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FARBER'S DISEASE (DISSEMINATED LIPOGRANULOMATOSIS): THE FIRST CASE REPORTED IN JAPAN

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Abstract. We report the first case in Japan, *i.e.*, the first case among oriental subject of Farber's disease. This is a rare disorder of lipid metabolism in infancy subsequent to a genetically-determined defect in ceramide degradation. Main features are characterized clinically by hoarseness, joint swelling, subcutaneous nodules and retarded psychomotor development. Lipid analysis and pathological investigation on the material obtained from a subcutaneous nodule confirmed clearly the presence of ceramide and intracytoplasmic inclusion bodies characteristic for Farber's disease. In this case, we experienced also corneal opacity and striking abnormalities in electroencephalogram, which have apparently not been noticed in the 17 cases hitherto reported.

Key words: Farber's disease, shpingolipid metablism, infancy.

Farber's disease is an inherited disorder of shpingolipid metabolism and can be included in the group of mucolipidoses (1) in a broad sense; it is characterized clinically by hoarseness, joint swelling, subcutaneous nodules, retarded psychomotor development and other minor findings, all of which appear in the early stage of infancy. This is an extremely rare disease and has been reported in a total of 17 cases (2) since Farber described his first case in 1952 (3). We would like to report herein the first case in Japan which was confirmed clinically, pathologically and biochemically.

CASE PRESENTATION

Fetal movement during the pregnancy and birth were normal, being 3,600 g of the body weight at birth. Soon after birth, his mother noticed hoarseness and

rather prolonged suckling time (Fig. 1). After progress from social smile at the 2nd month, head control at the 4th month and turning over in bed at the 5th month to sitting alone at the 8th month, further motor development apparently ceased. The body weight, however, increased to 6,200g at the 4th month and 8,500g at the 8th month, being almost within normal ranges. At the age of 1 year, the baby developed fever of 40°C for several days, and had a treatment under the diagnosis of pneumonia. At 1 year and 2 months old, he suffered from measles which was controlled uneventfully. Afterwards, however, once or twice a month he developed fever with coughing and stridor lasting for 2–3 days. Due to gradual loss of weight, hypotonus of the four extremities and incapable sitting alone and head control, at the age of 1 year and 5 months the patient was admitted to a local community hospital. He then was treated under the diagnosis of pneumonia, and gained his body weight to a certain extent. On the other hand, the patient manifested lowering deep reflexes, corneal opacity, swelling of hand and foot joints and increasing amount of protein, *i.e.*, albuminocytologic dissociation, in cerebrospinal fluid. At the age of 1 year and 7 months, he was transferred to the Department of Pediatrics, Okayama University Hospital, for further examination and therapies (Fig. 1).

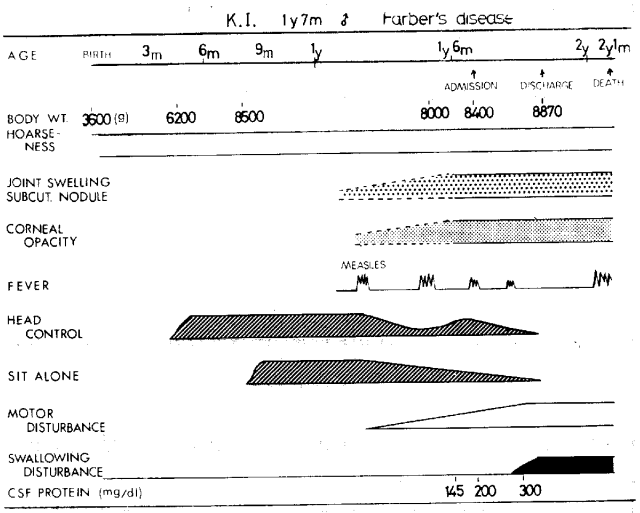

Fig. 1. Clinical course illustrating major signs and symptoms during the period of birth to death at the age of 2 years and 1 month.

