Jakob-Creutzfeldt Disease Associated with Wernicke Encephalopathy

S. Gaytan-Garcia, J.J. Gilbert, J.H.N. Deck and J.C.E. Kaufmann

ABSTRACT: Wernicke disease (WD) is a complication of alcoholism and malnutrition and usually presents acutely and is characterized by disturbances of consciousness, paralysis of the external ocular muscles, and ataxia. The disease results from deficiency of vitamin B 1, or thiamine, an essential coenzyme in intermediate carbohydrate metabolism. On the other hand, Jakob-Creutzfeldt disease (J-C) results from infection with an unconventional agent with a long incubation period and is characterized by a rapidly progressive dementia and histologically by a spongiform encephalopathy associated with neuronal destruction and pronounced astrogliosis. Combination of both diseases has not been reported in the literature previously and their relationship is uncertain. We present 3 cases with this interesting association and consider their relationship.

RÉSUMÉ: La maladie de Jakob-Creutzfeldt associée à une encéphalopathie de Wernicke La maladie de Wernicke est une complication de l'alcoolisme et de la malnutrition. Elle a habituellement une présentation aiguë et se caractérise par une altération de la conscience, une paralysie des muscles externes de l'oeil et de l'ataxie. Cette maladie est le résultat d'une déficience en vitamine B1, la thiamine, un co-enzyme du métabolisme intermédiaire des hydrates de carbone. D'autre part, la maladie de Jakob-Creutzfeldt est causée par une infection par un agent non-conventionnel qui a une période d'incubation prolongée. Elle se caractérise par une démence rapidement progressive. A l'histologie, on retrouve une encéphalopathie spongiforme associée à une destruction neuronale et à une astrogliose marquée. La combinaison de ces deux maladies chez le même patient n'a jamais été rapportée antérieurement dans la littérature et la relation entre elles est incertaine. Nous décrivons le cas de 3 patients qui présentent cette association pathologique intéressante et nous examinons l'interrelation entre ces deux pathologies.

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The aim of the present publication is to draw attention to a previously unrecognized association between J-C disease and WD. Despite its description over a century ago, WD continues to be under recognized; recent studies suggest that WD is the most common neuropathological finding underlying chronic malnutrition and that its prevalence at autopsy far exceeds its rate of recognition during life.[1,2,3] To the best of our knowledge the two diseases have not previously been reported as occurring together in the same patient. Such an association raises interesting questions about the reason for the combination.

PATIENT 1

Clinical History

A 67 year old, right handed woman suddenly developed severe vertigo, left hearing loss and tinnitus associated with an upper respiratory tract infection. In the first month of illness, she developed progressive unsteadiness of her gait. The family had noted a marked deterioration in intellectual capacity and an obvious loss of weight. Her past medical history included resection of an abdominal aortic aneurysm with excellent results one year before; there was no history of alcoholism.

On examination she was confused with poor general knowledge, poor ability to calculate and impaired short, immediate, and long term memory; her speech demonstrated normal comprehension, she was able to repeat and was fluent but had some difficulty in responding to questions. Reflexes were brisk throughout, her left toe was upgoing. Cranial nerves, muscle tone, strength and sensation were normal. Routine laboratory tests including complete blood count were normal. A computerized axial tomography (CAT) scan of the head showed mild generalized cerebral atrophy but no focal changes. An electroencephalogram (EEG) revealed left hemispheric abnormality with a left frontal component suggestive of a diffuse disorder. There were no periodic sharp wave complexes. During her stay in hospital she became mute, spastic in all four limbs and exhibited bilaterally upgoing toes. She developed a palmomental grasp reflex and myoclonic jerks in response to startle. There was no mention of nystagmus or eye palsies. She continued to deteriorate, intravenous therapy with thiamine was instituted for the next 2 months (total dose 1.5 g). She eventually expired 5 months after onset of her illness. Clinical diagnosis of J-C disease was made 2 months before death.

