Creutzfeldt-Jakob disease

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This label is applied to a group of patients whose neurological and psychiatric symptoms are somewhat varied and whose brains show pathological changes which are basically similar, although their distribution and extent in the nervous system may vary (Siedler and Malamud, 1963).

In the early 1920s A. Jakob (1921, 1923) described five patients aged between 30 and 50 who had presented with somewhat comparable symptoms and in whom the brains showed reasonably similar pathological changes. The patients complained of abnormal sensations in the limbs and tended to become spastic. Jerky movements occurred and mental changes developed which usually led to profound dementia. There were often bulbar signs such as aphonia and dysphagia. In necropsied cases there was degeneration in the brain with loss of numbers of nerve cells, degenerative changes in many of the surviving cells, and an increase in glial cells. These changes were found in the cortex, basal ganglia, and motor nuclei of the brain stem and spinal cord. In the brain stem and spinal cord the changes were comparable with those seen in amyotrophic lateral sclerosis (motor neurone disease). The similarities, both clinical and pathological, between Jakob's cases are great enough to enable one to feel that they are representative of a fairly specific disease process. Spielmeyer suggested that a patient described by Creutzfeldt in 1920 was also suffering from a similar disease. The brain of this girl, aged 20, showed somewhat similar pathological changes and Spielmeyer therefore suggested the name Creutzfeldt-Jakob disease. It is, I think, a pity that this case has been included as an example of the syndrome. Since that time there have been numerous reports; Kirschbaum (1968) collected 150 cases from the literature and there have been several later reports.

We have examined 12 cases of the syndrome. Macroscopically the brain may appear normal (Fig. 1), apart from slight generalized ventricular dilatation, though some cases show a much thinned cortical ribbon with marked loss of white matter, causing considerable ventricular dilatation (Fig. 2). Microscopically all of our cases showed status spongiosus in the grey matter of the cortex (Figs. 3,

Fig. 1 Coronal slice through the cerebral hemispheres of a case of Creutzfeldt-Jakob disease in which the cortical ribbon was not narrowed and the ventricles were not appreciably enlarged.

Fig. 2 Similar slice from a case of Creutzfeldt-Jakob disease in which there was great narrowing of the cortical ribbon, marked widening of the sulci, and considerable ventricular dilatation.

Fig. 3 Severe status spongiosus of the occipital cortex of a case of Creutzfeldt-Jakob disease. H & E, $\times 40$.

Fig. 4. The insular cortex of another case. As well as status spongiosus there is loss of nerve cells. H & E, $\times 190$.

Fig. 5 Occipital cortex of a case of Creutzfeldt-Jakob disease, to show loss of nerve cells. H & E, $\times 190$.

Fig. 6 Insular cortex of case shown in Fig. 5 to illustrate hypertrophy and proliferation of astrocytes. *Cajal gold-sublimate*, $\times 190$.

4). There was variable loss of nerve cells (Fig. 5) and the surviving neurones showed various degenerative changes ranging from ballooning, with eccentricity of the nucleus to shrinkage with darkly staining cytoplasm. Satellitosis and neuronophagia were often seen. There was a proliferation and hypertrophy of astrocytes (Fig. 6), most marked where status spongiosus was severe, and here also there was microglial proliferation. There was an excess of glial nuclei in the white matter of the hemispheres. The grey matter of the basal ganglia and thalamus showed varying degrees of degenerative change of the same nature as those in the cortex. In the brain stem there were usually some abnormalities in the grey matter comprising some of the nuclei. The cerebellum usually showed degenerative changes, especially loss of granule cells and gliosis. In some cases there was degeneration of the pyramidal tracts and anterior horns of the spinal cord. Many cases showed degenerative changes in the hypothalamo-neurohypophysial system.

If the distribution of the lesions is used as a basis

for classification, four major types of the syndrome may be described.