As to the family status, a rather heavy consanguinity was characteristic; the patient's father and mother were Japanese and also in a relationship of the 1st and 2nd cousins, respectively (Fig. 2). The paternal grandfather had diabetes mellitus. Baby's father had neurofibromas on the hand dorsum, and café-au-lait

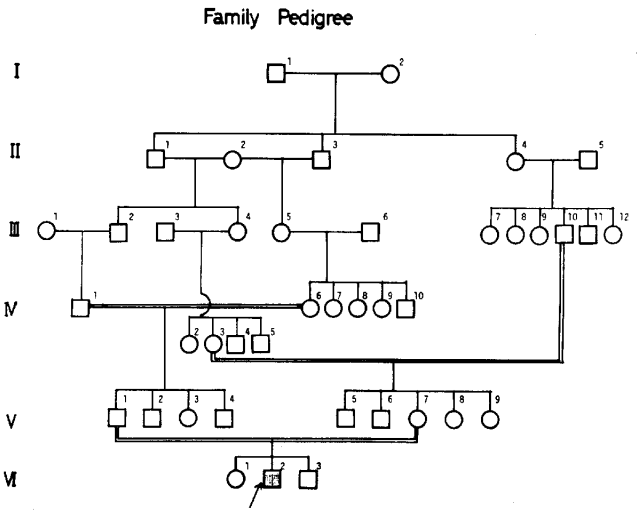

Fig. 2. The family pedigree; an arrow and Roman numerals indicate patient himself and generations, respectively.

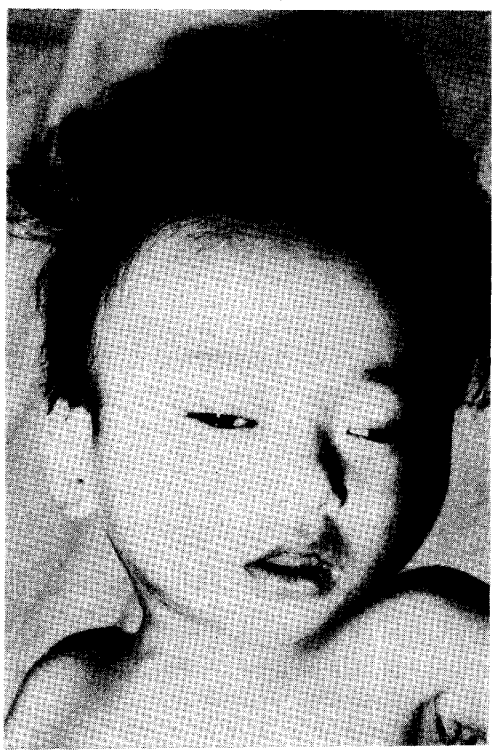

Fig. 3. The face showing rather poor facial expression and broader forehead than usual.