Pathological Findings

The brain weighed 1230 g. Symmetrical mild generalized atrophy of cerebral hemispheres was observed without discoloration or softening; coronal sections confirmed the slight atrophy. Striking changes in the

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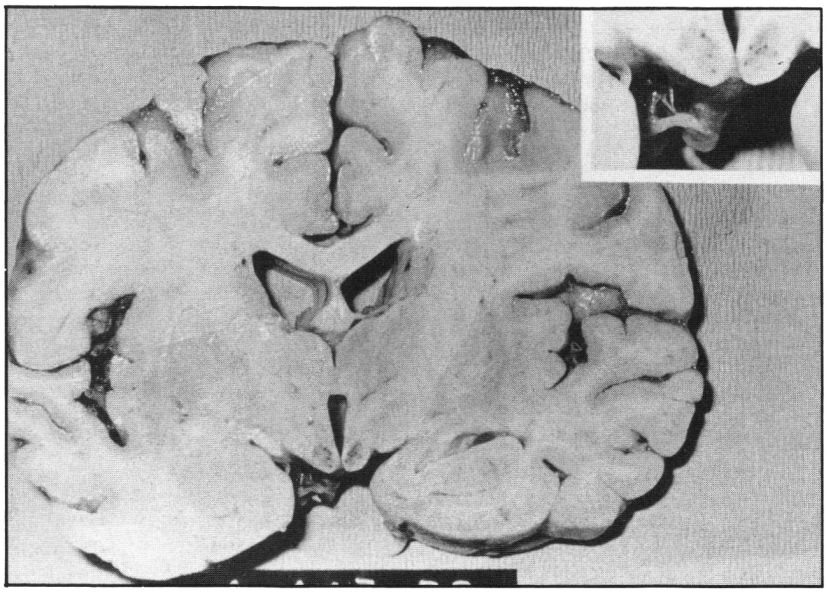

Figure 1 — Patient 1. Coronal section of the hemispheres shows numerous petechiae, and brownish discoloration of the mammillary bodies. Insert: close up of the cut surface of the mammillary bodies.

mammillary bodies were present; the cut surfaces were dark and contained numerous petechiae (Figure 1), while the dorsomedial nuclei of the thalamus were healthy as was the periaqueductal gray matter and the gray matter in the floor of the fourth ventricle. The cortex of the left temporal lobe, especially of the superior temporal gyrus appeared thinned and slightly brown and the ventricles were very slightly dilated; in the cerebellum, the anterior superior vermis appeared atrophic with smaller folia. There was minimal patchy atheroma with some stenosis affecting the internal carotid arteries and the vessels of the Circle of Willis.

Spongiform changes, neuronal loss and gliosis were striking findings in the cerebral cortex and diencephalon. The spongiform changes were most severe in the frontal and parietal cortex and not present in the hippocampus. The intensity of the spongiform changes varied from area to area. These vacuoles were small in the majority of the sections but in some areas, particularly the parietal cortex, they tended to be confluent (Figure 2); neurons could be seen indented by these vacuoles, and in some other areas cellular debris was visible in the vacuoles. Loss of nerve cells was diffuse in the cerebral cortex in spite of the appearance of hypercellularity given by the astrogliosis, and gemistocytic forms were prominent (Figure 3); inflammatory changes were not present. The diencephalic and thalamic nuclei showed similar changes in which there was a paucity of neurons, marked astroglial proliferation, and small vacuolar changes throughout. The cerebellum at the level of the vermis showed that the folia were slightly separated and at the level of

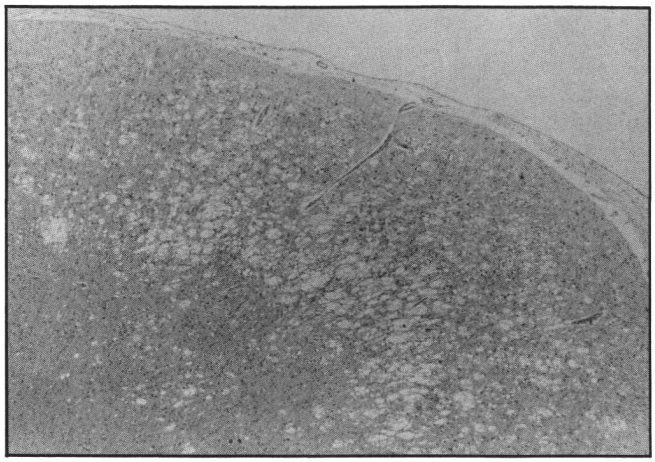

Figure 2 — Patient 1. Extensive spongiform change of the parietal cortex (Hematoxylin-eosin, X 37.5).

