

ON THE WHITE MATTER LESIONS OF THE CREUTZFELDT–JAKOB DISEASE

Can a New Subentity be Recognized in Man?

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SUMMARY

One case of CJD with severe involvement of the white matter is discussed. The patient was admitted after a 3-month clinical course with rapidly increasing mental deterioration, coma vigil-like state, myoclonic twitching of the limbs and of the facial muscles. The EEG showed the typical features of CJD. The first CT scan, performed 3 months after onset, revealed only a mild cortical and subcortical atrophy of the brain. The second CT scan, 12 months later, showed a considerable cortical and subcortical atrophy of the brain. The patient died 18 months after onset. Neuropathological examination showed a severe degeneration in the gray matter, with spongiosis, loss of neurones and hypertrophic glial reaction. The white matter was also involved with severe spongiosis, demyelination and hypertrophic glial proliferation.

The case is discussed in relation to the data in the literature. It is argued that cases of CJD with severe involvement of the white matter should be classified as a new neuropathological subentity of CJD.

Key words: *Creutzfeldt–Jakob disease – Spongiosis – White matter degeneration*

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INTRODUCTION

Degeneration of the white matter has not been hitherto considered as a relevant feature of Creutzfeldt–Jakob disease (CJD) (Kirschbaum 1968; Masters and Richardson 1978). Lesions of the white matter were mainly described in the “necrobiotic” form of CJD (Capon et al. 1967; Dioli et al. 1967; Reggiani et al. 1967) as well as in a few classical cases (Loiseau et al. 1972). However, recent reports of 11 adult and 1 adolescent cases (Takatzu et al. 1978; Tateishi et al. 1979; Park et al. 1980; Mizutani et al. 1981; Monreal et al. 1981) emphasized the occurrence of extensive lesions of the white matter in CJD (Table 1).

Mizutani et al. (1981) defined this pathological picture as “panencephalopathic

TABLE 1

REPORTED CASES OF CJD WITH EXTENSIVE LESIONS OF THE WHITE MATTER

Authors	Age (yr)	Sex	Survival	Clinical features	EEG	Pathology
Reggiani et al. (1967)	68	F	4 months	Disorientation. Choreo-athetoid movements. Hypertonia. Babinski sign, bilaterally. Dementia	Periodic discharges	Atrophy of the brain and cerebellum. Neuronal loss, spongiformity, lipophanerosis in the cortex. Extensive gliosis and myelin damage in the cerebral white matter
Capon et al. (1967)	68	F	13 months	Abnormal behaviour. Hemiplegia. Aphasia. Myoclonic jerks. Dementia. Coma	Diffuse slow waves	Neuronal loss, necrobiosis, spongiformity in the cortex. Demyelination and gliosis in the subcortical white matter with extension to the long tracts
Loiseau et al. (1972)	66	F	6 months	Visual disturbances. Diffuse muscle amyotrophy. Rigidity. Myoclonic jerks. Dementia	Diffuse slow waves. Periodic discharges	Neuronal loss and astrocytic proliferation in the cortex and subcortical structures. Diffuse demyelination in the occipital white matter
Takatzu et al. (1978)	42	M	1 year			Astrocytic proliferation in the cortex. Diffuse loss of axons and demyelination in the white matter. Foamy macrophages
Park et al. (1980)	77	F	1 year	Visual disturbances. Memory impairment. Mutism. Vegetative state lasting 1 year	Repetitive bitemporal sharp and slow waves	Atrophy of the brain. Total loss of neurones and hypertrophic gliosis in the cortex and subcortical structures. Marked loss of axons and of myelin sheaths in the cerebral hemispheres and in the cerebellum

TABLE 1 (continued)