1 Cases Described as the Jakob Type

Clinically mental disturbance, usually ending as severe dementia, is associated with curious painful sensations, spasticity of the limbs, and sometimes muscular atrophy. Thus an early case may present as an example of motor neurone disease, until the onset of mental deterioration points to an even more disturbing diagnosis. The degeneration of nerve cells is most severe in the cortical regions (Fig. 7) adjacent to the central sulcus (though it was present to some extent throughout the cortex) in the corpus striatum, thalamus, motor nuclei of the brain stem and spinal cord.

Fig. 7 Distribution of lesions in cases of the Jakob type.

Jakob described these cases as having spastic pseudosclerosis (a comparison with the spasticity seen in amyotrophic lateral sclerosis or motor neurone disease) and disseminated encephalomyelopathy. About one third of the cases in the literature fall into this group.

2 Cases Described as the Heidenhain Type (Heidenhain, 1928)

Visual disturbances are an early symptom in this variety of the syndrome. Again disturbances of sensation, eg, aching of the limbs, is common, going on to ataxia, disorientation, and dementia. Pathologically the changes in nerve cells, with an excess of glial cells, are most severe in the occipital region of the cortex (Fig. 8), becoming less striking in the parts of the hemisphere lying further forward. There are some changes in the striatum; sometimes in the cerebellar cortex.

Fig. 8 Distribution of lesions in cases of the Heidenhain type.

3 Diffuse Type

This makes up the largest group in the reports. Here again the basic pathological changes are seen as nerve cell degeneration and proliferation of astrocytes, but the changes are found to be spread throughout the grey matter of the brain, diffusely through the cortex (Fig. 9) as well as in the basal ganglia, the thalamus, midbrain, cerebellum, and spinal cord, although the severity of involvement of the latter two sites may be varied. A sub-variety described by Martin (1967) shows very severe involvement of the thalamus.

Fig. 9 Distribution of lesions in the diffuse type of disease. The thalamus is severely affected in some cases (Martin, 1967).

The diffuse cerebral and Heidenhain types of the disease tend to have a short course of six to nine months whereas the Jakob type may continue for from one to two years.

4 The Ataxic Form

In this type, brought to the fore by Brownell and Oppenheimer in 1965, ataxia is the most prominent

clinical feature and pathologically the most severely affected part of the brain is the cerebellum (Fig. 10).

A number of cases do not fall strictly into any one of these four main groups of the syndrome but may show some features of each.

Fig. 10 Distribution of lesions in the ataxic type of disease.

Pathologically a large number of cases show spongy change, ie, the presence of microcystic spaces scattered in the grey matter. The spongy change may be very difficult to see by the light microscope, especially in very advanced cases where the cystic spaces appear to collapse (Beck, Daniel, Matthews, Stevens, Alpers, Asher, Gajdusek, and Gibbs, 1969). It is probable that in a number of the reported cases spongy change has been overlooked. For long it was not clear in what element of the nervous system these microcysts developed. Recent work, however, with the electron microscope has shown that these microcysts develop mainly in the processes of nerve cells (Lampert, Gajdusek, and Gibbs, 1971). Intracytoplasmic and nuclear inclusion bodies have not been found and neurofibrillary changes are not seen in Creutzfeldt-Jakob disease. In general the condition occurs sporadically but familial cases have been reported (see Kirschbaum, 1968).

It is of interest that cases of Creutzfeldt-Jakob disease show none of the stigmata of a viral infection of the nervous system such as small focal areas of neuronal degeneration and round cell cuffing of the vessels. (In very advanced cases an occasional vessel may be lightly cuffed but this may be explained by the extent of the degeneration of nervous tissue which is taking place.) Nor do the pathological changes in Creutzfeldt-Jakob disease resemble in any way those seen in the demyelinating conditions such as multiple sclerosis.

On the whole the symptoms of the disease are explained by the pathological changes found. In those cases which show the picture of motor neurone disease there is loss of many nerve cells in the region of the motor cortex, including the giant Betz cells, as well as demyelination of the pyramidal tracts and

loss of anterior horn cells in the spinal cord. In cases where cerebellar ataxia is seen (and this in a mild form is commonly found and in a severe form is not unusual) there is a lesser or greater degree of degeneration of the cerebellar cortical and dentate neurones. The dementia which develops in all cases may be explained by the loss of nerve cells and disorganization of the cerebral cortex (comments on the dementia in this type of condition may be found in Daniel, 1971). In some cases there is only severe loss of nerve cells in a relatively restricted part of the brain, eg, the occipital involvement in Heidenhain cases which explains the early onset of blindness, but even in these cases there are abnormalities of the nerve cells throughout the whole of the cortex, which one imagines cause the mental disorder which is observed.

