Cerebellar Encephalomalacia Produced by Diets Deficient in Tocopherol

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WE have had the good fortune to examine the cerebella of chicks suffering from vitamin E deficiency induced in the L. B. Mendel Laboratory at the Elgin State Hospital.[1]

In histologic preparations using Klüver's method of staining, hemorrhages could be seen involving both the molecular and the granular layer of the cerebellum (Fig. 1). When the hemorrhages were well developed, the Purkinje cells disappeared entirely. No lesions were found in other parts of the brain, and hemorrhages were not preceded by visible changes in the blood vessels, although later thickening of the endothelium could be seen. The pathologic change affected all parts of the cortex.

With the present clinical vogue concerning unsaturated lipids in mind, we sought similar pathologic alterations in the cerebella of human beings and found one in an infant.[2]

CASE REPORTS

CASE 1. The infant (NA-58-232) was fourteen months of age at death. She was seen at the Research and Educational Hospital, University of Illinois. At the age of seven months the child had a bout of "flu," which was accompanied by nausea and vomiting, and she was hospitalized for four days. Following this episode, she was less robust in her eating habits and more selective in her acceptance of foods. No real feeding problem was apparent to the mother until about six weeks to two months before the child's admission to the hospital. During this period she would accept only limited quantities of whole milk, cereals and stewed prepared fruits. Prior to hospitalization, none of the vitamin supplements given to the child had contained any tocopherol. According to the mother, the child had not lost weight prior to entering the hospital; but since the child had a rapidly growing, large tumor mass, with an accumulation of pleural fluid and ascites, her actual body weight, aside from the tumor and fluid, might have decreased considerably.

Two weeks prior to hospitalization the baby began to vomit all feedings uncontrollably. This persisted up to the time of admission on July 29, 1958. During the six weeks of her hospitalization she presented a severe nutritional problem. Her condition became worse; at first she was fed daily through a Levin tube and then finally, from August 20 to September 9 (the day she died), intravenously with 300 cc. of Lipomul®, 250 cc. of Aminosol® (a modified fibrin hydrolysate) and an additional 5 per cent dextrose in water. Lipomul contains 15 per cent cottonseed oil which contains approximately 50 per cent linoleic acid.

In conjunction with the x-ray therapy (1,800 r tumor dose to the abdomen and 1,200 r to the chest), the child was found to have a bone marrow depression which may have been an additional factor in the production of the cerebellar hemorrhages. Her white cell count decreased from 15,000 per cu. mm. on August 29 to 2,150 per cu. mm. on September 8. As already stated, the vitamin preparations which the child had received had not contained any tocopherol.

Necropsy revealed a neuroblastoma of the right adrenal gland with metastases to the retroperitoneal lymph nodes, mediastinal lymph nodes, lower lobe of the right lung and right parietal pleura. There were no intracranial metastases. The brain appeared normal on inspection and section except for the cerebellum which seemed to be softer than normal and reddish, as though not sufficiently hardened. Microscopic examination did not reveal abnormalities in the cerebral hemispheres, but the cerebellum was the site of widespread hemorrhages,

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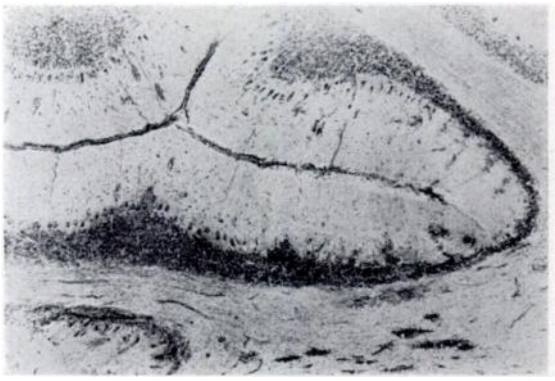

FIG. 1. Cerebellum of chick with vitamin E deficiency. Note that the Purkinje cells have disappeared in areas in which hemorrhages are well developed. Klüver stain.

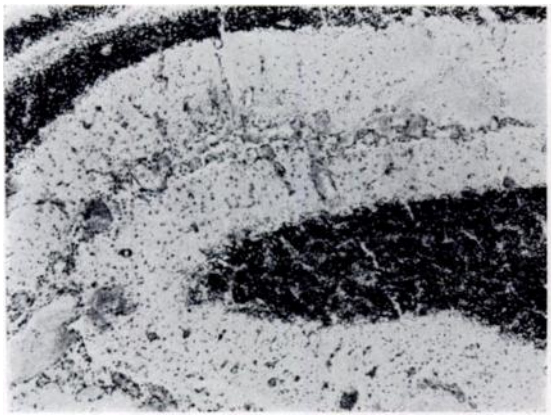

FIG. 2. Cerebellum of infant (Case I). Note hemorrhages, proliferation of endothelium of the capillaries and disappearance of Purkinje cells. Klüver stain.