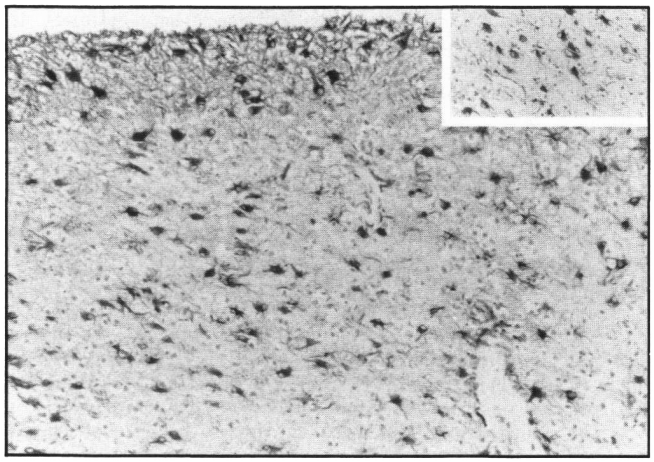

Figure 3 — Patient 1. Marked astrogliosis in the parietal cerebral cortex with prominent gemistocytic forms (glial fibrillary acidic protein, X 118).

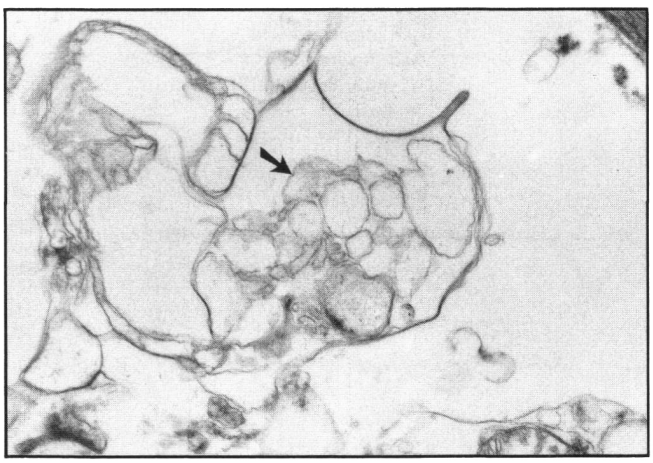

Figure 4 — Patient 1. Electron micrograph showing several swollen neurites with membranous structures and puffy formations (arrow), and occasional coalescence of vacuoles (Uranyl acetate-lead citrate staining, frontal cortex, X 21 500).

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the dentate nucleus showed proliferation of both astrocytic and microglial cells and moderate spongy change. Purkinje cells were unremarkable throughout although in areas there was a proliferating astrocytic response of the Bergmann glia; the granular layer was hypocellular.

The diencephalon and the mammillary bodies showed proliferation of capillaries and venules with very prominent endothelium, foci of haemorrhage and collections of macrophages containing iron pigment. Spongiform changes were seen. No abnormalities were detected in the periaqueductal gray matter, floor of the fourth ventricle, and dorsomedial nuclei of the thalamus. The midbrain, pons, medulla and spinal cord were normal.

Transmission electron microscopy showed vacuoles with obvious membrane alteration — splitting of the unit membrane and formation of puffy amorphous membranes (Figure 4); occasionally vacuoles coalesced and formed larger vacuoles; some areas showed apparent budding of membranes of vacuoles.

