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Regional cerebral blood flow in a patient with Nasu-Hakola disease

Tohru TAKESHITA,* Tatsuro KAMINAGA,* Tomoko TATSUMI,**
Yuki HATANAKA** and Shigeru FURUI*

*Departments of *Radiology and **Neurology, Teikyo University School of Medicine*

We report a functional neuroimaging study of a 43-year-old woman with Nasu-Hakola disease (NHD). Regional cerebral blood flow (rCBF) images were measured with technetium-99m ethyl cysteinate dimer single photon emission computed tomography (SPECT). rCBF was decreased in the bilateral frontal lobes and thalamus. This finding was consistent with the known underlying neuropathology in patients with NHD. Brain SPECT is useful for demonstrating the pathophysiologic brain region in patients with NHD.

Key words: Nasu-Hakola disease, brain single photon emission computed tomography (SPECT), ^{99m}Tc-ethyl cysteinate dimmer (ECD)

INTRODUCTION

NASU-HAKOLA DISEASE (NHD), also referred to as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), is a rare autosomal recessive disease characterized by a combination of psychotic symptoms, rapid progression to presenile dementia, and multiple bone cyst-like lesions.[1–4] After typical cases were described in the early 1970s,[1,2] more than 160 cases have been reported from Japan, Finland, and other countries.[3,4]

Functional neuroimaging studies using single photon emission computed tomography (SPECT) or positron emission tomography (PET) have been employed to examine various neuropsychiatric diseases, in an attempt to diagnose and understand their pathophysiology. However, there are only two reported cases of NHD which were evaluated with functional neuroimaging studies.[5,6]

We report a patient with NHD, in whom rCBF was measured using ^{99m}Tc ethyl cysteinate dimer (^{99m}Tc-ECD).

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For reprint contact: Tohru Takeshita, M.D., Department of Radiology, Teikyo University School of Medicine, 2–11–1 Kaga, Itabashi-ku, Tokyo 173–8605, JAPAN.
E-mail: tohru@med.teikyo-u.ac.jp

CASE REPORT

The patient was a 43-year-old, right-handed Japanese woman. Her parents' marriage was consanguineous. Her birth was uneventful, and she had shown normal psychomotor development. She had been in good health until the age of 25 years, when a pelvic bone, right femur, left tibia and fibula were fractured in a traffic accident. At that time, radiographs showed trabecular loss in the distal ends of the long tubular bones. Thereafter she experienced repeated pathological fractures of the lower extremities several times. At the age of 34, bone biopsy was done, and biopsy material from the left proximal tibia showed membranous cystic lesions in the adipose tissue of bone marrow (Fig. 1A). This pathological finding was compatible with Nasu-Hakola disease.[1–4] At age 39, urinary incontinence appeared and gradually worsened. At age 40, she developed personality change, depression of mood, memory disturbance, and loss of social inhibition and judgment, all of which gradually worsened. At age 43, she was unable to stand unassisted for a long time, and was admitted to Teikyo University Hospital. She was alert. On the Mini-Mental State Examination, she scored 24 out of 30. She also showed a mild degree of memory impairment and achieved scores of 61 for the general memory index, 67 for verbal memory index, 62 for the visual memory index, and less than 50 for the delayed recall index using the Wechsler Memory Scale-Revised. On the Hasegawa Dementia Score Revised, she scored 21 out of 30. On the

Wisconsin Card Sorting Test, the total number of categories was 5. Deep tendon reflexes were generally hyperactive. Bilateral Babinski and Chaddock reflexes were present. Cerebellar dysfunction, rigidity, bradykinesia and involuntary movement were not found. Neither muscle atrophy nor weakness was observed. There was no sensory disturbance. Routine laboratory analyses of blood and urine revealed no abnormality. The level of thryoid hormone, parathyroid hormone, cortisol, copper, ceruloplasmin, vitamin B_1, B_2, B_{12}, and very long fatty acid were within normal limits. Treponema pallidum agglutination test and anti-HTLV-1 antibody were negative. Cerebrospinal fluid examination showed no abnormality. An electroencephalogram demonstrated almost normal findings. Radiographic bone survey revealed multiple polycystic radiolucent lesions in the bilateral humerus, radius, ulna, femur, tibia, and fibula (Fig. 1B). Brain magnetic resonance images (MRI) showed marked atrophy of the frontal cerebral white matter and symmetrical dilatation of the lateral ventricles and widening of the cerebral cortical sulci (Fig. 1C). T2-weighted MR images revealed slight high signal intensity at the frontal white matter. Obvious signal loss was not seen in the basal ganglia and thalamus. MR angiography of the cervical and intracranial arteries was normal.

Before undergoing brain SPECT, radionuclide angiography was performed immediately after intravenous bolus injection of 600 MBq (16.2 mCi) of ^{99m}Tc-ECD. The passage of the tracer from the aortic arch to the brain was monitored in anterior view with a 128 × 128 matrix (magnification, 1.0) for 100 s at 1-s intervals using one detector of a two-headed gamma camera (MAXUS; GE Medical Systems, USA) equipped with low-energy, high-resolution, parallel-hole collimators (GE Medical Systems, USA). Regions of interest (ROIs) were placed manually over the aortic arch and bilateral cerebral hemispheres, and time-activity curves of these ROIs were plotted. rCBF was calculated with a method which was described by Matsuda et al.[7] Five minutes after completion of the radionuclide angiography, brain SPECT imaging was performed. The acquisition protocol was 32 projection images arranged at 6-degree intervals for each head, sampling time of 30 seconds at each head position, and 64 × 64 matrices. The image set was processed with a Butterworth filter (cut off frequency = 0.45 cycle/cm, order = 10) followed by reconstruction of transverse images with Ramp filtered back projection. Attenuation correction was performed using Chang's method.[8]

