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Membranous Lipodystrophy

A Case Report

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Summary. The case is described of a 35-year-old housewife diagnosed as having membranous lipodystrophy (as described by Nasu et al. in 1970 and called lipomembranous polycystic osteodysplasia by Hakola in 1972). The main symptom of this patient was a slowly progressive dementia. Skeletal symptoms were not seen. The computerized tomogram of the brain showed calcification of bilateral basal ganglia and the plain roentgenograms of the bones revealed cystic radiolucent areas at the distal end of the bones of the patient's extremities. Histological examination of the curetted material from the right talus revealed a 'membranocystic' pattern. The fatty tissue curetted from the cyst of the talus and the lysosomal enzymes of the white blood cells were biochemically normal. A possible relationship between this disease entity and connective disorders is considered.

Key words: Membranous lipodystrophy – Lipomembranous polycystic osteodysplasia – Calcification of basal ganglia – Dementia – Enzyme deficiency

Zusammenfassung. Klinische und histologische Befunde des Knochens bei einer 35jährigen Hausfrau mit membranöser Lipodystrophie (Nasu) oder lipomembranöser polycystischer Osteodysplasie (Hakola et al.) wurden beschrieben. Hauptsymptome der Patientin war progressive Demenz. Knochensymptome waren bis jetzt nicht bemerkt. Das Computertomogram des Gehirns zeigte Verkalkung der Basalganglien beiderseits. Multiple cystische Herde wurden auf dem Röntgenogramm der Beine dargestellt, und membrano-cystische Struktur wurde im Knochenmark des Talus mikroskopisch gefunden. Die chemische Analyse der Fettsäure des Talusknochenmarkes und Lysosomenzyme der weißen Blutkörperchen enthalten keine spezifischen Befunde. Mögliche Beziehung zwischen membranöser Lipodystrophie und Bindegewebserkrankungen wurde diskutiert.

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Schlüsselwörter: Membranöse Lipodystrophie – Lipomembranöse polycystische Osteodysplasie – Verkalkung der Basalganglien – Demenz – Enzymdefekt

Introduction

Membranous lipodystrophy is a disease that was first described by Nasu et al. (1970) from a pathological view point. Similar conditions were simultaneously and independently described in Finland as hereditary polycystic osteodysplasia associated with sclerosing leucoencephalopathy (Sourander 1970; Hakola et al. 1970) or lipomembranous polycystic osteodysplasia (Hakola 1972). Membranous lipodystrophy in Japan is now considered to be the same disease as lipomembranous polycystic osteodysplasia and the other related conditions described in Finland. Besides Japanese and Finnish patients, a recent report described an American patient with membranous lipodystrophy (Colin 1978).

Hakola (1972) published a monograph dealing with details of the clinical features of this condition. In the majority of cases, skeletal symptoms preceded neuropsychiatric symptoms. Histological examination showed an accumulation of peculiar undulating membranous structures in the affected bone marrow and sudanophilic or sclerosing leucodystrophy in the brain. Nasu (1973) proposed that the disorder might result from a hereditary impairment of systemic lipid metabolism, but this has not yet been ascertained.

Results of some clinical, biochemical and pathological investigations in a patient with membranous lipodystrophy are reported in this paper.

Case Report

A 34-year-old housewife first attended our clinic in August 1979, presenting with the complaint by her family that she had been unable to do housework for the preceding 6 months. Her parents were consanguineous and a younger sister of her mother, aged 58, had been in a psychiatric hospital for 12 years, diagnosed as a chronic schizophrenic. The patient had three siblings and two children who were all healthy. After graduation from high school, she worked as a store clerk until she got married at 23 years of age. She had her first son at the age of 23 and the second at the age of 27. She had no apparent abnormalities during the pregnancies or deliveries. She had been in good health until her family noted, when she was 33 years old, that she gradually became incompetent at looking after the house and family: she cooked the same meals every day, she did not clean, she did not care about neighbourhood associations and yawned and dozed frequently even in the daytime.

When she was brought to our clinic by her family on 7 August 1979, she seemed awkward, distracted, restless, indifferent to her surroundings and somewhat childish and euphoric. She showed a serious change of her personality due probably to chronic organic brain syndrome. However, her orientation, capacity of calculation and common sense were relatively well preserved. Her IQ was below 60 (WAIS, Verbal IQ: 60, Performance IQ < 60), with a mental age of 5 years and 4 months (Owaki's method). Testing of related word-pairs (Miyake's method) revealed marked impairment of recent memory imprinting (first try 1/10, second 2/10 and third 2/10). She scored 92 points on the Bender-Gestalt Test. Rorschach test showed 5 organic signs. Her height was 150 cm and her weight 54.5 kg. She was slightly obese and had no physical abnormality except for a minor anomaly of the uvula. An ECG was normal. Neurological examination revealed hyperreflexia of the jaw jerk and deep tendon reflexes, more exaggerated on the left side. Bilateral Babinski reflexes were positive. Slight atrophy of the optic disc was observed.