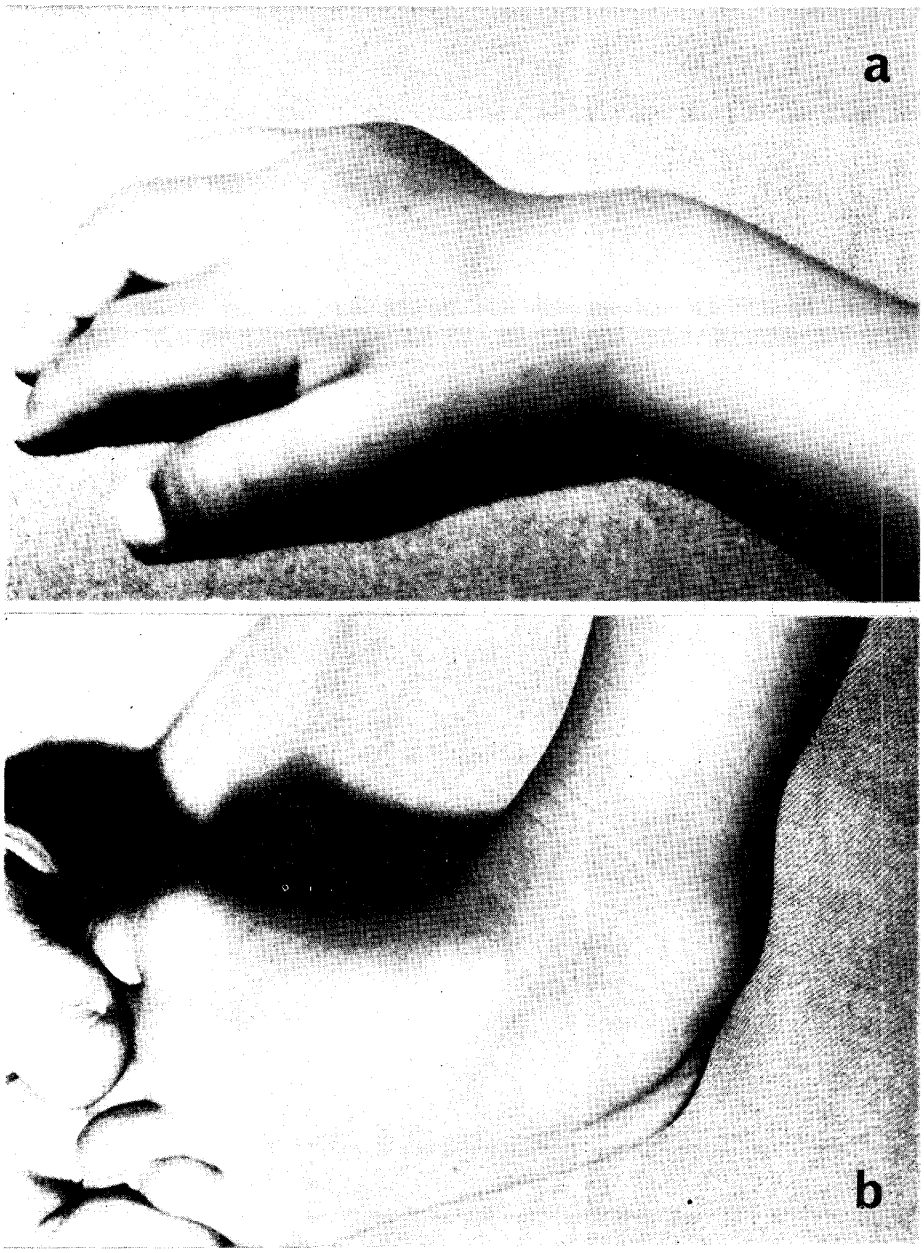

Fig. 4a. The right hand showing deformed wrist joint, swollen matacarpophalangeal joints and flexion contracture of proximal interphalangeal joints.

Fig. 4b. The left foot showing nodular swelling of ankle joint.

spots were present in paternal grandfather, father and an elder sister aged 4.

On the admission, the body length and weight were 79 cm and 8,400 g, respectively. The baby's facial expression was rather poor, although he responded with cry and smile to pain and dandling, respectively. He spoke only a few words, recognized his mother most fondly, and showed some interest towards toys which made a noise. His crying was rather weak with hoarseness and stridor. There was generalized muscle hypotonus, although the upper part of the body was somewhat prominent as compared to the lower part, with unstable head control and sitting alone lasting only several minutes. He was brachycephalic with frontal prominence and rather broader forehead than usual (Fig. 3). There was generalized lymphadenopathy measuring up to adzuki-bean size at the occiput, neck and axillae. Liver was palpable 1 cm below the right costal margin with normal consistence, whereas the spleen not palpable. Otherwise, the heart, chest, abdomen, umbilicus and external genitalia were nothing particular.

As to the four extremities, bilateral wrist joints were deformed due to swelling of the extensor tendon sheats, both metacarpophalangeal joints were swollen, and the proximal interphalangeal joints of both middle, ring and small fingers had a flexion contracture (Fig. 4a). Likewise, the articular capsule of both knee and ankle joints, extensor tendon sheaths of the ankle and metacarpo-

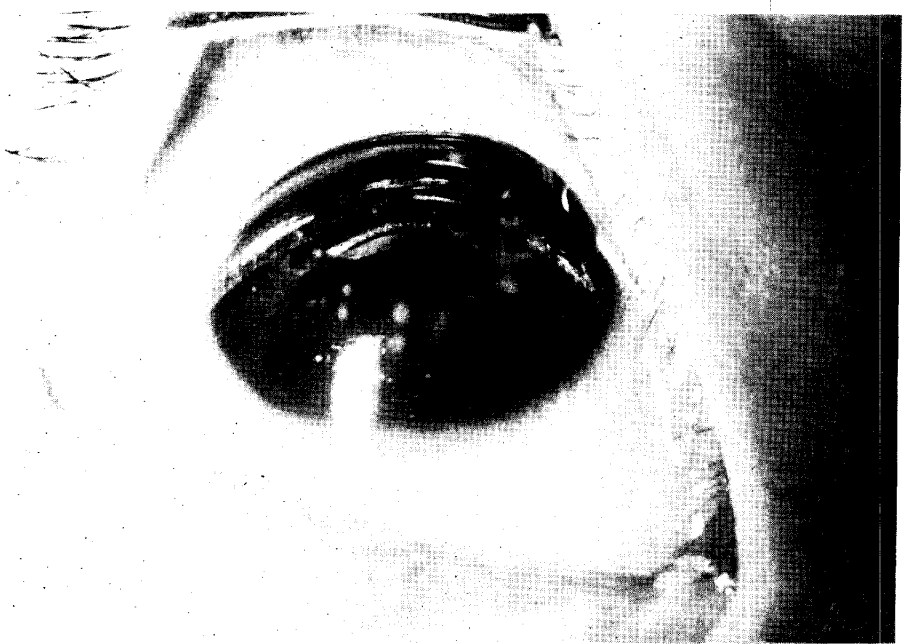

Fig. 5. The right eye with several sharply-defined white patches on the cornea indicating nodular corneal opacity.

