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Alcoholic Pellagra Encephalopathy Combined with Wernicke Disease

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Clinical and postmortem findings of a case that had combined alcoholic pellagra encephalopathy and Wernicke disease are described.

This 51-year-old malnourished and chronic alcoholic man presented with progressive mental deterioration, pellagra dermatitis, hypertonus of the neck and other musculatures, myoclonic jerks with bizarre involuntary movements, in addition to total external ophthalmoplegia and gait disturbance. After administration of multivitamins, including thiamine and nicotinamide, these neurologic abnormalities were dramatically improved in a few days. However, the patient died thereafter because of sepsis associated with pneumonia.

Postmortem examination revealed marked abnormalities in CNS, characterized by diffuse atrophy of gray matter and widespread neuronal degeneration and characteristic central chromatolysis in pontine nuclei, dentate nuclei, cranial nerve nuclei in the brain stem, Betz cells of the cerebral cortex, and Clarke's column and anterior horn cells of the spinal cord. There were also atrophy and gliosis of the mammillary bodies, degeneration and vascular proliferation of periaqueductal gray matter, and massive gliosis around the third ventricle.

These neuropathological changes were compatible with symptoms of both alcoholic pellagra encephalopathy and Wernicke's disease, but they were also strongly suspected on clinical grounds.

Key Words : *Alcoholic pellagra encephalopathy, Central chromatolysis, Wernicke disease, Alcoholism, Malnutrition.*

INTRODUCTION

The term "alcoholic pellagra" or "pseudopellagra" was first used by Leudet in 1869 (cited from Sedaru et al., 1988). Two cases of "alcoholic senile deterioration", who were suffering from weakness, delirium stupor or coma, and "jerking of all muscles", were described by Meyer in 1901, with neuropathological findings and neuronal chromatolysis (cited from Sedaru et al., 1988). The association of chronic alcoholism and pellagra was stressed by many authors (Still, 1976 ; Spivak and Jackson, 1977 ; Ishii and Nishihara, 1981 ; , Lishmann, 1981 ; Sedaru et al., 1981, 1988). Alcoholic pellagra encephalopathy (APE) has been thought to be due to a deficiency of niacin and possibly other B-group vitamins (Jolliffe et al.,

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1940 ; Barrett-Connor, 1967 ; Spivak and Jackson, 1977 ; Ishii and Nishihara, 1981). Recently, Sedaru et al. (1988) described 22 patients who suffered from clouding of consciousness, marked hypertonus, and myoclonic jerks, while Hauw et al. (1988) observed the chararcteristic central chromatolysis in their autopsied brains.

In his famous textbook, Wernicke (1891) reported the clinical features and characteristic pathology of the disorder that bears his name. Since then, Wernicke disease(WD) has been characterized clinically by mental confusion, ataxia of gait, and ophthalmoplegia and is now accepted as a disorder due to a thiamine deficiency. Neuropathologic studies in patients who died of WD show symmetrical lesions in the paraventricular regions of the thalamus and hypothalamus, in the mammillary bodies, the periaqueductal region of the midbrain, the floor of the fourth ventricle, and in the superior vermis. Lesions are consistently in the mammillary bodies but less consistently in other areas.

Being related to chrornic alcoholism, both APE and WD could be combined in a same patient, which was already recognized by Lishman (1981).

With an experience of a case concurring with two vitamin deficiency encephalopathies—APE and WD—we report this case with a brief review of the literature.

CASE REPORT

A 51—year—old alcoholic man was brought to the emergency room of Youngdeungpo City Hospital, Seoul, on April 26, 1989, because of progressive mental deterioration and gait disturbance.

He had been drinking a large amount (about 100gm per day) of alcohol for 25 years without any concern for nutritional intake. Ten years ago, he suffered from two episodes of withdrawal syndrome. Recently, he had stopped drinking 2 weeks before admission, when he gradually developed disorientation, hyperirritability, aggressiveness, hallucinations, and desquamation of the dorsum of the hands. He denied having a history of pulmonary tuberculosis, diabetes, or hypertension.