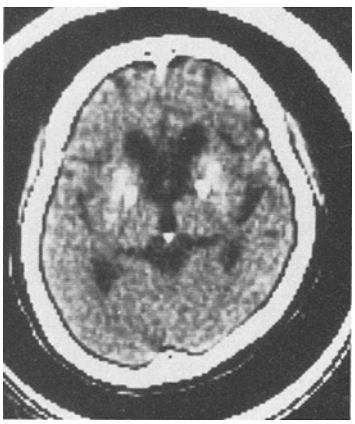

Fig. 1. Brain CT showing moderate cerebral atrophy and calcification of the bilateral basal ganglia

She could not understand the rules of our ward and she exhibited some unusual behaviour which embarrassed the nursing staff: she watered flowers in the garden whilst it was raining, took food from other patient's trays, wore heavy clothes in the warm ward, washed a single pair of slacks on the high water level of a washing machine. Tiny particles, such as hair or waste threads strongly captured her attention and she was occupied with picking them up, preventing her from performing her work. Other conspicuous features included her peculiar manner of speech: she used stereotyped phrases in a high-pitched voice.

Routine laboratory analyses of blood and urine were all within normal limits, except for a slight decrease in urinary inorganic phosphate. Phosphate tubular reabsorption rate was 89.3%. The EEG showed sporadic theta activity of 5–6 Hz suggesting diffuse cerebral hypofunction without background asymmetry or paroxysmal pattern. On admission CSF contained 1 lymphocyte per μl and 123 mg/dl total protein. The total protein value later returned to within the normal range, 21–37 mg/dl. Computerized tomography (CT) of the brain showed dilatation of all ventricular systems and cortical sulci suggesting moderate brain atrophy. The most conspicuous finding on CT was the calcification of bilateral basal ganglia in the putamen, the globus pallidus and the capsula interna (Fig. 1). No decreased density area could be found in either the grey or the white matter.

Roentgenographic examination revealed radiolucent cystic lesions in the distal portion of the extremities; carpal, metacarpal, tarsal, metatarsal and phalangeal bones (Figs. 2, 3). The distribution of the lesions was symmetrical. No roentgenographic abnormality was found in the skull, the spine or the pelvis. The scintigraphy of the brain ($^{99m}TcO_4^-$) and the bone (^{99m}Tc-MDP) showed no abnormal collection of the isotope. The conduction velocity of peripheral nerves and EMG studies revealed no abnormalities.

There were no remarkable changes in levels of ANF, CH-50, RA-T, RAHA etc., related to immunological and connective tissue disease. The serum lipids were normal, although the percentage of pre-β-lipoprotein showed slight elevation (32.1%). The total serum protein was normal, but electrophoresis revealed a relative increase of α_1-globulin (4.3%). Serum immunoglobulins were all within normal limits.

Endocrinological investigations showed serum parathormone to be in the normal range (0.48 ng/ml), and other serum hormones such as T_3, T_4, TSH and corticosteroids were also within normal limits. A 50 g glucose tolerance test showed a normal pattern. The effects of insulin and thyroid releasing hormone on growth hormone and prolactin were normal. The lysosomal enzymes of the white blood cells showed no abnormal deficiency (Table 1). The glycoprotein concentration in urine was measured and there was no significant difference between that of the patient and the control.

Microscopically a biopsy specimen of skin from the right hip showed no change in epidermis, dermis or hypodermis. No specific change, such as demyelination, was found in the specimen of the left sural nerve.

