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Case report

Progressive multifocal leukoencephalopathy associated with prolonged hemodialysis treatment

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Summary. The association of progressive multifocal leukoencephalopathy (PML) with prolonged hemodialysis treatment (PHT), not previously reported, was observed in a 56-year-old Japanese man who received PHT for 11 years. He suffered from recurrent bouts of fever and progressive neurological signs, such as irritability, speech disturbance, gait disturbance and dysphagia for seven months, and finally fell into a deep coma and died. Clinical signs and symptoms were highly suggestive of progressive dialysis encephalopathy. Necropsy revealed that the PML mainly involved the brainstem and cerebellar white matter. The aluminium content of the brain tissue was lower than that of controls. Possibly the virus causing PML is one of the causes of progressive dialysis encephalopathy, since clinically PML is not easily distinguished from progressive dialysis encephalopathy. It is essential to differentiate PML of viral etiology from progressive dialysis encephalopathy of unknown cause.

Key words: Hemodialysis – Papova virus – Progressive dialysis encephalopathy – Progressive multifocal leukoencephalopathy (PML)

Introduction

More than 100 cases of progressive multifocal leukoencephalopathy (PML) have been reported to date. Over half of these had either leukemia or lymphoma, and most were thought to be in an immuno-suppressed state (Johnson et al. 1977). The typical features of the disease include confusion, amnesia, dementia and abnormality of speech (Adams 1976). However, the clinical features of progressive dialysis dementia or progressive dialysis encephalopathy also include speech disturbance, seizure disorders, dementia and behavioural disturbances (Bone 1978), which are very similar to those in

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PML. Although it has been suggested that uremia and prolonged hemodialysis may cause immunological abberations (Dobbelstein 1976) and be associated with opportunistic infection with a slow virus, we can find no previous record of an association of PML with PHT. This paper reports a case in which the two were associated.

Case report

A 56-year-old Japanese man had received PHT for 11 years. His chronic renal insufficiency was believed to be due to gouty kidneys, although conclusive evidence for this was lacking. Dialysis was initiated on July 28, 1967. Peritoneal dialysis was performed only twice and subsequently the patient received PHT. At the time of initial peritoneal dialysis, the blood urea nitrogen was 111 mg/100 ml (normal: 8–20); creatinine 11.6 mg/100 ml (0.8–1.3); and serum potassium 4.4 mEq/l (3.3–4.8). He received PHT twice a week until 1970 and then three times a week. Clotting difficulties in his A–V shunt for PHT required a total of 22 access operations. In October, 1978, he suffered from recurrent bouts of fever of up to 38.5° C, which frequently occurred after the hemodialysis treatment. Isoniazid acid hydrazide (INAH) was prescribed for suspected insidious tuberculosis, even though the lungs appeared normal in X-ray films of the chest. His fever did not subside, and INAH was discontinued after four weeks. In December, 1978, his family noticed a gradual change in his behavior; namely, he became irritable and quick-tempered. In January, 1979, speech disturbance, gait disturbance and ataxia of the left arm were noticed. Later, dysphagia, facial asymmetry, right ptosis, deviation of the tongue to the left and aphonia developed. At this time, the blood urea nitrogen was 80 mg/100 ml; creatinine 14.4 mg/l; uric acid 8.4 mg/100 ml (3.6–7.7); sodium 145 mEq/l (138–147); potassium 4.0 mEq/l; chloride 109 mEq/l 98–112); calcium 11.7 mg/100 ml (8.6–9.9); inorganic phosphate 6.5 mg/100 ml (2.4–4.8); and magnesium 3.6 mg/100 ml (1.7–2.1). An electronencephalogram (EEG) showed diffuse slow waves with prominent 5–6 c/s activity and paroxysmal synchronous bursts of delta waves. CT scanning of the brain revealed only moderate atrophic change. Chemical and bacteriological analyses of the cerebrospinal fluid showed no abnormalities. On April 8, 1979, he fell into a deep coma and died of sudden respiratory failure.