His blood pressure was 120/80mm Hg, pulse rate 106 per minute, respiratory rate 24 per minute, and temperature 35.5℃

On physical examination he appeared dirty, dehydrated, and chronically-ill. The lung sound was coarse, but his heartbeat was regular. Multiple bed sores were noted on the sacral and trochanteric areas. Generalized muscle tenderness was noted even on slight touch. The skin showed oozing lesions with erosion, ulceration, and crust on the dorsum of the hands and forearms (Fig.1).

On neurologic examination he was drowsy and apathetic, while his eyes opened spontaneously with roving eyeball movement. His speech was scarce and incoherent and his voice severely husky. The pupils were isocoric (3.0/3.0mm) but reacted sluggishly to light. External ocular movement was absent, so the eyeballs were fixed in the midline and nystagmus was absent. The corneal reflexes were brisk and the nasolabial folds symmetric. The tongue showed neither atrophy nor deviation. Severe hypertonus was conspicuously noted. The arms were extended, the legs full-flexed. The hypertonus also involved the neck and abdominal muscles. Myoclonic jerks were frequently observed in the face and limbs, and bizarre involuntary movements were also noted in the four limbs. Deep tendon reflexes were absent in the four limbs, and the plantar responses were flexor. Sitting, standing, and gait were all impossible. The sucking and rooting reflexes were prominent, and the glabella sign was present. Sensory and the cerebellar function tests could not be checked due to poor cooperation.

The urine was normal and leukocytosis (29,200/mm^3 with 82% neutrophils) was noted. The hematocrit and platelet counts were normal, and ESR was 50mm per hour. The test for bleeding tendency was normal, as were the glucose, total bilirubin, uric acid, calcium, phosphorus, cholesterol, electrolytes, creatinine kinase, lactic dehydrogenase, and alkaline phosphatase tests. The urea nitrogen was 151mg/dl and the creatinine 4.1mg/dl. The protein was 6.2g/dl(albumin 2.3g and globulin 3.9g). The serologic tests for syphilis, HBsAg, and HBsAb were negative. The culture of the pus from the right elbow showed the penicillin-sensitive strain of staphylococcus aureus. The X-ray films of the chest revealed a decrease in left lung volume and a hazy infiltration in both lung fields. A lumbar puncture yielded clear, colorless CSF that contained 1 red cell, no white cells, and no microorganisms ; cultures for bacteria and fungi were negative. A cranial CT scan, performed before and after the intravenous injection of contrast material, showed diffuse cerebral atrophy, slight ventricular dilatation, and prominent cerebellar folial markings but no focal

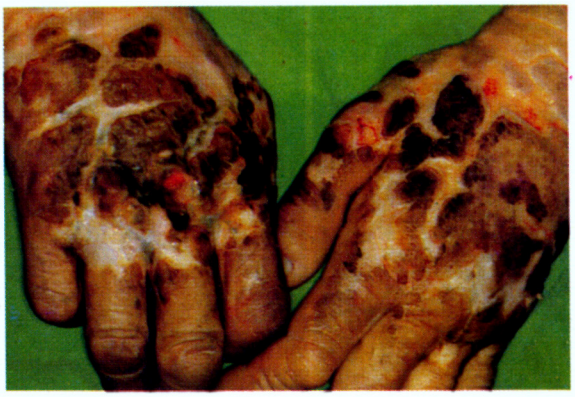

Fig .1. The hands of this patient shows sharply defined scaling lesions on the dorsal aspect. Brown pigmented areas alternate with areas of depigmented atrophic skin.