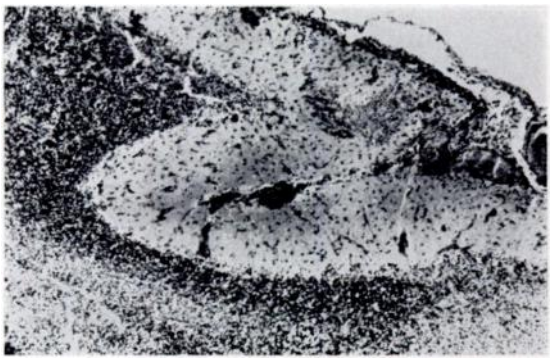

FIG. 3. Cerebellum of woman (Case II). Again, note hemorrhages, prominence of capillaries and absence of Purkinje cells. Klüver stain.

proliferation of the capillaries and absence of the Purkinje cells (Fig. 2).

Since then we have found another patient with a similar pathologic alteration.

CASE II. The patient, an eighty-three year old woman (NA-251-58) at the time of her death, was seen at the University of Illinois, Research and Educational Hospital. She had been fairly well until about a year before admission to the hospital when she lost her appetite, became weak and noticed swelling in her abdomen. Since she lived alone and was admitted to the hospital in a comatose condition, it was impossible to obtain any details concerning her diet. She seemed to have eaten little of anything during the weeks preceding her admission to the hospital and had suffered from recurrent diarrhea.

On admission she could be aroused with difficulty to answer questions. Her abdomen was distended markedly. Her blood pressure was 120/60 mm. Hg. Her serum nonprotein nitrogen level was 64 and rose to 95 mg. per 100 ml. before her death, serum sodium fell to 120 mEq. per. L., serum potassium rose to 6 mEq. per L. and serum carbon dioxide content fell to 16 mEq. per L. She underwent paracentesis, and 4 L. of straw-colored fluid was removed; this contained a total protein of 1.8 gm.; no cells or bacteria were present. She died in coma about three weeks after admission.

Necropsy disclosed cirrhosis of the liver with ascites and pleural effusion, arteriosclerotic heart disease with atherosclerosis of the aorta, pulmonary and coronary arteries and fibrinous pericarditis with effusion.

While she was in the hospital no special therapy was instituted pertinent to our theme, dietary or otherwise. The only information that could be obtained concerning her history was from a stepdaughter who said the patient had lived alone, was "not eating at all" during the last weeks of her life and would not accept the suggestions of those who tried to help her. Although dietary information is lacking, the case is presented here because of the resemblance of the histopathologic alterations in the cerebellum to those in Case I.

Grossly the brain was normal except for some small petechiae visible over the left cerebellar hemisphere. Microscopically pathologic alterations were only found in the cerebellum. In particular there were none in the visceral brain, hypothalamus or midbrain. In the cerebellum, as shown in the microphotograph (Fig. 3), there were numerous small hemorrhages in all layers, with widespread proliferative endarteritis. The Purkinje cells were absent

in most folia and usually shrunken and pyknotic elsewhere. There was some degeneration also in the granular layer and slight demyelination in the white matter.

COMMENTS

Although degenerative changes in the cerebellum are found frequently at necropsy, they are not of the nature found in these two cases. Most commonly the degeneration is of the granular layer,[3] which is associated with many exhausting diseases such as malignancy,[4] gross metabolic disorders such as lipidosis,[5] renal insufficiency,[6] or poisoning with organic mercury compounds.[7]

In hereditary disorders such as the lipidoses,[5] the Purkinje cells may disappear. In heat stroke the Purkinje cells alone drop out.[8] Lately many cases involving degenerative changes in the cerebellum have been reported in association with the administration of large doses of Dilantin.[9,10]

Our cases are different. Although the Purkinje cells disappeared and there may have been some degeneration in the granular layer, other changes appeared which are alien to the aforementioned types, notably hemorrhages and proliferation of small blood vessels. These changes remind one of the findings in Wernicke's encephalitis, an affliction often found in chronic alcoholics due to lack of vitamin B_1 (thiamine).[11,12] In that condition also there is marked hyperplasia and hypertrophy of blood vessels, small fresh hemorrhages, phagocytes containing old blood pigment with necrotic changes in neurones and sometimes slight hypertrophy of astrocytes. However, these changes occur in the mammillary bodies and in the walls of the third ventricle and aqueduct and in the floor of the fourth ventricle. In the cerebellum only type II astrocytes of Alzheimer are found, probably due to associated hepatic disease and, rarely, degenerative changes in the granular layer, probably related to inanition.

It seems possible that the location of the lesions which we have described in our cases is specific for vitamin E deficiency. That similar changes should be produced in two different locations by two different vitamins would be additional evidence of the extraordinary specificity of the metabolism of various centers in the central nervous system.[13,14] The variation of effects produced by different vitamins occurs also in chicks.[15]

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