Pathological findings

Necropsy was done 30.5 h after death. The kidneys (80/70 g) showed marked contraction with multiple small cysts on the surface. Histological examination revealed severe interstitial fibrosis, cystic dilatation and atrophy of tubules and marked intimal fibrous thickening of intra-renal arteries. No remnants of intact glomeruli were observed, and the exact cause of the end-stage state of his kidneys could not be determined. Marked atherosclerosis of the aorta with calcification was seen. The lungs (785/980 g) showed diffuse edema. Secondary hyperplasia was observed in the four parathyroid glands. There were five small diverticulae in the caecum. Several foreign body granulomas with oxalate deposition were found in the myocardium, liver and kidneys. The brain (1,340 g) showed swelling with a bilateral tentorial pressure cone and slight tonsillar herniation. The cerebral basal arteries showed no atherosclerotic change or stenosis. In cut-sections, small round foci of softening of the white matter were seen in the right frontal (Fig. 1) and left occipital lobes, and diffuse areas of softening of the white matter in the left cerebellar hemisphere (Fig. 2) and the ventral part of the pons (Fig. 3). On histological examination, macroscopic regions of softening were found to consist of multiple or confluent foci of demyelination, cells with hyperchromatic nuclei (Fig. 4) and proliferation of atypical astrocytes (Fig. 5), with lipid-laden macrophages and perivascular cuffing by mononuclear cells. Similar lesions were observed in all the white matter of the cerebellar vermis, the left dentate nucleus, the left trigeminal nucleus, the left nucleus ambiguus and the left facial nucleus. Blocks of formalin-fixed tissue of the pons, cerebrum and cerebellum were processed for electron microscopy, dehydrated by passage through a graded series of ethanol, and embedded in Epon. Sections of 1 μm thickness were stained with toluidine blue to select areas containing cells with nuclear inclusions. Ultrathin sections were stained with

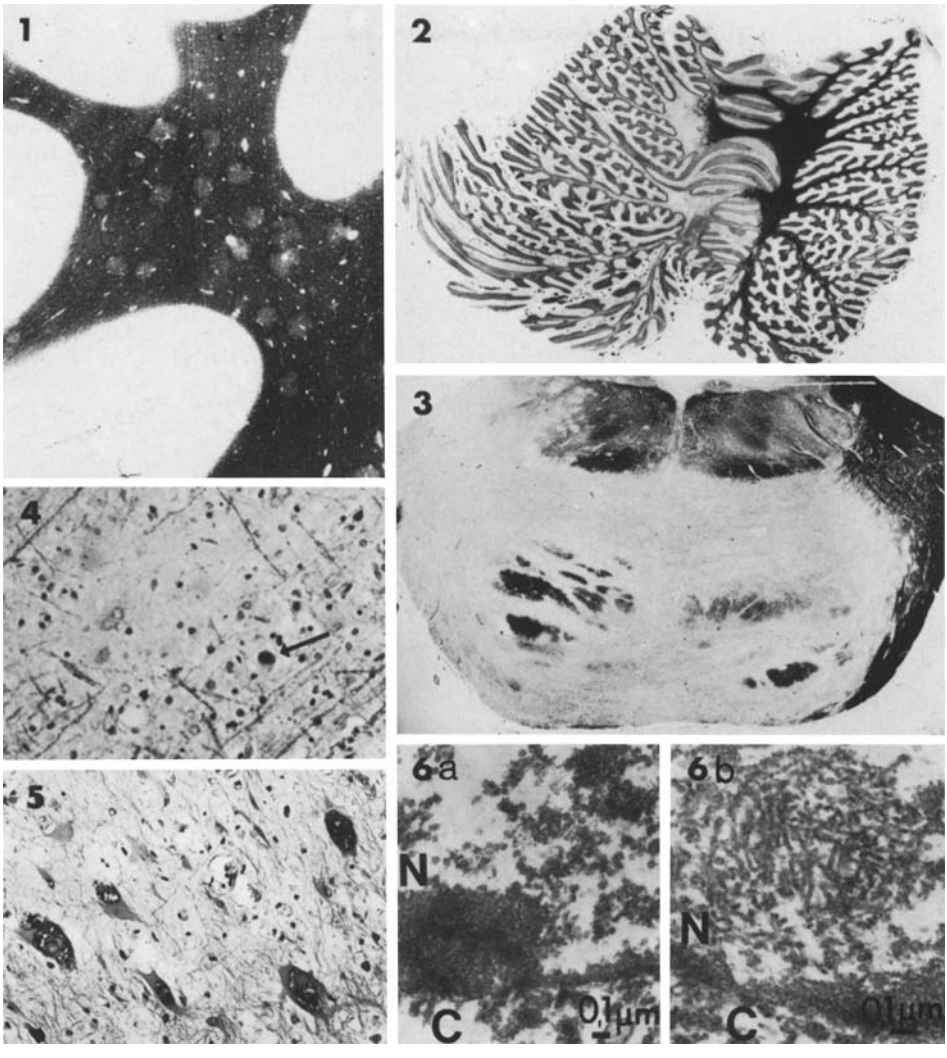

Fig. 1. Coronal section of the right frontal lobe. Note multiple round demyelination foci. Klüver-Barrera, × 5.25

Fig. 2. Horizontal section of the cerebellum. Note diffuse demyelination in the left hemisphere. Klüver-Barrera, × 0.98

