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Canavan Disease (Spongy Cerebral Degeneration)

- A Case Report -

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= Abstract = **We report a case of Canavan disease in a 6 month-old male Korean baby who presented with aggravating tonic-clonic seizure for 5 days. Pathologic findings could be summarized as follows; increase in brain volume and weight, spongy degeneration in the deep layers of the cerebral cortex and subcortical white matter, and hyperplasia of Alzheimer type II astrocytes throughout the cerebral cortex. Ultrastructurally, there was an abnormal accumulation of fluid in astrocytes and between splitting myelin lamellae.**

Key words : *Canavan disease, Spongy cerebral degeneration, N-acetylaspartic acid, Aspartoacylase*

INTRODUCTION

Canavan disease (CD), or spongy degeneration of brain, is an autosomal recessive leukodystrophy associated with mental retardation, megalencephaly, hypotonia and death, usually in the first decade of life (Globus and Strauss, 1928; Canavan, 1931; Van Bogaert and Bertrand, 1949). It is characterized by spongy degeneration of white matter, and is particularly prevalent in Jewish people of Ashkenazi origin. The first patient with leukodystrophy and N-acetylaspartic (NAA) aciduria due to aspartoacylase (ASP) deficiency was reported by Hagenfeldt *et al.*, in 1987. Matalon *et al.* (1988), correlated aspartoacylase deficiency with CD by finding the characteristic spongy degeneration in brain biopsy of three children with NAA aciduria. This enzyme specifically hydrolyzes NAA to aspartate and acetate. In Korea, still no reported case was found, therefore, we report a typical case of Canavan disease with clinicopathologic study.

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CLINICAL HISTORY

This 6 month-old male baby was brought to Seoul National University Children's Hospital due to aggravating tonic-clonic seizure for 5 days. Seizure was of non-febrile nature and was associated with a mild cyanosis. The seizure developed about 10 times per day and lasted for 3 to 4 minutes. He was born to a 37 year-old

healthy mother by fullterm Caesarean section delivery, and the birth weight was 2.3 kg. His father was 41 years old and he had a 9 year-old elder brother. Family history of neurologic disorders was denied. His sucking was poor and he couldn't control his head. The height, weight, and head circumference were 74 cm (90-97 percentile), 8.5 kg (50-75 percentile), and 46.5 cm (90-97 percentile), respectively. On neurologic examination, consciousness status was lethargic (Glasgow coma scale was E2M3V1). Light reflex and ocular movement were normal. Facial palsy was not noted, and uvular deviation was not observed. The motor power and sensory function were slightly decreased. Laboratory data revealed that hemoglobin 12.5 gm/dl, hematocrit 34.9%, WBC 5,770/mm^3, platelet 556,000/mm^3. Blood chemistry was within normal limits. Twenty four hour urine amino acid analysis revealed increased glutamic acid and glycine up to 83 mol (normal 13-22) and 11,071 mol/gCr (normal 1315-8804), respectively. Arylsulfatase A activity in 24 hours urine was 1.00 mg/24hr urine vol/hr (normal range : 0.36-58. 94 mg/24hr urine vol/hr). Electroencephalogram revealed normal stage II-III sleep record. N-acetyl-L-aspartic acid quantification by gas chromography-mass spectrometry was 53.8 mg/g creatinine (normal range : 19.7 ± 10.8 mg/g creatinin, Canavan disease : typically $>$ 400 mg/g creatinine). Computed tomography (CT) demonstrated symmetrical low density throughout the white matter of both cerebral hemispheres, extending into the core of gyri and the external capsule. Magnetic resonance imaging of the brain showed expansion of the cerebral gyri with a mild enlargement of the ventricle. The white matter showed decreased signal intensity on T1 weighted image and increased signal intensity on T2 weighted image reflecting increased water content probably due to demyelination. The enteric subcortical white matter was involved. And internal capsule, exter-