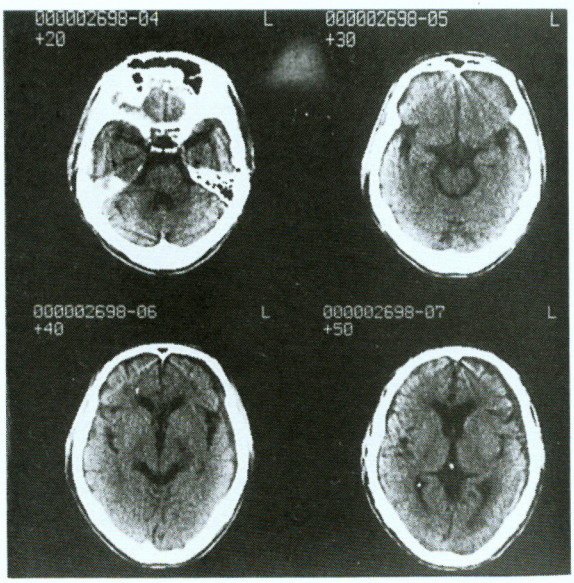

Fig .2. Precontrast CT scans showing diffuse cerebral atrophy ventricular dilatation, and prominent cerebellar folial markings.

lesion (Fig.2).

Under the impression of alcoholic pellagra encephalopathy and Wernike disease, intravenous multivitamin therapy (thiamine 700−1,200mg, nicotinamide 400−600mg per day) was started immediately along with antibiotics. On the fifth hospital day the patient became alert, relatively oriented, and obeyed simple commands. The movements of the external ocular muscles were markedly improved up to 80 percent of the normal range of motion. The hypertonus and myoclonic jerks became less prominent, and the skin lesions also improved. On the sixth hospital day a sudden respiratory collapse with high fever developed. Chest X-ray revealed increased pneumonic infiltration in both lung fields. The patient was intubated and managed intensively. However, his general condition worsened progressively, and he expired on the eleventh hospital day.

PATHOLOGIC FINDINGS

At autopsy the patient showed marked emaciation and generally dark skin. Both hands showed irregular crackings and ulceration in addition to dark discoloration on the dorsal surface. General autopsy findings were bilateral confluent bronchopneumonia, alcoholic hepatitis, mucosal atrophy of the bowel, and sepsis changes. The brain was grossly atrophic, weighing 1,250gm. The cerebral hemispheres were symmetrical, but the gyri were narrowed and the sulci were deepened. The brain stem and cerebellum appeared smaller than expected. The mammillary bodies were grossly smaller than expected (Fig.3).

There were no specific abnormalities in the white matter. However, the cortical neurons were definitely reduced in number, and glial replacement was noted. Both primary motor and sensory cortices showed prominent chromatolysis in the large motor neurons. Glial proliferation was also seen. The brain stem showed massive central chromatolysis in the griseum pontis and locus ceruleus. Almost all the cells of the griseum pontis showed massive neuronal loss and moderate central chromatolysis (Fig.4). Scattered axonal retraction balls, gliosis and capillary proliferation were seen in the periaqueductal gray matter in the midbrain. Central chromatolysis was also seen in the oculomotor nucleus together with widespread gliosis. The medulla oblongata showed chromatolysis and gliosis in dorsal vagal nuclei but very minimally in the hypoglossal nuclei. The inferior olive showed neuronal loss and considerable replacement by gliosis. The cerebellar cortex was diffusely atrophied. The interfolial space was prominent, and the leptomeninges were edematous. The atrophic vermis showed thin molecular layer that contained scattered nuclei. The Purkinje cells were significantly reduced in number and replaced partly by Bergman's glias. The remaining Purkinje cells were either pyknotic or distorted. Scattered corpora amylacea were seen. The granular layer was also thinned out and the cells were

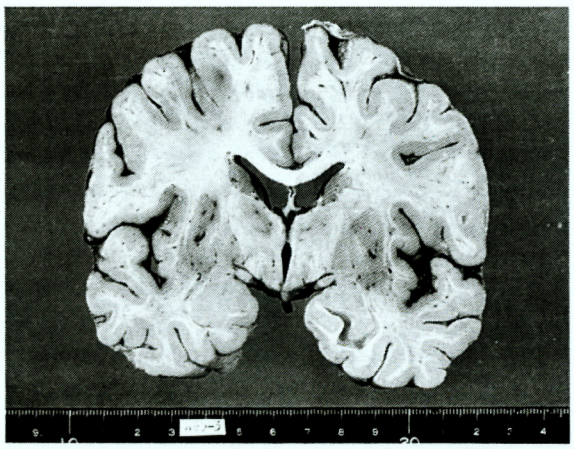

Fig .3. A coronal section of the brain shows a mild ventricular dilatation, cortical atrophy and smaller mammillary bodies.