PATIENT 2

Clinical History

The patient, a 68 year old woman with a prior history of hypertension and myocardial infarction, was admitted to hospital 3 months before death with speech disturbance, decreased memory and tearfulness, gait disturbance and odd posturing. She demonstrated perseverative speech and motor function, apraxia, dystonic posturing of the trunk, staggering gait and left sided weakness. There was no history of alcoholism.

Complete blood count and folate values for serum and RBC were normal. Arteriograms and CAT scan were normal. The EEG showed periodic sharp wave complexes and the diagnosis of J-C disease was considered. She deteriorated rapidly and was eventually unable to communicate. There was no nystagmus or paralysis of eye movement. She was maintained on intravenous fluids in which vitamins had been included during the last two months of her life and considerable loss of weight was noted.

Pathological Findings

The brain weighed 1060 g. Diffuse generalized atrophy was observed which was most severe in the frontal and the occipital lobes. Mild atherosclerosis of the vessels of the Circle of Willis and basilar artery without occlusions was noted.

The cortex appeared slightly atrophic and the ventricles were mildly dilated. The striking feature was the presence of petechiae and gray discoloration of the walls of the third ventricle and mammillary bodies (Figure 5); the fornices and basal ganglia were normal. In the periaqueductal area and in the tegmental region there was gray discoloration and haemorrhage, which extended to the midpons and was in close apposition to the fourth ventricle; small haemorrhages were also noted below the fourth ventricle in the medulla. The cerebellum was mildly atrophic.

There was marked loss of neurons throughout the cerebral cortex with spongiform changes (Figure 6). Most of the remaining cortical cells were astrocytes. Some areas of the cortex had collapsed and the vacuoles were replaced by glia. The spongiform changes were present diffusely in the neuropil and not confined to any particular cortical layer. The hippocampus was relatively normal with a sharp demarcation from the neuronal loss and marked gliosis and vacuolation in the parahippocampal gyrus. The globus pallidus was relatively normal but the caudate was markedly affected with some vacuolation and neuronal dropout. The subjacent white matter was strikingly vacuolated.

In the diencephalon there were microhaemorrhages, gliosis of tracts, loss of neurons and patchy necrosis; capillary proliferation was seen near to the midline particularly in the mammillary bodies. The brainstem showed extensive involvement with WD, including microhaemorrhages near to the midline structures, neuronal loss, gliosis, and necrosis of the colliculi and the periaqueductal gray matter at the level of the fourth nerve exit zone; the substantia nigra was relatively preserved. Near to the floor of the fourth ventricle there were gliosis, microhaemorrhages, and early iron deposition; there was adjacent necrosis of the medial longitudinal fasciculus. The cerebellum was relatively spared, but there was patchy loss of Purkinje cells.

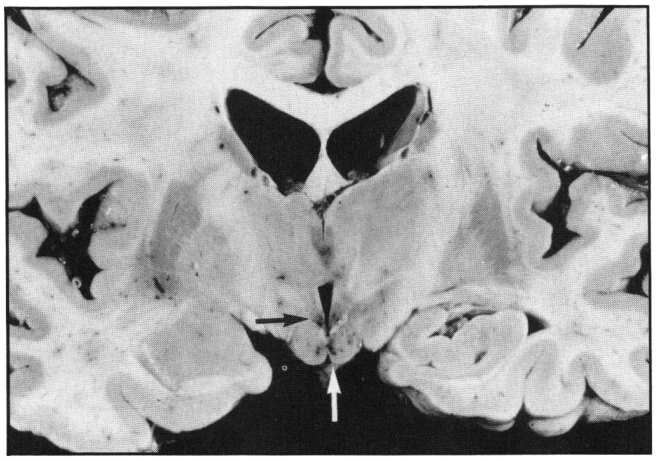

Figure 5 — Patient 2. Gray discoloration and petechiae around the third ventricle and mammillary bodies (arrows).