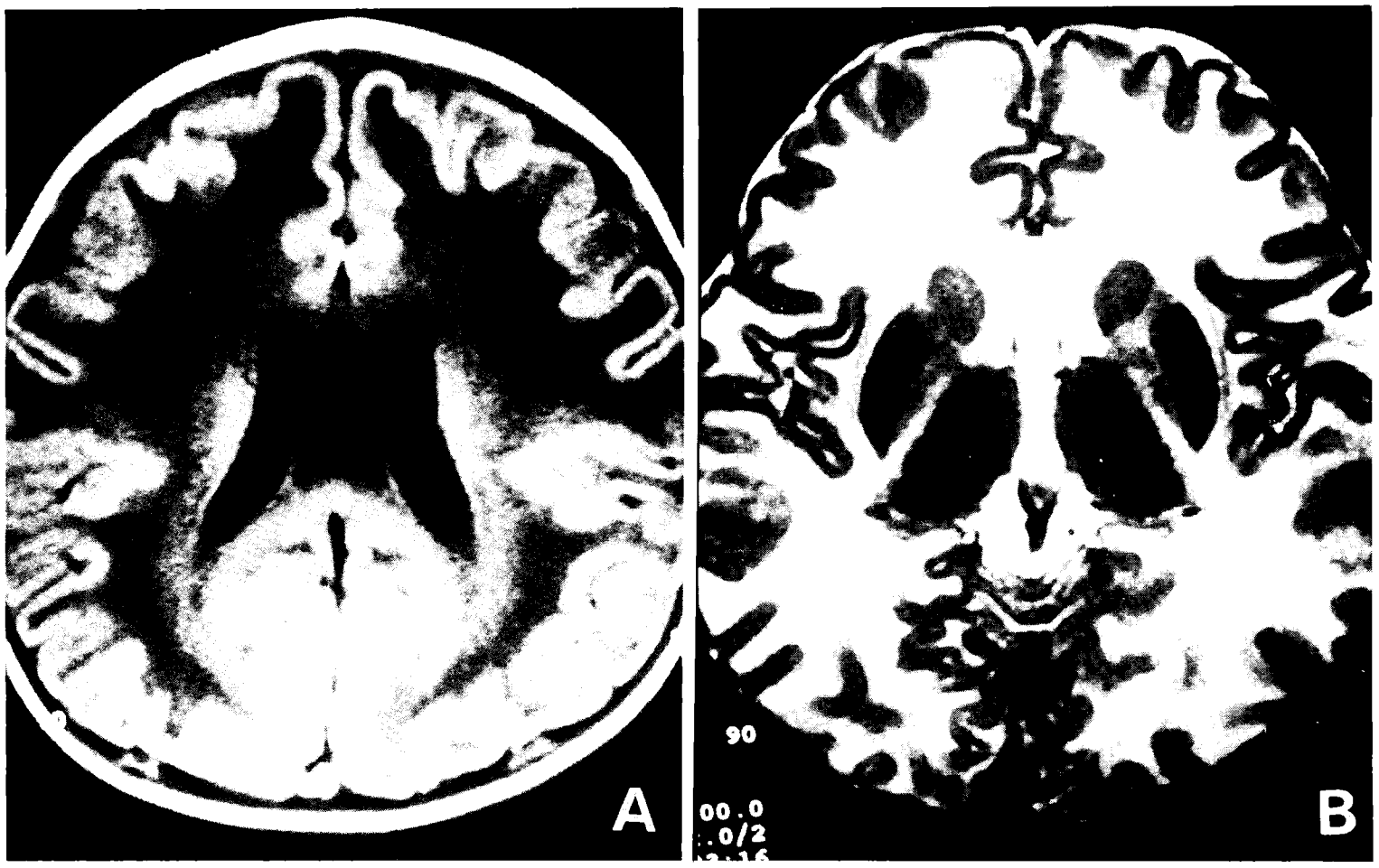

Fig. 1. Brain MRI(A) T1-weighted axial image. (B) T2-wighted axial image. MRI shows extensive white matter demyelination with gyral extension.

nal capsule, and extreme capsule were also involved (Fig. 1). The involved white matter did not show enhancement after contrast infusion.

Proton MR spectroscopy showed relatively high peak of the NAA (N-acetylaspartate) comparing with that of choline in the left deep whit matter (Fig. 2A). The left basal ganglia region revealed nearly equal peak of NAA and choline (Fig. 2B).