Authors	Age (yr)	Sex	Survival	Clinical features	EEG	Pathology
Mizutani et al. (1981)	44-73	6M/ 2F	5 7 7.5 months 8.5 9 11 2 2.5 years	Psychotic symptoms. Deterioration with neurological and mental disturbances. Myoclonic jerks. Muscular rigidity. Convulsive seizures (cases 6, 7). Dysarthria (cases 1, 2, 4, 5, 6). Pyramidal signs (cases 1, 4, 5). Chorea-athetoid movements (cases 1, 5, 6)	Periodic discharges	Atrophy of the brain and cerebellum. Enlargement of the ventricles. Severe neuronal loss and hypertrophic gliosis in the cortex and subcortical structures. Cavitation and diffuse demyelination of the white matter in the cerebral hemispheres
Monreal et al. (1981)	16	M	28 months	Impairment of memory. Disorientation. Mutism. Vegetative state lasting 8 months	Periodic discharges	Marked atrophy. Spongiform changes associated with neuronal loss and gliosis. Diffuse reduction in cerebral white matter
This report (1983)	57	F	18 months	1st phase (3 months) Mental deterioration. Coma vigil-like state. Decorticate posture. Spasticity. Myoclonic twitchings. CT scan: no atrophy 2nd phase (15 months) Coma vigil-like state. Reduction of the twitching movements. CT scan: diffuse atrophy of the brain with involvement of the white matter	Disorganization of background activity. Paroxystic triphasic sharp waves Progressive disappearance of periodic discharges. Monomorphous activity	Brain atrophy. Softness of white matter. Enlargement of the ventricles. Total loss of neurones, hypertrophic gliosis, spongiosis and necrobiosis in the gray substance. Severe damage of the white matter in the cerebral hemispheres with loss of axons and myelin and extraordinary hypertrophic gliosis. Foamy macrophages

type" of CJD. The case described by Tateishi et al. (1979) has been transmitted to small animals (rodents). However, on the basis of clinical history and pathological picture this case should be classified, in our opinion, as Gerstmann-Sträussler syndrome (Gerstmann et al. 1936; Masters et al. 1981).

The recent reports on white matter involvement and the neuropathological findings in a personal case warrant reconsideration of the white matter lesions in CJD.

Case report*

A 57-year-old female, with a 3-month history of rapidly increasing mental deterioration, was admitted in a coma vigil-like state with decorticate posture. Spasticity of the limbs, brisk tendon reflexes and extension plantar responses were present. Myoclonic twitching of the limbs and of the facial muscles occurred either spontaneously or was elicited as exaggerated startle responses. The EEG showed wide-

* A preliminary report of the clinical history has been recently published (Villa et al. 1982).

spread disorganization of the background activity and paroxysmal recurring of triphasic sharp waves (Fig. 1A).

The CT scan revealed only a mild cortical and subcortical atrophy of the brain (Fig. 2A).