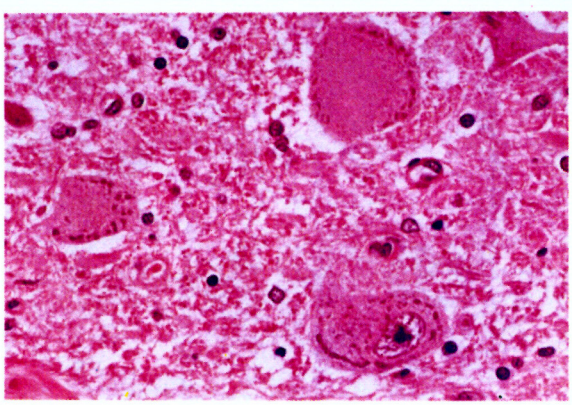

Fig .4. Characteristic central chromatolysis is seen in the neurons of cranial nerve nuclei of the brainstem H&E ×400.

sparse. The subcortical white matter was reduced due to wallerian degeneration and glial cell proliferation was present. The deep nuclei showed intact cells with frequent lipofuscin pigment filling the cytoplasm. The mammillary body decreased in size. There was an active loss of neurons, and the remaining cells were either small in size or pyknotic. Many rod cells were seen proliferating diffusely among the degenerating nerve cells. The vessels were not particularly proliferative (Fig.5). The hypothalamic nucleus in the periventricular area showed central chromatolysis. There was also massive patchy gliosis in the thalamus (Fig.6). Central chromatolysis was also seen in the Clarke's column and anterior horn cells of the spinal cord.

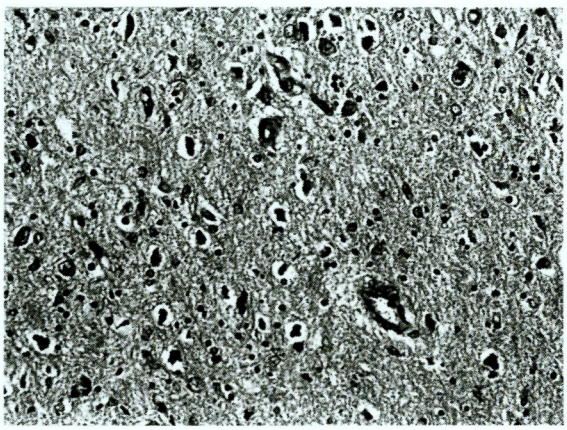

Fig .5. Mammillary body section shows neuronal loss and isomorphic gliosis. However, the vascular proliferation is minimal. H&E ×400.

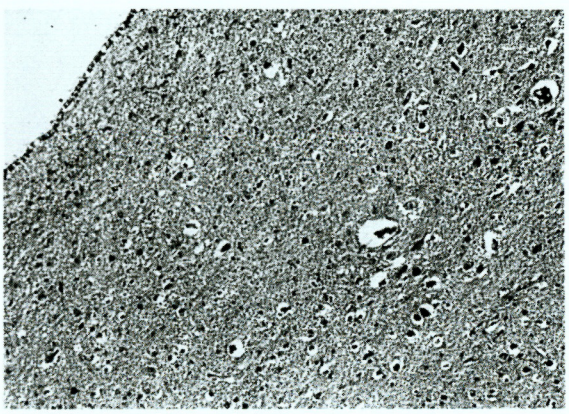

Fig .6. Periventricular thalamic nuclei showing diffuse gliosis and neuronal degeneration and disappearance H&E ×200.

DISCUSSION

Nonendemic pellagra is usually not characterized by the classical triad, since dermatitis and diarrhea are often lacking and is mostly secondary to malabsorption (Tabaqchali and Pallis, 1970), isoniazid administration (Ishii and Nishihara, 1985), or alcoholism (Klauder and Winkelman, 1928 ; Zimmerman et al., 1934 ; Jolliffe et al., 1940 ; Spillane, 1947 ; Spivak and Jackson, 1977 ; Ishii and Nishihara, 1981). The diagnosis, which can only be suspected on clinical grounds, is confirmed by a response to niacin or by postmortem neuropathological study.