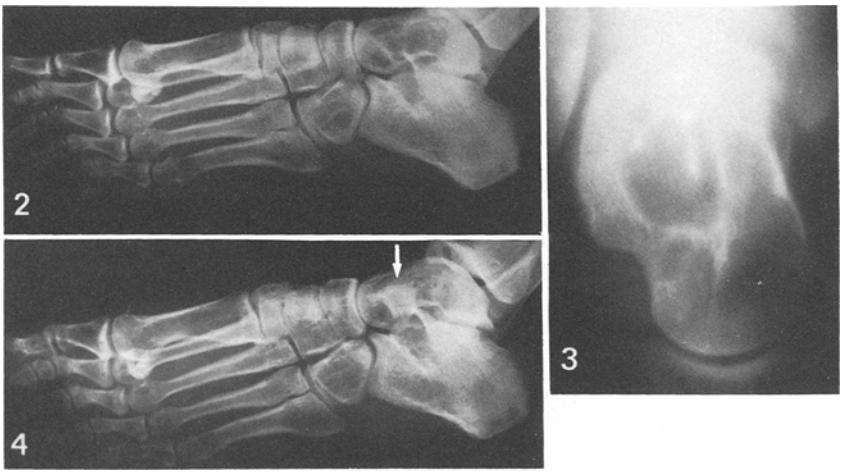

Fig. 2. Roentgenogram of the right foot showing radiolucent cystic lesions in the tarsal, metatarsal and phalangeal bones

Fig. 3. The cystic radiolucency with trabeculae of the right talus can be better seen in a plain tomography film

Fig. 4. The grafted bone was still intact in the talus about one year after the operation (↓)

Table 1. Lysosomal enzymes of white blood cells

	nmol/mg protein/h	Normal range
β-D-galactosidase	74.0	(51 –92)
α-D-galactosidase	36.8	(21 –56)
β-D-glucosaminidase	1020	(606 –1116)
β-D-glucuronidase	72.8	(6.7–70)
α-D-mannosidase	95.5	(27 –151)
α-L-fucosidase	19.6	(29 –43)
α-D-glucosidase	18.2	(9 –21)
β-D-glucosidase	11.1	(5 –19)
Arylsulphatase A	105.8	(58 –91)

These analyses were performed at the Department of Neurology, Neurological Institute, Kyushu University (Courtesy Dr. I. Goto)

Pathological and Chemical Findings of Bone Marrow

Curetting and bone-grafting of the right talus was performed on 30 January 1980. On surgical exploration, there was no change in the skin, the articular capsule or the surface. The cortex of the bone was thin. The cyst of the bone was easily opened and was filled with yellow gelatinous material and fluid. The inner surface of the cyst was smooth.

Microscopically, the fat cells and other cell components were decreased in number. The lesion was composed mostly of both membranous structures and amorphous or granular substance. The membranous structures were eosinophilic and formed clusters of varying sizes. By special staining techniques such as PAS and luxol fast blue, the membranous structures became more prominent (Fig. 5). Using electron microscopy, these structures were found to be in contact with neutral fat existing in the inner cavity and consisted of an accumulation of minute tubular structures and amorphous granular material (Fig. 6).

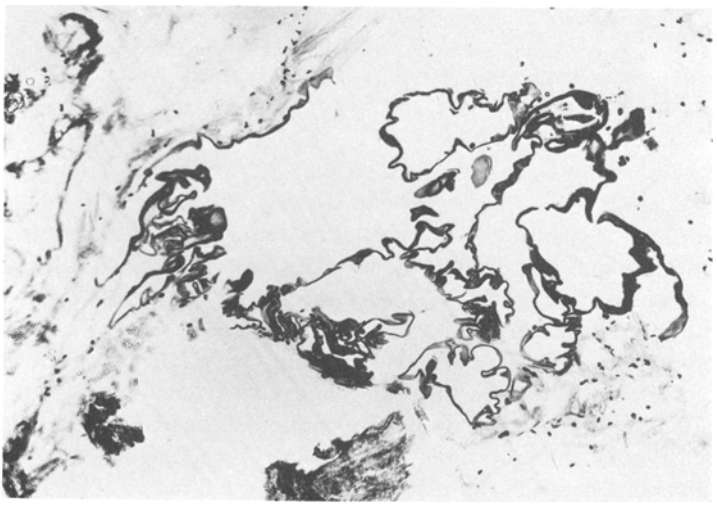

Fig. 5. A characteristic membranous structure of varying size observed in the curetted material from the right talus. LFB, × 118