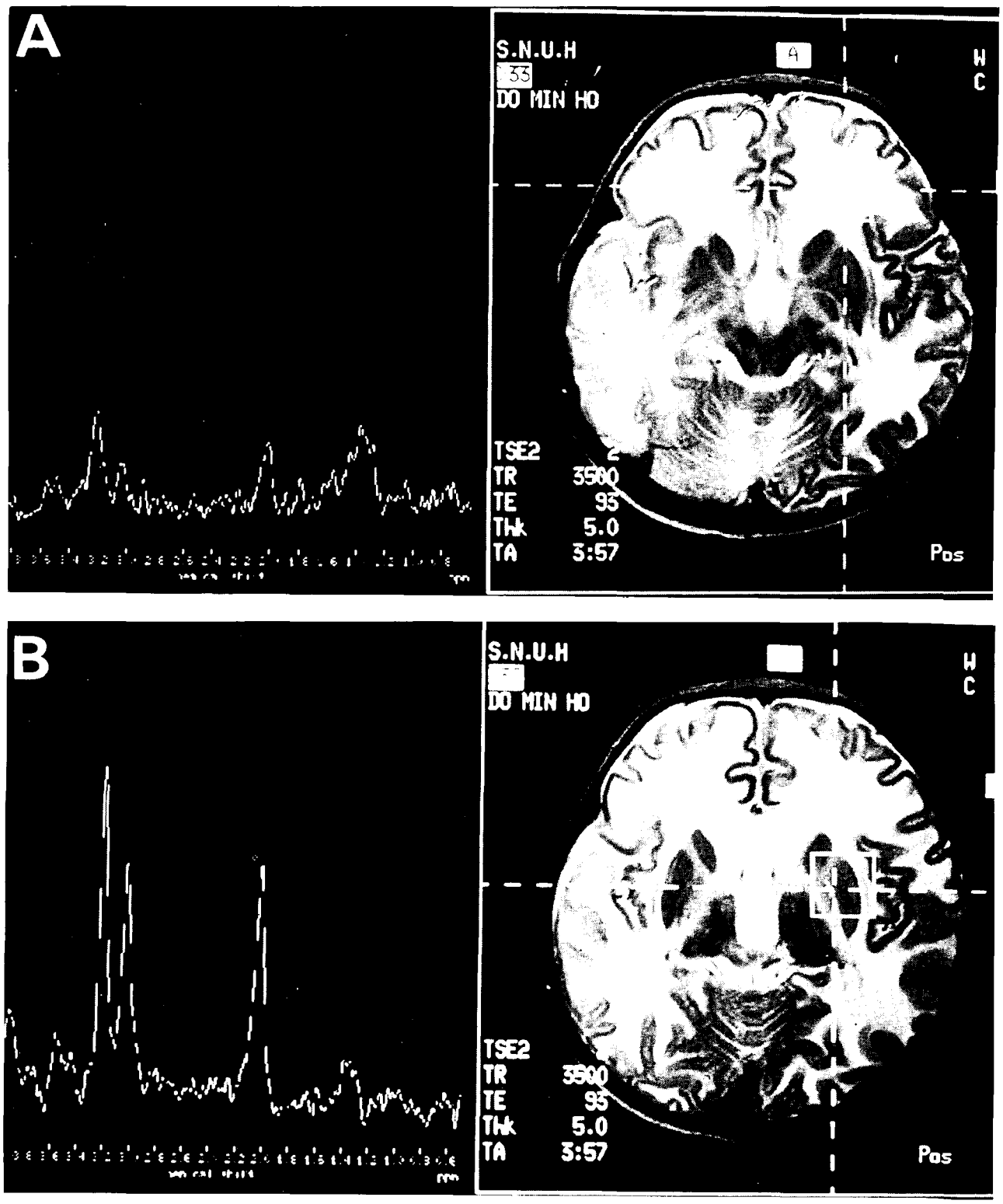

Fig. 2. Proton MR spectroscopy showing relatively high peak of the NAA comparing with that of choline in the left deep white matter (Fig. 2A); Left basal ganglia region reveals nearly equal peak of NAA and choline (Fig. 2B)

PATHOLOGIC FINDINGS

The reviewed specimen was a 1.5×1.0×1.0 cm-sized brain tissue, composed of cortical gray and white matter. The specimen was fixed in 10 % formalin and routinely processed. Hematoxylin & eosin, Masson trichrome, Luxol fast blue and Bodian stains were done. For electron microscopy, specimen was fixed in 2.5% glutaraldehyde solution. This specimen was washed in cold 0.1 mol/L phosphate buffer (pH 7.4) alone and put into 1% osmium tetroxide, buffered with 0.1 mol/L phosphate and embeded in epoxy resin. Sections were cut with ultramicrotome stained with uranyl acetate and lead citrate.