PATIENT 3

Clinical History

This 62 year old man, a non-drinker, was admitted to hospital with the sudden onset of dizziness and unsteadiness of gait. Blood pressure was 140/100 mm Hg and he was dysarthric and lethargic. There was no abduction of the right eye; on looking to the left there was jerking nystagmus with a fast component to the left. He had impaired rapid alternating movements of the hands greater on the left than the right, intention tremor on the left with dysmetria and dysdiadochokinesis and impaired heel-knee-shin test on the left; reflexes were 2+ throughout and the right plantar response was upgoing. Routine investigations showed the following values: Vitamin B12, 254.5 pmol/L, serum folate 17.2 nmol/L, folate RBC 629.9 nmol/L, Hb 153 to 176 g/L, WBC 9.6 to

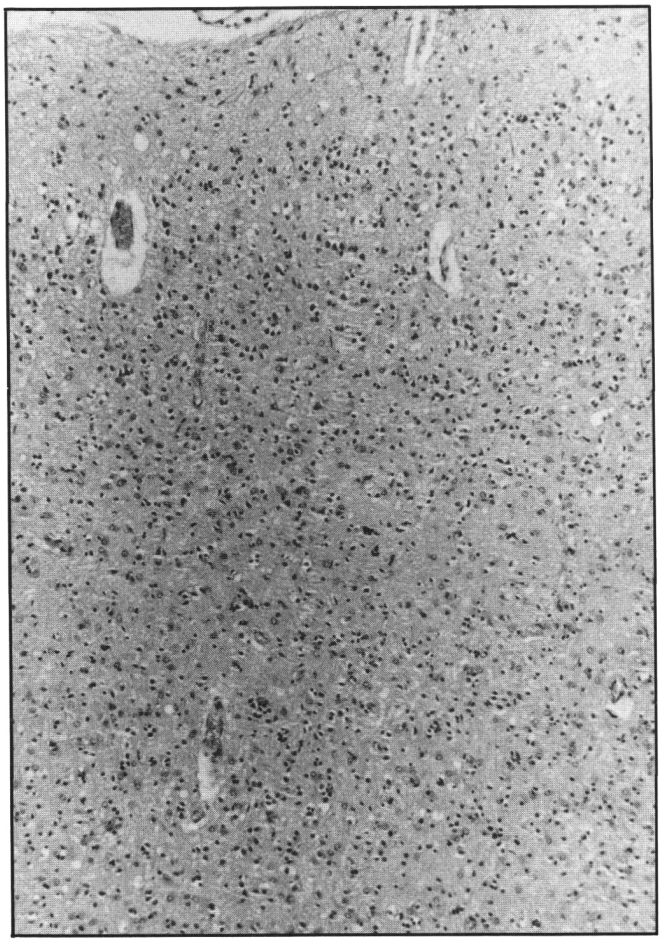

Figure 6 — Patient 2. Frontal cerebral cortex showing marked loss of neurons and astrogliosis with scanty spongiform changes (Hematoxylin-eosin, X 123).

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11.1 x 10^9/L, RBC 4.79 to 5.38 x 10^{12}/L, Hct 0.43 to 0.50, MCV 91 to 93 fL, MCH 31.7 to 32.9 pg, MCHC 345 to 349 g/L. The first EEG was normal but 6 weeks later there were periodic sharp wave complexes on a disorganized background. Diagnostic possibilities were: ataxic form of J-C, progressive multifocal leucoencephalopathy, metabolic encephalopathy and paraneoplastic syndrome. The patient showed the features of a rapidly developing dementia, ataxia became worse, there was increasing muscle tone, incontinence, disorientation, bilateral grasp reflex, and he began to have left sided seizures and myoclonus in the upper limbs. Intravenous therapy was given for the last two months, without vitamin supplementation. He developed severe rigidity and decorticate posturing. He became emaciated and remained so until death three months after the onset of symptoms.