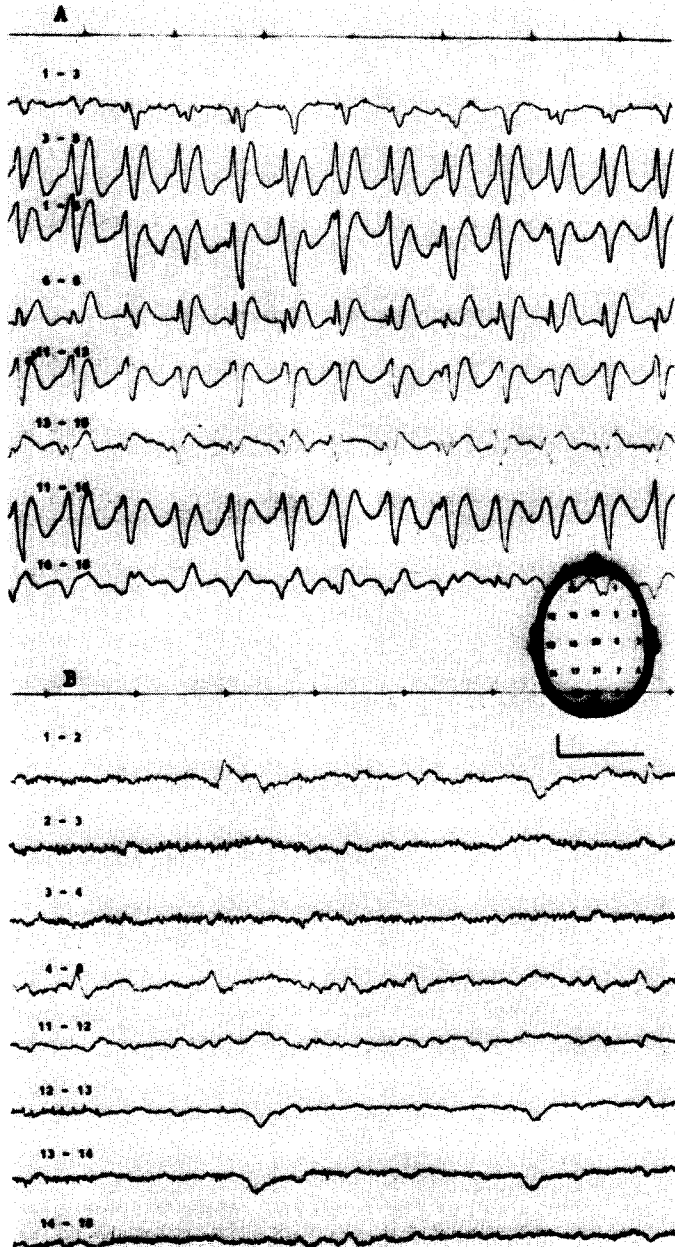


Fig. 1. *A*: The EEG, in the 3rd month of illness, shows widespread disorganization of the background activity and paroxysmal triphasic sharp waves. *B*: 15th month of illness; the EEG shows slow monomorphic activity.

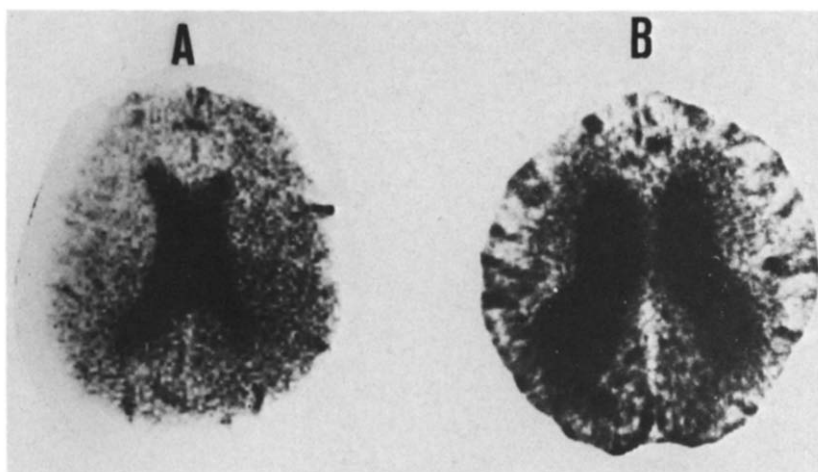


Fig. 2. *A*: CT scan, in the 3rd month of illness: mild cortical and subcortical atrophy of the brain; *B*: CT scan in the 15th month of illness: marked atrophy of the brain involving both cortical and subcortical structures.

Routine haematological examination and serum immunoglobulins were within a normal range, as was the CSF (IgG level of 2.6 mg/100 ml; IgG-albumin ratio of 15%).

Skin tests (PPD, Trichophyton, Candida, SKPD), DMCB (dinitrochlorobenzol) test, and PHA-induced lymphocyte proliferation showed an anergic response. Methisoprinol, 6 g/day as used in subacute sclerosis panencephalitis and herpes virus encephalitis (Buge et al. 1979; Uttenlocher and Mattson 1979) was administered in the following months until death.

The clinical picture remained relatively unmodified; with progression the intensity of twitching movements decreased; the periodic discharges of the EEG disappeared gradually to be replaced by a slow monomorphous activity typical of pre-agonal states (Fig. 1B).

CT scan, performed 12 months after hospitalisation, showed a marked atrophy of the brain involving both cortical and subcortical structures (Fig. 2B). The patient died 3 months later, after 18 months of illness.

NEUROPATHOLOGICAL FINDINGS

Autopsy was performed 24 hours after death. Post mortem examination did not reveal significant changes involving the visceral organs. The brain weighed 800 g and was very soft to touch. On transverse sections the cortex appeared extremely thin and could easily be detached from the underlying white matter. The latter was diffusely thinner and softer than normal. The ventricles were enlarged. The cerebellum and brain stem did not show macroscopical lesions.

