 6.—Case 2. (a) *Fibrillary gliosis* and (b) *lack of myelin in the occipital lobe.* ((a) Holzer. $\times 1$; (b) Luxol fast blue/Nissl. $\times 1$.)

FIG. 7.—Case 3. *Spongy change in the thalamus.* (Haematoxylin and eosin. $\times 128$.)

Discussion

The histological changes in the brains of the 3 children described in this paper are like those seen in Creutzfeldt-Jakob disease (Siedler and Malamud, 1963; Daniel, 1972) and in kuru (Klatzo, Gajdusek, and Zigas, 1959): degeneration mainly of the cortical grey matter with a loss of nerve cell, spongy change, and gliosis. They do not resemble the various conditions where the pathological changes, including the spongy change, are almost confined to the white matter, for example the degeneration of van Bogaert and Bertrand, or Canavan's type of diffuse sclerosis (van Bogaert and Bertrand, 1967). 33 cases of progressive degeneration of grey matter of unknown aetiology similar to those reported here, but some with affected sibs, were reviewed by Jellinger and Seitelberger (1970). They were selected after exclusion of 37 other cases where the aetiology could be determined. The aetiological factors included anoxia and convulsions, liver disease, vascular lesions, and toxic brain oedema. It is particularly difficult, even when a detailed clinical history is

available, to evaluate the contribution of anoxia and convulsions in any individual case. The changes in the grey matter in the cases described here are much more extensive than the lesions that are encountered as a result of anoxia. Anoxia may have contributed to the changes in the hippocampus, brainstem, and cerebellum. Others (Sandbank and Chemke, 1965; Crompton, 1968; Klein and Dichgans, 1969; Hopkins and Turner, 1973) have drawn attention to the similarity between the infantile and adult spongy degeneration of the grey matter. In Creutzfeldt-Jakob disease the youngest reported cases were 20 years old (Siedler and Malamud, 1963). Kuru in New Guinea affects children and adults. These two conditions are of unknown aetiology but have a common feature in that they are transmissible from patients into monkeys (Gajdusek, Gibbs, and Alpers, 1966, 1967; Gajdusek *et al.*, 1968; Gibbs *et al.*, 1968; Roos, Gajdusek, and Gibbs, 1973). It would be worthwhile to find out whether the 'idiopathic' spongy degeneration in children is also transmissible. It was by using brain biopsy material that Creutzfeldt-Jakob disease was first transmitted (Beck *et al.*, 1969) and a biopsy would be preferable to 'fresh' necropsy material for this purpose since it would help to exclude other diseases and to establish the ultrastructural changes.

I thank Professor C. E. Stroud and Drs. H. E. Gamsu and M. Millard for permission to study their cases, and Mr. Alex Campbell for assistance in preparing the illustrations.

REFERENCES

- Beck, E., Daniel, P. M., Matthews, W. B., Stevens, D. L., Alpers, M. P., Asher, D. M., Gajdusek, D. C., and Gibbs, C. J., Jr. (1969). Creutzfeldt-Jakob disease. The neuropathology of a transmission experiment. *Brain*, **92**, 699.
- Crompton, M. R. (1968). Alper's disease. A variant of Creutzfeldt-Jakob disease and subacute spongiform encephalopathy? *Acta Neuropathologica*, **10**, 99.
- Daniel, P. M. (1972). Creutzfeldt-Jakob disease. *Journal of Clinical Pathology*, **25**, Suppl. (Royal College of Pathologists) 6, 97.
- Gajdusek, D. C., Gibbs, C. J., Jr., and Alpers, M. (1966). Experimental transmission of a kuru-like syndrome to chimpanzees. *Nature*, **209**, 794.
- Gajdusek, D. C., Gibbs, C. J., Jr., and Alpers, M. (1967). Transmission and passage of experimental 'kuru' to chimpanzees. *Science*, **155**, 212.
- Gajdusek, D. C., Gibbs, C. J., Asher, D. M., and David, E. (1968). Transmission of experimental kuru to the spider monkey (*Ateles geoffroyi*). *Science*, **162**, 693.
- Gibbs, C. J., Jr., Gajdusek, D. C., Asher, D. M., Alpers, M. P., Beck, E., Daniel, P. M., and Matthews, W. B. (1968). Creutzfeldt-Jakob disease (spongiform encephalopathy): transmission to the chimpanzee. *Science*, **161**, 388.
- Hopkins, I. J., and Turner, B. (1973). Spongy glio-neuronal dystrophy: a degenerative disease of the nervous system. *Journal of Neurology, Neurosurgery and Psychiatry*, **36**, 50.
- Jellinger, K., and Seitelberger, F. (1970). Spongy glio-neuronal dystrophy in infancy and childhood. *Acta Neuropathologica*, **16**, 125.
- Klatzo, I., Gajdusek, D. C., and Zigas, V. (1959). Pathology of kuru. *Laboratory Investigation*, **8**, 799.
- Klein, H., and Dichgans, J. (1969). Familiäre juvenile glioneuronale Dystrophie. *Archiv für Psychiatrie und Nervenkrankheiten*, **212**, 400.
- Roos, R., Gajdusek, D. C., and Gibbs, C. J., Jr. (1973). The clinical characteristics of transmissible Creutzfeldt-Jakob disease. *Brain*, **96**, 1.
- Sandbank, U., and Chemke, J. (1965). A case of infantile Jakob-Creutzfeldt disease. *Acta Neuropathologica*, **4**, 331.
- Siedler, H., and Malamud, N. (1963). Creutzfeldt-Jakob's disease. Clinopathologic report of 15 cases and a review of the literature (with special reference to a related disorder designated as subacute spongiform encephalopathy). *Journal of Neuropathology and Experimental Neurology*, **22**, 381.
- van Bogaert, L., and Bertrand, I. (1967). *Spongy Degeneration of the Brain in Infancy*. North Holland, Amsterdam.

Correspondence to Dr. I. Janota, Department of Neuropathology, Institute of Psychiatry, De Crespigny Park, London SE5 8AF.