1) Light microscopic findings

The characteristic features were prominent vacuolization of the tissue having a predilection for white matter and diffuse demyelination (Fig. 2 & Fig. 3). The cortex was relatively well preserved. The vacuoles were tightly crowded, rounded or oval. They were optically empty, and no abnormal contents were demonstrable with histochemical reactions in paraffin embeded sections. The long axis of the vacuoles tended to be oriented parallel to the prevailing course of fibers in white matter. The neuronal population of gray matter remained relatively unaffected, but marked astrcytic proliferation, especially of Alzheimer type II astrocytes having vesicular nuclei and scanty cytoplasm, was prominent (Fig. 3 & Fig. 4). Oligodendrocytes presented slight decrease in number. Generally the axons were spared. The neuronal population of gray matter remained unaffected.

2) Electron microscopic findings

Electron microscopic examination revealed alterations in fine structure; intramyelinic accumulation of the fluid and excessive swelling of astrocytes. The swollen astrocytes had enlarged nuclei with sparse chromatin granules. The intramyelinic accumulation of fluid formed empty cystic spaces which were lined with layers of split myelin sheath (Fig. 5).

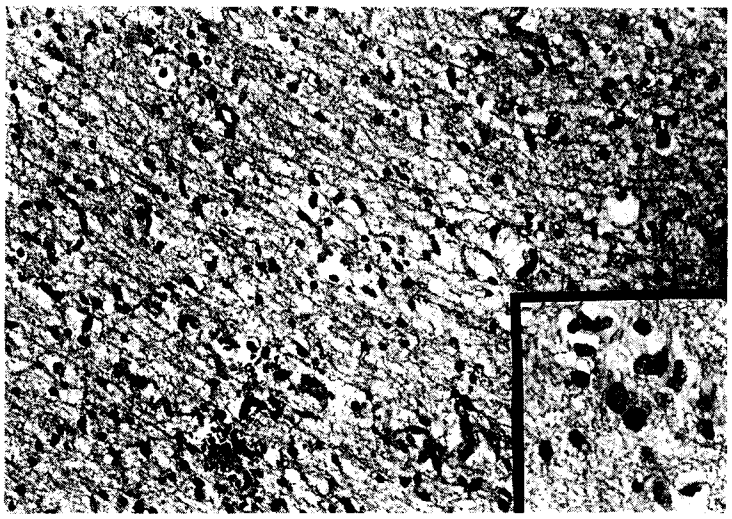

Fig. 3. Spongy degeneration. Vacuoles in the white matter have their axis pararallel to the course of fibers. Inset: Proliferative astroglial cells resembled Alzheimer type II glial cells in their nuclear features and in the absence of cytoplasm.

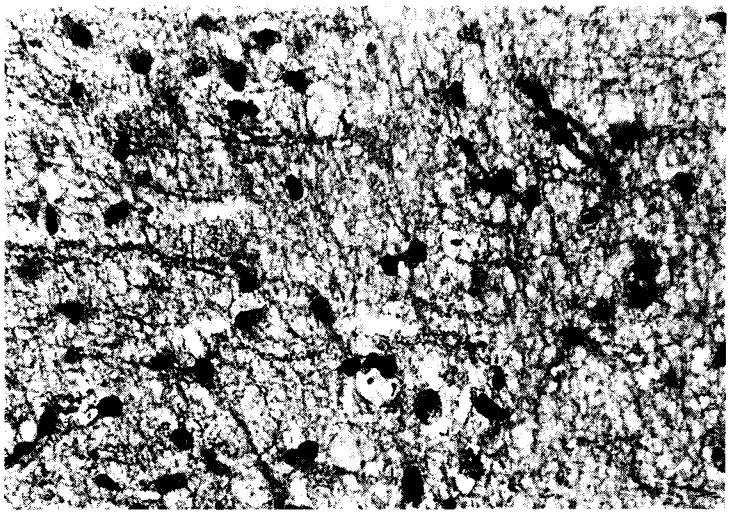

Fig. 4. Marked decrease of myelin fibers in Luxol fast blue stain

DISCUSSON

Canavan disease, also known as spongy degeneration of the brain, was first described in 1928 by Globus and Struss and in 1931 by Canavan. The detailed description of this entity in its current sense was done by van Bogaert and Bertrand in 1949 who reported three Jewish infants. The following reports suggested that the disease is inherited as an autosomal recessive disorder with higher prevalence among people