Samples of brain tissue, formaldehyde-fixed, were embedded in paraffin, sectioned and stained with hematoxylin and eosin, cresyl violet, Weil stain for myelin, Holzer stain for glial fibers, and silver stain for axons and astrocytes. Frozen sections were stained with Sudan III and PAS.

Except for the molecular layer, the cortex was diffusely affected by a spongiotic and necrobiotic process (Fig. 3). The main lesion was represented by a nearly total loss of neurones and a diffuse proliferation and hypertrophy of glial protoplasmatic

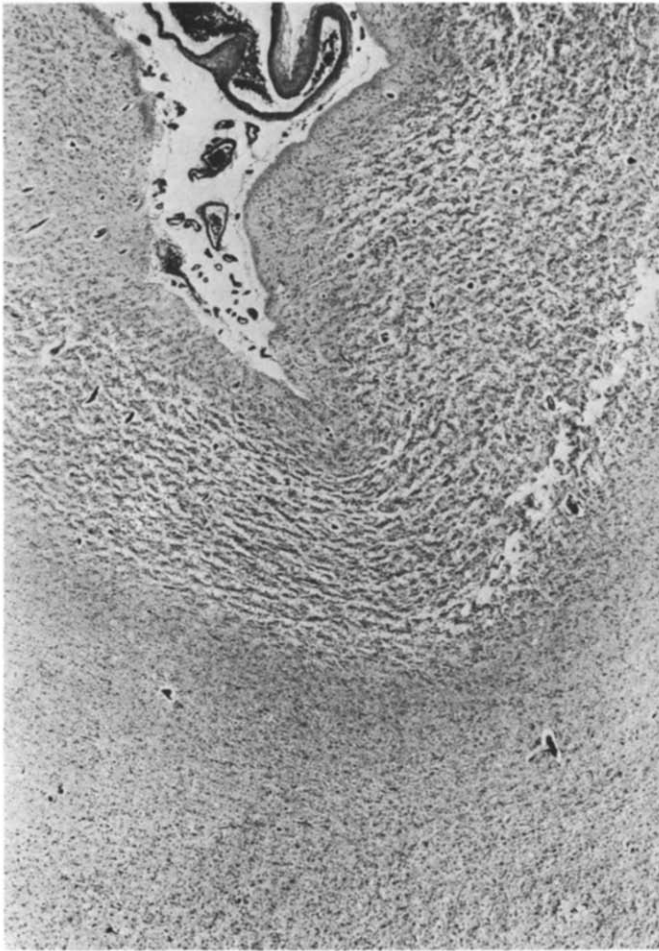


Fig. 3. Severe spongiosis and necrosis in the cortical gray matter. Cresyl-violet; $\times 25$.

cells throughout the cortex (Fig. 4A). Severe damage of the white matter was observed all over the forebrain. The number of myelinated fibers was greatly reduced (Figs. 5A and B), the axons were severely affected and a marked proliferation of hypertrophic glial cells, mainly of gemistocytic type, dominated all the other lesions (Fig. 4B). Severe spongiosis was evident in the white matter. Scattered and perivascular foamy macrophages were disseminated everywhere; no specific lesions of the vessels were seen in the white and gray matter. No amyloid plaques and no neurofibrillary tangles were found in the gray matter.

The basal ganglia were extensively affected by cell depopulation and gliosis. The spongiosis was less severe than in the cortex. Slight demyelination was observed in the internal capsule. Regressive neuronal changes and gliosis were also observed diffusely in the thalamus.