phalangeal joints of the foot were swollen (Fig. 4b). Roentgenologically, the bones around the wrist and knee joints were slightly osteoporotic, though no bone destruction, and the periarticular density of the metacarpo- and inter-phalangeal joints in both hands was increased. No other bones or joints showed any particular abnormalities.

Neurologically, both pupils reacted promptly to light without anisocoria. There was bilateral nodular corneal opacity (Fig. 5) with impaired corneal reflex. In both optic fundi the central foveas were weakly reddish, though no cherry-red

TABLE 1. LABOLATORY DATA ON THE PATIENT WITH FARBER'S DISEASE

Blood picture	
RBC	$460 \times 10^4/\mu l$
Ht	37%
Hb	9.8 g/dl
WBC	9,750/μl
Differentials	Seg 46, Eo 6, Ly 45. Mo 3 (%)
Myelogram	normal
ESR	37 mm/hr
CRP	(±)
CPK	normal
LDH	normal
Serum protein	
Total protein	6.6 g/dl
Albumin	3.7 g/dl
Globulin	2.9 g/dl
Lipids	
Triglyceride	94 mg/dl
Cholesterol	184 mg/dl
Phospholipid	189 mg/dl
Free fatty acid	455 μEq/l
Urine	normal
Cerebrospinal fluid	
Initial pressure	125 mmH_2O
Cell count	4/3
Sugar	64 mg/dl
Protein	200 mg/dl
Immunological data	
NBT test	normal
CH50	48
RA	(−)
ANF	(−)
Ig G	1,320 mg/dl
Ig A	64 mg/dl
Ig M	246 mg/dl
T cells	74.2%
PHA blastogenesis	75%
Chromosome	46XY

spots were present. Gag reflex was rather weak although no swallowing disturbance, and the tongue showed fasciculation despite no apparent atrophy. All the deep tendon reflexes, except for increased Achilles reflex, were decreased markedly or disappeared entirely. The abdominal reflex was demonstrated weakly. No other pathological reflexes, including Babinski and patellar or ankle clonus, were present.

Among laboratory data (Table 1), protein in cerebrospinal fluid was increased to an unusually-high level. Serum lipids were all within normal limits. In electromyogram, the maximum conduction velocity of the right tibial nerve was decreased (26 m/sec). However, synchronization and fasciculation voltages were not detected; this indicated damaged lower motor neurons, although it was not clear if there was any disturbance in the anterior horn cells.

Regarding electroencephalogram, while awoke, the basic pattern was dominated by dysrhythmic, 4–7 per sec, irregular slow waves with low to medium voltage and without noticeable alpha rhythm. Besides these waves, diffuse, but posterior-dominant, 2.5–3 per sec, irregular slow wave bursts of high voltage appeared with a periodic tendeney. During the stage 1 of natural sleep, one noticed spike-and-wave complex and high voltage slow wave bursts, which were diffusely distributed, irregular in their shapes, of 2–3 per sec of frequency and observed periodically; a burst-burst interval was approximately 10–11 sec (Fig. 6). Computed transaxial tomographic scanning of the brain revealed mild to moderate dilatation of the ventricles and subarachnoid space, indicating a diffuse brain atrophy.

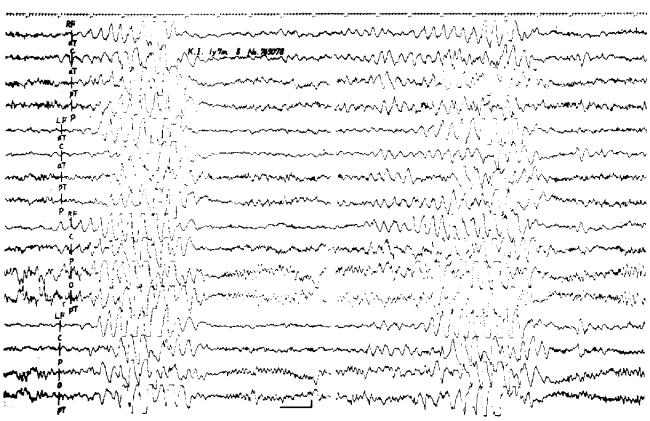

Fig. 6. Electroencephalogram during the stage 1 of natural sleep showing irregular, 2.5–3 per sec, high voltage slow wave bursts with periodic tendency; the averaged amplitude of each burst is 200–300 μvolts and acompanied by spikes. (A calibration indicates 1 sec and 50 μvolts.)