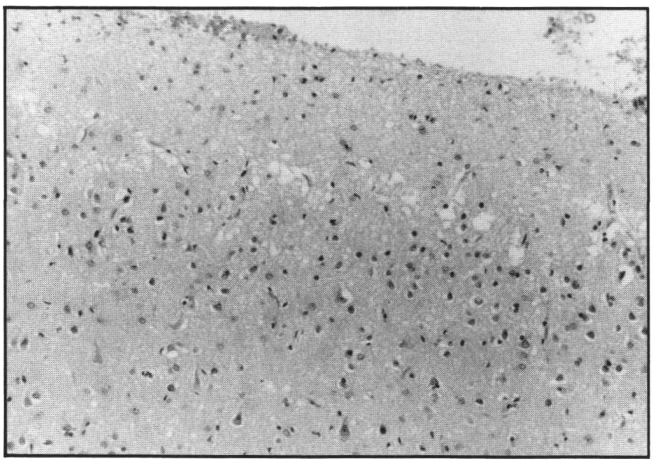

Figure 7 — Patient 3. Frontal cerebral cortex showing spongiform changes, astrogliosis and degenerative changes of the neurons (Hematoxylin-eosin, X 204).

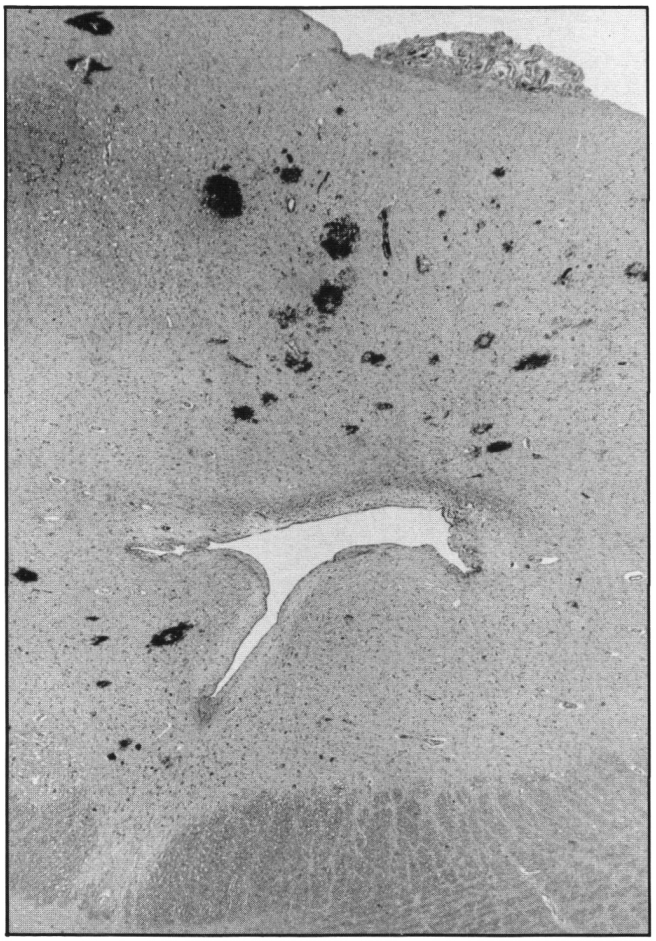

Figure 8 — Patient 3. Section of the midbrain showing petechial haemorrhages in the gray matter of the periaqueductal area (Hematoxylin-eosin, X 20).

Pathological Findings

The brain weighed 1335 g, and there was mild cerebral and cerebellar atrophy. The right half of the brain was frozen. Coronal sections of the left cerebral hemisphere revealed only very slight thinning of the cortex, mild dilatation of the ventricular system, and petechial haemorrhages in the thalamus and hypothalamus. Horizontal sections of brainstem and cerebellum revealed similar petechial haemorrhages around the periaqueductal area, in the left inferior colliculus of the midbrain and around the fourth ventricle in the pons and medulla.

The cortex of the frontal and parietal lobes, the insular cortex, the basal ganglia, thalamus and hypothalamus showed spongiform changes in the neuropil, some neurons were indented by these vacuoles, and there was extensive proliferation of astrocytes. Numerous neurons showed degenerative changes or appeared frankly necrotic (Figure 7). The putamen showed a small old infarct.