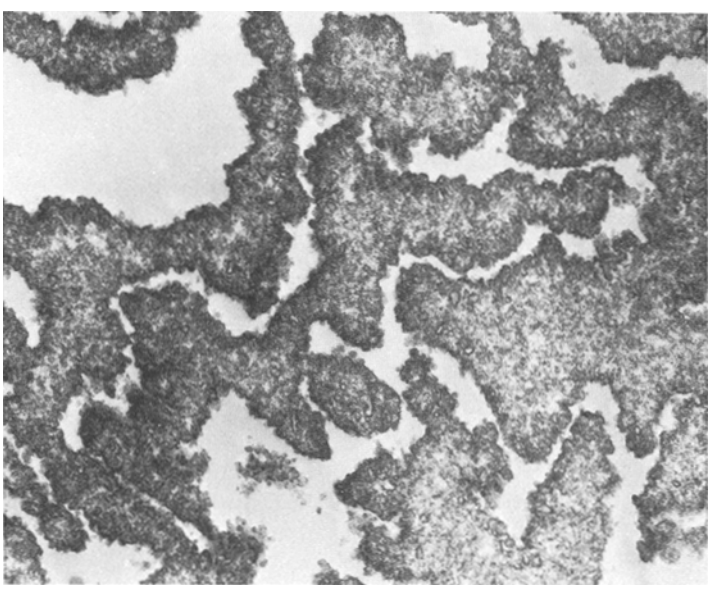

Fig. 6. Electron micrograph of the membranous structure in the talus. The undulating membrane was in contact with neutral fat existing in the inner cavity and consisted of minute tubular structures and amorphous granular material. × 17,000

The composition of fatty acids in the hypodermis, sponge bone and bone marrow of this patient showed no remarkable difference from that of the control and there were no abnormal peaks.

Course of her Illness

In February 1981, about one year after the operation on the right talus, the grafted bone was alive and showed no reabsorption, deformity or fracture (Fig. 4). Her mental function had been gradually deteriorating and she was unable to do any housework at all.

Discussion

Skeletal symptoms such as pain and pathological fracture are usually observed prior to the manifestation of neuropsychiatric disturbances in most cases of membranous lipodystrophy (Hakola 1972; Akai et al. 1977). In this patient, however, the mental deterioration preceded the skeletal symptoms. Several cases of membranous lipodystrophy with no skeletal symptoms have been reported in Japan (Hanawa et al. 1981), but the distinct diagnosis of membranous lipodystrophy is impossible without histological confirmation of the membranocystic lesion in the affected bone. Membranous lipodystrophy was diagnosed in the present case following histological examination of the curetted material from the right talus.

The total lipodystrophy suggesting a disturbance in systemic metabolism in the case of Nasu et al. (1973) was not seen in this patient. On the contrary, she was relatively obese and no membranocystic lesion was seen in the skin biopsy specimen, though these lesions have been reported in other cases (Yagishita et al. 1976) and aid the diagnosis of membranous lipodystrophy. The parents of this patient were consanguineous, supporting the hypothesis that the disease is related to a hereditary disorder, perhaps autosomal recessive.

Sudanophilic or sclerosing leucodystrophy has been shown in autopsy cases of membranous lipodystrophy (Sourander 1970; Nasu et al. 1973; Harada 1975; Tanaka 1980) and the mental deterioration in the present case would possibly be attributed to leucodystrophy. In some cases such as metachromatic leucodystrophy (Austin et al. 1965) and Krabbe's disease (Malone 1970; Suzuki et al. 1970; Andrews et al. 1971) the leucodystrophy resulted from an enzyme deficiency. Aryl sulphatase A, β-galactosidase and other lysosomal enzymes of the white blood cells were investigated in this case, but no deficiency was detected.

Calcification of the basal ganglia has been reported in some cases of membranous lipodystrophy (Sourander 1970; Hakola et al. 1973; Harada 1975; Tanaka 1980) as well as in the present case. Brain CT was used to find the lesion in our patient and the number of cases of membranous lipodystrophy showing calcification of the basal ganglia seems to have increased since brain CT has come into more general use. The area of calcification contains variable amounts of polysaccharide, calcium and iron salts, and the histochemical properties are identical with the membranocystic structures of affected bone (Slager et al. 1956; Yagishita et al. 1976; Fujiwara 1979; Tanaka 1980). The calcification of the basal ganglia and the membranocystic structure in bone and other adipose tissue might be considered to have a common origin, with abnormal metabolism of acid mucopolysaccharides as one of the suspected causes (Yoshida et al. 1977). Since acid mucopolysaccharides are known to have a certain relationship with anoxia, the hypothesis of vascular bed damage originally proposed by Järvi (1970) may not easily be discounted.

Membranocystic lesion combined with calcification has also been found in cases of dermatomyositis, systemic lupus erythematosus profundus and other connective tissue diseases (Abrikossoff 1929; Arnold 1956; Nasu et al. 1977); lipodystrophy has been reported to be associated with connective tissue disease (Ipp et al. 1976; Segvia et al. 1976; Hall et al. 1978). A female patient who had partial lipodystrophy with erythema, dactylate deformities, calcification of the basal ganglia, immunological disorder and a low IQ level was recently reported in Japan (Horikoshi et al. 1980). Though there was no abnormality in the laboratory tests relating to connective tissue disease in our case, these combinations suggest that membranous lipodystrophy has a close relationship with connective tissue disorders.

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