In the brain stem, the long ascending and descending fiber tracts were relatively

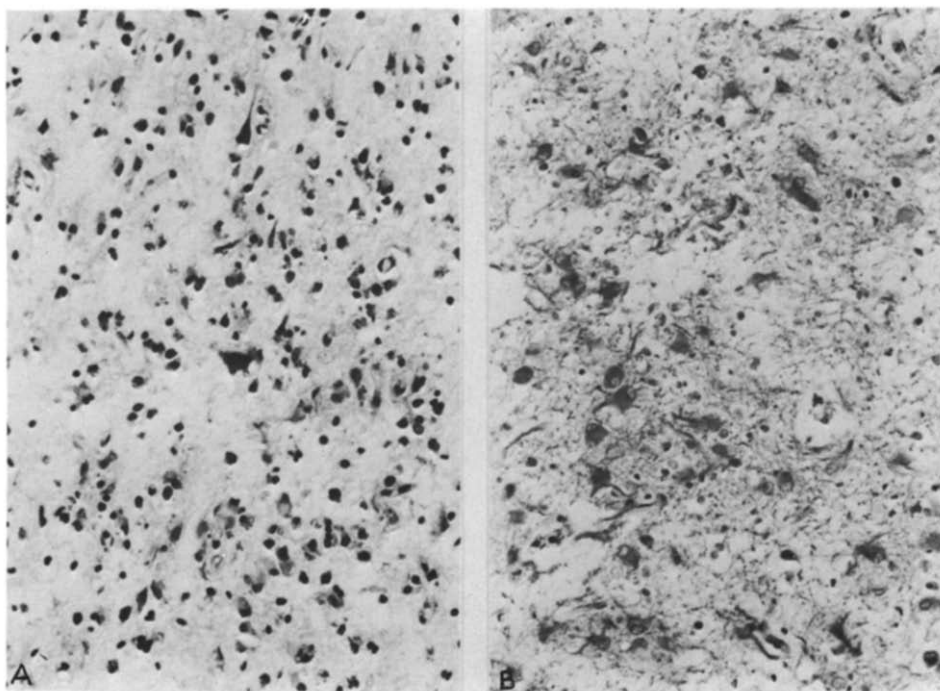


Fig. 4. *A*: Neuronal loss, severe spongiosis and glial proliferation in the cortex. Cresyl-violet; $\times 100$. *B*: Gemistocytic proliferation of glial cells and spongiosis in the white matter of the centrum semiovale. Haematoxylin-eosin; $\times 250$.

well preserved. Slight demyelination was observed only in the superior cerebellar peduncle. Acute and chronic regressive changes, pigment degeneration of the neurones and reactive gliosis appeared prevalently in the red nucleus, in the cranial nerves nuclei and in the raphe. In the cerebellum, the spongiosis was prevalently evident in the granular layer and in the immediately underlying white matter. The deep nuclei were relatively spared.

No electron-microscopic examination could be performed in the autopsy material which reached the laboratory formaldehyde-fixed.

DISCUSSION

Prior to the cases described in Japan (Takatzu et al. 1978; Tateishi et al. 1979; Mizutani et al. 1981) and U.S.A. (Park et al. 1980; Monreal et al. 1981), the white matter lesions in CJD, although sporadically mentioned, had not been considered as relevant features of the disease. On the basis of the recent descriptions, including the present one, the question arises how the white matter lesions in CJD should be classified: are they secondary to the involvement of the gray matter, or do they represent primary lesions like the severe destruction of the gray matter? In our opinion, a secondary involvement is unlikely, in view of the fact that in CJD