A granulomatous lesion at the left ankle (Fig. 4b), which derived from thickened tendon of the extensor digitorum longus muscle, was biopsied for biochemical and histological studies. For biochemical study, *i.e.*, lipid analysis using thin-layer chromatography, the obtained material was developed with a solution consisting of chloroform and methanol in 19 : 1 v/v of ratio and sprayed on silica gel plates with a solution consisting of sulfuric acid and postassium bichromate. The patient's material was proved to contain a signifiantly-large amount of ceramide, since this showed the spot at the same Rf value as the authentic ceramide (Fig. 7). Patient's urine failed to show such a spot. Histologically, the granuloma consisted of a massive proliferation of foamy to spindle-shaped cells among hyalinized collagen fibers (Fig. 8). Histochemically, these spindle-shaped cells contained the substance positive for periodic-acid-Schiff and acid mucopolysaccharide stainings. And electron microscopically, these cells were found to be filled with very unique inclusion bodies which were made up of so-called curvilinear tubular structures (4). The pathological studies will be

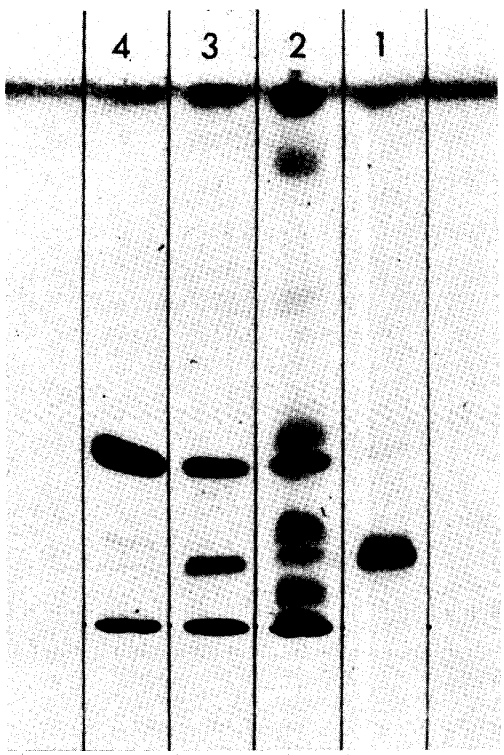

Fig. 7. Thin-layer chromatogram for lipid analysis showing ceramide in patient's biopsied material from the left ankle. 1: authentic ceramide; 2: patient's urinary sediment; 3: patient's biopsied material; and 4: control cerebrocortex.

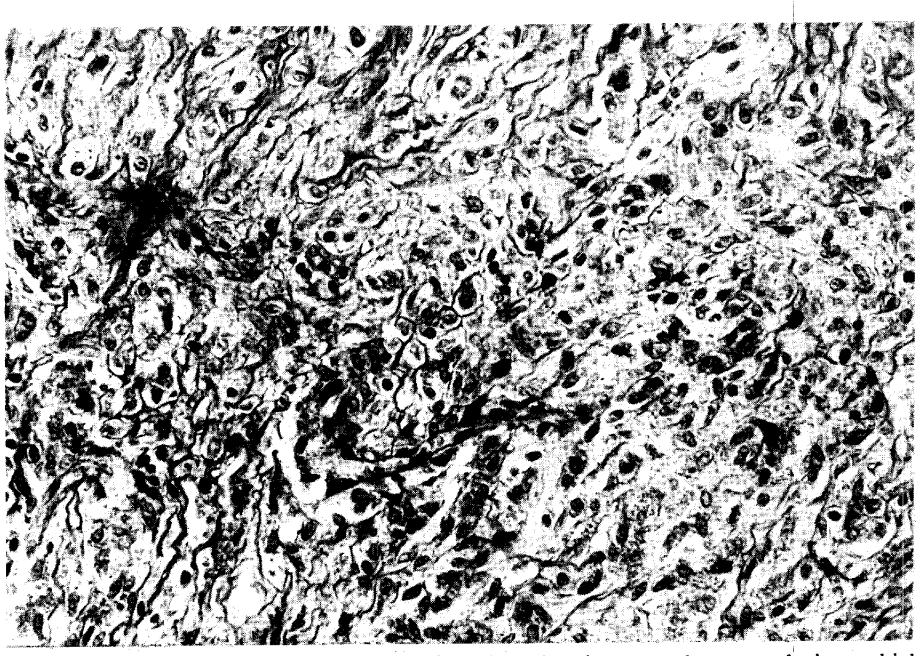

Fig. 8. Biopsied material from the left ankle showing granulomatous lesion, which consists of proliferating foamy to spindle-shaped cells among hyalinized collagen fibers. Hematoxylin-eosin, ×400.

published elsewhere more in details.