Our patient showed the typical pellagra dermatitis, mental deterioration, hypertonus of whole musculatures (especially in the 4 limbs, neck, and abdomen), and myoclonic jerks with unspecified bizarre involuntary movements but no diarrhea. These clinical signs had been improved by high-dose nicotinamide therapy until the unexpected death. Neuropathological study revealed the characteristic central chromatolysis in the neurons of the widespread regions such as pontine nuclei, locus ceruleus, Betz cells, oculomotor nuclei, hypothalamic nuclei, Clarke's column, and anterior horn cells, these findings were almost identical to that of many authors' reports (Meyer, 1901 ; Klauder and Winkelman, 1928 ; Zimmermanet al., 1934 ; Koeppen and Barron, 1978 ; Ishii and Nishihara, 1981 ; Hauw et al., 1988).

All the cases previously reported in the literature showed the confusion and/or clouding of consciousness, but the causes of this sign are numerous. Thus this sign of APE is rather nonspecific. Sedaru et al. (1988) defined it as a profound apathy alternating with restlessness. The anatomical substratum of hypertonus is unknown but usually unrelated clinically to a disturbance of the pyramidal system. Gruner (1956) thought that lesions of the pontine nuclei might be responsible for the marked hypertonus found in alcoholic pellagrins, because the pontine nuclei were heavily involved in alcoholic pellagra, and only the pontine nuclei were involved in some patients with prominent hypertonus. In the various CNS structures implicated in the causation of myoclonus (Fahn et al., 1986), Sedaru et al. (1988) pointed out that the dentate nuclei, which were markedly involved, could account, at least in part, for the appearance of myoclonus in the patients of his series due to the paucity of changes noted in the cerebral cortex, corticospinal tracts, basal ganglia, and medullary olives.

Besides chronic alcoholism (Lishman, 1981 ; Novak and Victor, 1974 : Harper, 1983 : Reuler et al., 1985), numerous causes of Wernicke disease (WD) have been implicated with many conditions, i.e., anorexia nervosa (Handier and Perking, 1982), hyperemesis gravidarum (lavin et al., 19 83), intravenous hyperalimentation (Kramer and Goodwin, 1977), and chronic hemodialysis (Lopez and Collins, 1968). Our patient presented no basis for WD other than chronic alcoholism, and the duration and amount of alcoholic intake strongly suggested that the skin and CNS lesions in this case were related to it.

Our patient showed all the criteria of WD clinically, including mental confusion, ataxic gait, and total external ophthalmoplegia. Furthermore, there were changes in the mammillary bodies at postmortem examination. Atrophy, loss of neurons, and massive gliosis were seen. These findings were also seen in the thalamus and hypothalamic nuclei of the paraventricular region, along with capillary proliferation in the periaqueductal gray matter. These neuropathologic findings were identical to those of Harper's report (1983) in which he classified the disease into three stages (acute, acute on chronic, and chronic). According to his classification, our case seemed to belong to the acute on chronic stage. The fact that thiamine administration (1.0gm per day) improved ophthalmoplegia up to 80 percent of the normal range of motion was in good agreement with the usual WD patients.

Since both APE and WD are related to chronic alcoholism, these two conditions could be combined in a same patient, as in our case. In fact, Sedaru et al. (1988) reported 5 cases of WD that are associated with APE. The incidence was 5 out of 22 cases. To our knowledge this kind of combination has not been described in Korea. Unfortunately, in our case nicotinic acid and thiamine assay in blood could not be done. However, typical clinical features combined with a postmortem histology of CNS and others seem enough for the diagnosis of both APE and WD.

Therefore, neuropathological study seems mandatory for the confirmation of these diseases in chronic alcoholics, and in suspected cases, multivitamins, including high doses of thiamine and nicotinamide, must be started without hesitation.

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