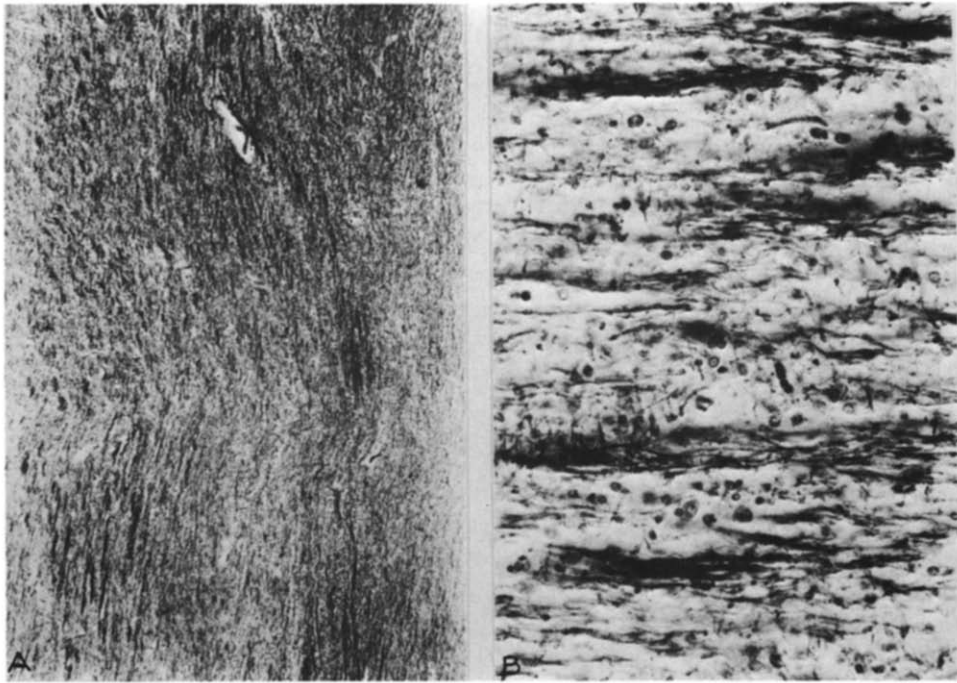


Fig. 5. Reduction of myelinated fibers in the centrum semiovale. Weil stain; $\times 25$ (A), $\times 250$ (B).

extensive lesions of the white matter are an exceptional finding whereas lesions of the gray matter are an essential feature. In this respect the present report confirms that loss of neurones, gliosis and spongiotic lesions of the gray matter are the morphological basis of CJD. On the other hand, hypertrophic glial reaction of the white matter, mainly represented by a gemistocytic proliferation, is a common finding in primary lesions and is rarely found in secondary degenerations of the white matter, where a fibrillary gliosis is prominent. Therefore, the occurrence of gemistocytic glial reaction supports the hypothesis that the involvement of the white matter represents a primary lesion.

The results of the transmission to small laboratory animals cannot solve the problem of a primary or secondary involvement of the white matter. Up to date only one typical chronic case of spongiform encephalopathy with lesions of the white matter and disseminated plaques of kuru type was transmitted to rodents and has led to spongiotic lesions and intralamellar vacuolization of the myelin (Tateishi et al. 1980). However, the importance of these data are difficult to evaluate, since vacuoles in the white matter were also described after transmission of typical cases of CJD in mice (Sato et al. 1980).

The clinical history of cases with lesions of the white matter raises another problem of classification: are they related to a particular course of the disease or do they belong to a true subtype of spongiform encephalopathy? In only two of the cases described by Mizutani et al. (1981) the course of the disease had been

relatively long (2 years in one case and 2½ years in the other), while in all the other cases the survival was within the range typical for CJD. On the other hand, some cases of CJD survived longer than one year and did not show lesions of the white matter (Kirschbaum 1968). Therefore, the hypothesis that the latter may be related to the course of the disease seems unlikely. In the present case the course of the disease, as controlled with CT scan, was biphasic. After 3 months of illness, when the patient was already in a coma-vigil like state, the CT scan had not shown atrophy of the white matter. The latter was evidenced in the 15th month of illness, when the coma vigil-like state had already lasted for many months. Therefore, the pathological process probably involved the white matter only in the second period of the disease.

Since no comparable observations, i.e. with CT scan control, have been reported in the literature one does not know if a similar evolution of the anatomoclinical process could have been present in some of the published cases. The possibility that the treatment could have influenced the course of the disease and could have determined lesions outside the gray matter, cannot be ruled out. However, this hypothesis seems unlikely since no similar effects of methisoprinol have been hitherto documented. Moreover, the cases with severe lesions of the white matter published up to now (Park et al. 1980; Mizutani et al. 1981) had not been treated with this drug.

The present study supports the idea that cases with severe involvement of the gray matter and extensive lesions of the white matter represent a pathological process different from typical forms of CJD as well as from the transmissible form of Gerstmann-Sträussler disease (Masters et al. 1981). Apparently, in agreement with Mizutani et al. (1981), lesions of the white matter represent primary changes and define a new neuropathological subentity of the group of CJD.

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