During the admission for 3 months (Fig. 1), head control, sitting alone and speaking a few words became gradually incapable, wheras hoarseness and low-pitched voice became more marked than before admission. Motor disturbance of the four extremities progressed also gradually, and Achilles tendon reflex previously increased shifted from normal to decrease. Subcutaneous nodules measuring 1.5–2 cm in diameter at the occiput and tumorous lesion at the right hand dorsum were increased in their size. Protein in cerebrospinal fluid ranged from 150 to 300 mg/dl (Fig. 1). Since aspiration pneumonia occurred, at the age of 1 year and 9 months, due to increased bronchial secretion, nasal tube-feeding had been maintained. In the beginning of 1 year and 10 months old, he was discharged because of domestic circumstances.

When the patient was 2 years and 1 month old, he developed fever of 38.0°C for several days with increased sputa, tachypnea stridor, and expired; the cause of death could be attributed to tracheal obstruction by massive sputa. Approximately 12 h after the death, owing to the family's request, only limited necropsy was made, including whole spleen and a partial removal of the liver, lung and abdominal skin.

DISCUSSION

Prensky *et al.* (5) reported ceramide deposit in various organs with Farber's disease, and Sugita *et al.* (6) proved a marked deficiency in acid-ceramidase activity in the kidney and cerebellum. Since then, the Farber's disease has been regarded to be a disease of abnormal lipid metabolism subsequent to a genetically-determined defect in ceramide degradation.

Our present case had suffered from low-pitched voice and hoarseness immediately after the birth, repeated respiratory infections during his life and progressing psychomotor disturbance since 8 months old, and apparently died of respiratory ailment at the age of 2 years and 1 month. When he was 1 year and 5 months old, periarticular nodular swellings were pointed out, together with increased protein level in cerebrospinal fluid. Lipid analysis and pathological investigation on the material obtained from one of these nodular swellings identified clearly the presence of ceramide and intracytoplasmic inclusion bodies characteristic for Farber's disease.

When we compared this case with the cases previously reported, corneal opacity and abnormalities in electroencephalogram were most striking, for so far we have not noticed the two findings in these cases (7, 8, 9). As far as eye lesions were concerned, blindness (10), xanthoma-like growth of eyelids (7) and cherry-red maculae (11) have been described previously. In our case, visual following as well as acuity were normal in spite of the presence of nodular corneal opacity in both eyes. This may have been caused by accumulated ceramide in the cornea. Among electroencephalographic abnormalities in this case, the presence of periodic bursts was most interesting. This phenomenon is defined by a stereotyped recurrence of almost similar paroxysmal and synchronous discharges with relatively constant intervals; and the mechanism of its manifestation has been considered as a combined involvement of both cortex and subcortical structure (12, 13). Therefore, neurophysiologically, the presence of the periodic burst in the Farber's disease may well suggest the existence of neurological lesions involving not only the cortical but subcortical matters rather diffusely. Although this phenomenon was said to be rather pathognomonic to the patients with subacute sclerosing panencephalitis (14, 15), recently similar finding has been observed among a few other diseases, such as herpes-simplex encephalitis.

Farber's disease appears to be inherited through the autosomal recessive gene. Cultured fibroblasts derived from the skin with Farber's disease had markedly decreased acid-ceramidase activity, and fibroblasts from his parents contained the activity of approximately one half the mean of normal control values. Thus far, it has been suggested to utilize the cultured fibroblasts in order to determine a carrier and to make prenatal diagnosis (2). Since the parents of our

case were of a close consanguinity, they were presumed to be carriers for Farber's disease. Unfortunately, however, we were unable to secure family's consent to obtaining a skin fragment for tissue culture.

As stated before, intensive pathological as well as enzymological investigations on this patient are currently in progress and will be reported elsewhere. At the same time, the details as to how we differentiated similar disorders, such as mucopolysacchridosis, from the present case will be also discussed.

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