Fig. 3. Horizontal section of the pons. Note widespread demyelination of the ventral part. Klüver-Barrera, × 1.88

Fig. 4. A small round demyelinated focus in the right frontal lobe. Note a cell with a hyperchromatic nucleus (*arrow*) and several reactive astrocytes. Klüver-Barrera with cresyl violet, × 188

Fig. 5. Diffusely demyelinated lesion of the pons. Note atypical astrocytes having giant and monstrous nuclei with homogeneous vesicular invaginations. No presence of a malignant glial tumor in the tissue. Hematoxylin and eosin, × 263

Fig. 6a, b. Electron photographs of an nuclear inclusion. Note nucleus (*N*) filled with spherical virions **a** and filamentous profiles **b**. *C*, cytoplasm. Tissue of the pons, formalin-fixed, postfixed with osmic acid, and stained with uranyl acetate and lead citrate, **a** × 21,400; **b** × 33,000

uranyl acetate and lead citrate and observed with a Hitachi H-500 electron microscope. The nuclei of almost all the cells with nuclear inclusions contained small round particles (Fig. 6a) and some filamentous profiles (Fig. 6b), although the tissues were poorly preserved. The round particles were 33 to 44 nm in diameter. Neurons and macrophages did not contain particles. The cerebral cortex and basal ganglia did not show atrophy or any abnormalities. There were no senile plaques, granulovacuolar degenerative alterations, Alzheimer's neurofibrillary changes, Pick's bodies, Hirano's bodies or other intracytoplasmic inclusions.

Aluminium content of brain tissue

Samples of the brain tissue (15–20 g) from the left temporal cortex and white matter were analysed for aluminium by non-destructive and instrumental neutron activation analysis using a lithium-drifted germanium detector. The controls used were brain tissues of a 58-year-old man who died of acute myocardial infarction (non-uremic), and a 55-year-old man who had received hemodialysis for three years (uremic-PHT) but who did not show encephalopathy. The tissue aluminium contents of the cerebral cortex were 110 ± 10 (value $\pm$ possible confidence limits) μg/g dry tissue in this patient, 96 ± 2 μg/g in the non-uremic patient, and 220 ± 10 μg/g in the uremic-PHT patient; those of the white matter were 82 ± 2, 170 ± 10 and 130 ± 10 μg/g, respectively. Thus the aluminium content of this patient was not higher than that of controls.

Discussion

It is now well established that PML is an opportunistic papova virus infection of the central nervous system in immunologically deficient hosts (Åström et al. 1958; Padgett et al. 1971; Johnson et al. 1977). In the present case, the diagnosis was certain because of the presence of multiple and confluent foci of demyelination, cells with nuclear inclusions, reactive and atypical astrocytes and virions, although unfortunately the diagnosis was not confirmed by cultivation or immunological identification of the virus. This involvement of the central nervous system was fully responsible for the neurological signs and symptoms, including dementia, in this patient.

Dementia or encephalopathy is now a recognized complication in prolonged hemodialysis. Progressive dialysis encephalopathy was first described by Alfrey et al. (1972), and later by others (Mahurkar et al. 1973; Chokroverty et al. 1976; Bone 1978). In the case described in the second report of Alfrey et al. (1976), the cerebral gray matter had a significantly increased content of aluminium, and several subsequent reports by others support this finding (Kaehny et al. 1977; Platt et al. 1977; Berkseth et al. 1978; Bone 1978). However, it is controversial whether or not the aluminium content is always increased. In the present case, the aluminium contents of the cerebral cortex and white matter were not higher than those of controls. There are only a few histopathological reports of findings in progressive dialysis encephalopathy (Burks et al. 1976; Chokroverty et al. 1976). These reports describe loss and shrinkage of neurons, astrocytic gliosis and lacunar infarction; these changes are not specific and may be related to other factors, such as an anoxic-ischemic state, hypertension, congestive heart failure, uremia, anemia, acidosis, hyperkalemia, and recurrent seizures. In fact, no specific neuropathological features of progressive dialysis encephalopathy have been established. Moreover, the pathogenesis of this condition is unknown, and it may have a variety of etiologic agents. Barratt

et al. (1976) suggested that slow virus infection might be a cause, but the disease was not transmitted by injection of brain material into monkeys (Burks et al. 1976; Bone 1978). Cameron et al. (1978) isolated a foamy virus from a patient with dialysis encephalopathy. Possibly the virus of PML is one of the causes of progressive dialysis encephalopathy, since clinically PML is not easily distinguished from progressive dialysis encephalopathy. It is essential to differentiate PML of viral etiology from progressive dialysis encephalopathy of unknown cause.

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