Petechial haemorrhages were seen in the thalamus, anterior hypothalamus, inferior colliculus of the midbrain, and in the pons and medulla (Figure 8). The left inferior colliculus and periaqueductal area also showed capillary proliferation; the left mammillary body was only moderately affected showing some gliosis and increased vascularity. The cerebellum showed degenerating Purkinje cells, empty basket cells and swollen axons, there was proliferation of Bergmann glia, and the granular cell layer was hypocellular and showed spongiform changes.

Discussion

The association of J-C disease and WD has not been reported in the literature previously and the question arises as to whether these diseases could have a relationship which is other than fortuitous.

J-C disease is classified as one of subacute spongiform encephalopathies.[4] These represent a group of transmissible encephalopathies caused by unknown agents considered by some observers to represent unconventional viruses.[5,6] They have a long incubation period of many months or years and a characteristic, unremitting always fatal course.[7,8] Clinically J-C disease is characterized by progressive dementia and/or disturbance of consciousness with myoclonus and EEG changes. The neuropathological findings are spongiform changes in the neuropil with varying degrees of neuronal degeneration and astrogliosis, and although white matter involvement in J-C disease is usually secondary to neuronal loss, cases have been described recently in which white matter vacuolation and degeneration appear as primary phenomena.[8,9]

On the other hand WD is a disease process characterized pathologically by symmetrical lesions consisting of proliferation and dilatation of capillaries, astrogliosis, haemorrhages and ischaemic changes of the neurons in the mammillary bodies, the walls of the third ventricle, the periaqueductal area and the floor of the fourth ventricle. Clinically the disease is characterized by disturbance of consciousness, paralysis of the external ocular muscles, ataxia and sometimes polyneuritis.[10,11] A prerequisite for the development of WD is a poor nutritional state,[1,12] a component of which is thiamine deficiency. The role of thiamine deficiency in the pathogenesis of clinical[11] or experimental[16] WE is well established.

Forced or self-imposed starvation or malabsorption may precipitate the disease.[13,14,15] It is common in chronic alcoholics whose carbohydrate load (alcohol) is high and who consume a diet deficient in thiamine. Acute WD may also develop rapidly after institution of intravenous therapy in high risk patients.[1,12]

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What are the factors important in the pathogenesis of WD in our three patients with JC disease? In all three cases JC disease was responsible for the clinical presentation and for admission to hospital. JC disease may have directly contributed to some nutritional deficiency since dementia, and the involvement of diencephalic and hypothalamic structures will alter appetite. In patient 1 weight loss had occurred prior to admission to hospital and in all patients thiamine stores may have been somewhat depleted. The cessation of oral feeding and the use of parenteral dextrose as the sole caloric supply during the terminal phase would profoundly affect thiamine stores since increased carbohydrate load increases thiamine requirements. It is therefore to be expected that WD should have developed in patient 3 where no vitamin supplementation was given.

It is somewhat more surprising that WD developed in patients 1 and 2 and it must be concluded that although vitamin supplementation was provided, the supply was inadequate in the face of the increased carbohydrate load. However even in populations of thiamine deficient patients it is recognized that only a few develop WE. Blass and Gibson[18] described a genetic defect in patients with WE in which fibroblast transketolase bound less avidly with coenzyme thiamine pyrophosphate than controls. It could be postulated that there is a group of the population with a partial defect in transketolase binding that remains subclinical until unmasked by a reduction in the availability of thiamine, leading to WE.[17] It is remarkable how infrequently the diagnosis of WD is made clinically before death.[2,3] Wernicke-type pathology may be more common than suspected in patients with J-C disease and other disorders with dementia. WD may develop surreptitiously without clinically obvious episodes or perhaps its expression may be masked by symptoms of the dementing disease.

In our patients it is quite probable that survival was shortened by WD. We conclude that the effect on appetite of JC disease, IV carbohydrate loading, inadequate thiamine intake and, possibly individual susceptibility to thiamine deficiency are the factors leading to the development of WD in patients with JC disease.

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