The abnormal sensations or pains in the limbs, so commonly complained of in the early stages of the disease, have no obvious pathological concomitant. Is it possible that degenerative changes in the thalamus may cause pain of central origin? Or are the changes which were found in the posterior root ganglia of one case (Hierons and Strich, 1967) the cause of the curious peripheral sensations of which these patients complain?

Creutzfeldt-Jakob disease appeared to be a degenerative condition of the nervous system until material from a case of W. B. Matthews was inoculated into a chimpanzee by Gajdusek and Gibbs. The results of this experiment were interesting (Beck *et al*, 1969).

Rather more than a year after inoculation the animal developed ataxia with intention tremor and also showed signs of visual disturbance. He became increasingly lethargic and somnolent and appeared to become demented and was killed some two months after the onset of symptoms. The grey matter of his brain was found to have extensive spongy change, with loss of nerve cells, glial proliferation and hypertrophy. The cerebellum was also affected. The general appearance was somewhat similar to that seen in the donor brain from the case of Creutzfeldt-Jakob disease. Since that time many animals have been inoculated with material from different Creutzfeldt-Jakob cases and have developed a comparable disease (see Gajdusek in this volume).

It is unfortunate that certain cases of Creutzfeldt-Jakob disease and the other transmissible degenerative diseases of the nervous system have come to be called slow virus infections, for the thoughts of workers in this field are bound to be influenced when such a specific name is used. It seems to me that we are likely to be dealing with a new natural phenomenon which does not fit into any known biological category and that a really open mind is needed in order to open up such an unknown and untitled field.

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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**, 699-716.
- Brownell, B., and Oppenheimer, D. R. (1965). An ataxic form of subacute presenile polioencephalopathy (Creutzfeldt-Jakob disease). *J. Neurol. Neurosurg. Psychiat.*, **28**, 350-361.
- Daniel, P. M. (1971). Transmissible degenerative diseases of the nervous system. *Proc. roy. Soc. Med.*, **64**, 787-794.
- Heidenhain, A. (1928). Klinische und anatomische Untersuchungen über eine eigenartige organische Erkrankung des Zentralnervensystems im Praesenium. *Z. ges. Neurol. Psychiat.*, **118**, 49-114.
- Hierons, R., and Strich, S. J. (1967). Subacute spongiform encephalopathy. *Acta neuropath. (Berl.)*, Suppl. 3, 14-15.
- Jakob, A. (1921). Über eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswerten anatomischen Befunde (Spastische Pseudosklerose-Encephalomyelopathie mit disseminierten Degenerationsherden). *Z. ges. Neurol. Psychiat.*, **64**, 147-228.
- Jakob, A. (1923). *Die extrapyramidalen Erkrankungen*, pp. 215-245. Springer, Berlin.
- Kirschbaum, W. R. (1968). *Jakob-Creutzfeldt Disease*. Elsevier, New York.
- Lampert, P. W., Gajdusek, D. C., and Gibbs, C. J., Jr. (1971). Experimental spongiform encephalopathy (Creutzfeldt-Jakob disease) in chimpanzees: electron microscopic studies. *J. Neuropath. exp. Neurol.*, **30**, 20-32.
- Martin, J. J. (1967). Les lésions de la couche optique dans la maladie de Creutzfeldt-Jakob et les formes apparentées: Étude topographique de treize cas. *Acta neuropath. (Berl.)*, Suppl. 3, 92-103.
- Siedler, H., and Malamud, N. (1963). Creutzfeldt-Jakob's disease. Clinicopathologic report of 15 cases and review of the literature (with special reference to a related disorder designated as subacute spongiform encephalopathy). *J. Neuropath. exp. Neurol.*, **22**, 381-402.