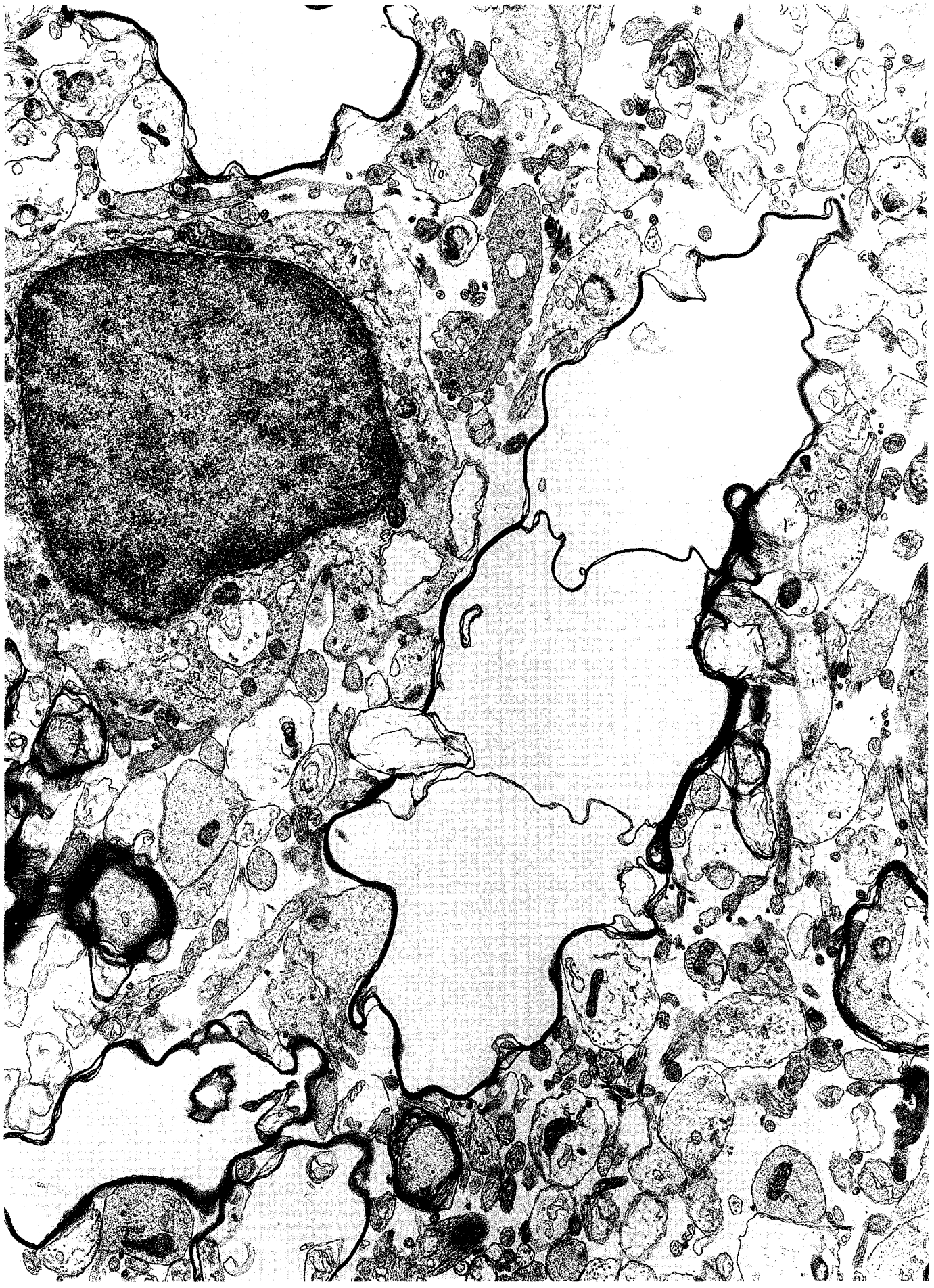

Fig. 5. Large vacuoles form from splitting of myelin sheaths and intramyelinic fluid accumulation

of Ashkenazi Jewish origin (Adachi *et al.*, 1973; Banker *et al.*, 1964; van Bogaert *et al.*, 1967; Buchanan *et al.*, 1965; Ganbetti *et al.*, 1969; Menkes *et al.*, 1985; Sacks *et al.*, 1965; Ungar *et al.*, 1983). Banker and Victor (1979) described 48 Canavan patients, of whom 28 were Jewish. However, Canavan disease has also been reported among other ethnic groups.

Adachi *et al.*, have described three clinical variants of the disease: (a) congenital form in which the disease is apparent at birth, or shortly thereafter; (b) an infantile form that is the most common and in which symptoms manifest after the first 6 months of life; and (c) a juvenile form in which the disease manifests after the first 5 years of life. The diagnosis of Canavan disease can be suggested by the clinical features which include leukodystrophy, megalencephaly, mental retardation and optic atrophy. Death usually occurs in the first decade of life. Further studies to substantiate the diagnosis would include CT and MRI showing a decreased attenuation of cerebral and cerebellar white matter in an enlarged brain with relatively normal ventricle in early stage and nonspecific atrophy in its late stage. However, the most confirmatory and reliable diagnostic measure prior to the discovery of the enzyme defect was a brain biopsy. The characteristic light microscopic features is abundant vacuolization of the tissue having a predilection for certain portions of white matter and cerebral cortex. The vacuoles are usually 5 to 100μm in diameters. No abnormal contents are demonstrable in these vacuoles in both frozen and paraffin-embeded sections. There is no consistent topographic relation between vacuoles and other tissue elements. The vacuolization of the tissue in the cerebral hemispheres is maximal at the junction of cortex and subcortical white matter. It involves the deeper cortical layers, diminishing toward the surface. Oligodendroglial nuclei may be present in normal numbers in the initial phase of the disease, but their number diminishes with its progression. Axons are initially spared, but scattered axonal swelling is noted in the later stage. The neuronal population of gray matter remains unaffected in the infantile form of the disease, but a marked proliferation of astroglia, especially of Alzheimer type II astrocytes is seen, particularly in the cerebral cortex and the basal ganglia. Electron microscopic examination reveals that two types of alterations ; intramyelinic accumulation of fluid and excessive swelling of astrocytes. The swollen astrocytes have enlarged nuclei with sparse chromatin granules and prominent nucleoli. The "watery" cytoplasm contains enormously elongated abnormal mitochondria, which may reach 15μm in length. No mitochondrial changes are seen in cells other than astrocytes. The mitochondria contain a central core of a striated or filamentous matrix composed of fine granules arranged in chains. The intramyelinic accumulation of fluid forms huge cystic spaces that do not contain electron dense material and are lined with the sheaths of adjacent nerve fibers. The vacuoles are formed by the splitting of the sheaths between two major dense lines at the level of the intermediary dense line. Secondary rupture of the myelin leaflets results in communication between the vacuoles and extracellular spaces. This edema is known to be secondary sequence of ion pump dysfunction, resulted in megalencephaly. For diffential diagnosis one has to consider other types of leukodystrophy, as well as neurodegenerative disorders associated with megalencephaly, but apart from Alexander disease, all other disorders can be excluded by proving enzyme deficiency in fibroblast or other peripheral blood cells. For example, the most common leukodystrophies result from known disturbances in the synthesis or catabolism of myelin such as block in the catabolism of sulphatides and of galactocerebrosides, e. g., in metachromatic leukodystrophy or Krabbes disease, or from synthesis an abnormal proteolipid protein in Pelizaeus-Merzbacher disease. The major histopathologic findings of Alexander disease and Canavan disease are the description of massive Rosenthal fibers and spongiosis, respectively. Radiologically, in Alexander disease, demyelination may be associated with predominant and early abnormality of the frontal white matter and in Canavan disease, that is diffuse and symmetric.

The cause of demyelination in Canavan dis-

sease remains obscure. Matalon *et al.*, discovered increased excretion of NAA and aspartoacylase deficiency in CD and D'Adamo *et al.*, & Shigematsu *et al.*, stressed the important role of NAA in myelination. Brain is the only organ where biosynthesis of NAA has been demonstrated and NAA is essential component in a series of reactions required for the conversion of linoceric acid to cerebronic acid, a component of myelin, and formation of glutamic acid. It is synthesized from acetyl CoA and aspartate by L-aspartate-N-acetyl transferase (Patel *et al.*, 1980). It is metabolized to aspartate and acetyl by aspartoacylase, and aspartate is transformed into acetyl CoA by brain acetate thiokinase. Acetyl CoA is essential for membrane lipid synthesis. Increased NAA level in urine and the deficiency of aspartoacylase in skin fibroblasts are the most reliable diagnostic factors in CD. Thus prenatal diagnosis is possible as a preventive measure in affected families by demonstration of decreased aspartoacylase activity using either amniocytes or chorionic villi biopsy (Matalon *et al.*, 1989).

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