Axial rCBF image was obtained. rCBF was 30.07 m*l*/100 g per min in the right anterior lobe, 29.41 m*l*/100 g per min in the left anterior lobe, 36.44 m*l*/100 g per min in the right parietal lobe, 36.01 m*l*/100 g per min in the left parietal lobe, 35.54 m*l*/100 g per min in the right temporal lobe, 34.59 m*l*/100 g per min in the left temporal lobe, 40.27 m*l*/100 g per min in the right occipital lobe, 39.74 m*l*/100 g per min in the left occipital lobe, 37.03 m*l*/100 g per min in the right lenticular nucleus, 32.09 m*l*/100 g per min in the left lenticular nucleus, 25.94 m*l*/100 g per min in the right thalamus, and 20.69 m*l*/100 g per min in the left thalamus. rCBF was markedly decreased in the bilateral frontal white matter and thalamus (Fig. 1D).

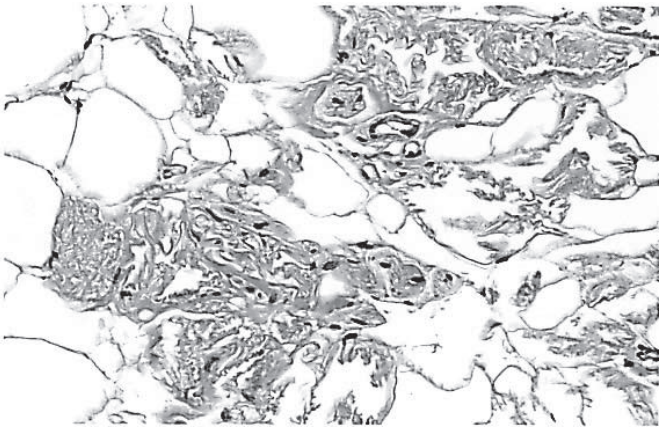
DISCUSSION

NHD has its onset at around 20 years of age with pain and tenderness of the ankles and feet and later pathological fractures.[1–4] Neuropsychiatric symptoms such as loss of social inhibitions, personality changes, euphoria, hallucinations, and rapid progression to presenile dementia develop at the age of 30–40 and gradually worsen.[1–4] Pathologically, NHD is characterized by sudanophilic leukodystrophy or sclerosing leukoencephalopathy of the brain and by membranous cystic structures in the adipose tissue of the bone marrow.[1–4] The pathogenic mechanism of NHD is still unknown. Recently, the mutations in two genes (TYPOBP and TREM2) encoding different subunits of a membrane receptor complex in natural killer cells and myeloid cells have been associated with NHD.[9,10]

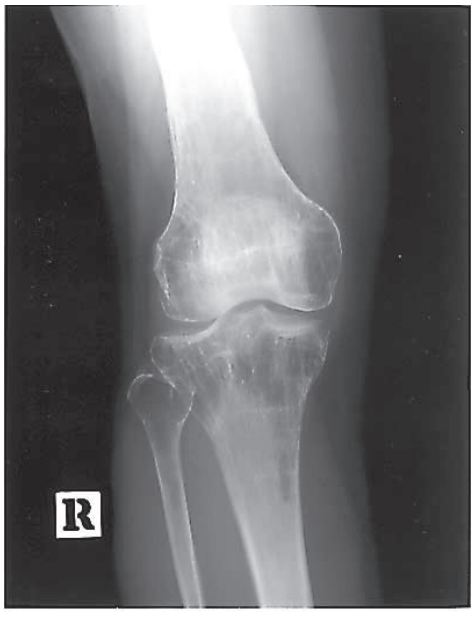
The most common neuropathological changes observed in brain autopsies of the patients with NHD are diffuse atrophy of the cerebral white matter with diffuse and marked astrocytosis and fibrillary gliosis, predominantly in the frontal lobe, and moderate neuronal loss with astrocytic proliferation is also found in the basal ganglia and thalamus.[1–4] On the other hand, Amano et al. reported an unusual case of NHD with extensive lesions in the frontal cerebral cortex as well as in the cerebral white matter, basal ganglia and thalamus.[3]

Reported MR findings of NHD are atrophy of cerebral white matter with dilation of ventricles, increased signal intensity of white matter, and decreased signal intensity of the thalamus, putamen, caudate nucleus, and cerebral cortex on T2-weighted MR images.[11] The diagnosis of NHD in our case is based on the combination of the characteristic clinical features, radiological findings, and pathological finding from the bone biopsy.

To our knowledge, two cases of NHD have been studied by brain SPECT or PET studies.[5,6] Yamamoto et al. described the results of brain SPECT in a 32-year-old woman with NHD.[5] *N*-isopropyl-*p*-^{123}I iodoamphetamine SPECT by visual assessment showed a marked decrease of rCBF in bilateral frontal lobe, temporal lobe and basal ganglia.[5] Ueki et al. reported an ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) PET study in a 38-year-old woman with NHD, which demonstrated a marked decrease of glucose metabolism in the bilateral frontal white matter with mild hypometabolism in the thalamus and basal ganglia.[6] These glucose metabolism alterations were prominent on the right side, suggesting that hypometabolism of the right frontal white matter could be associated with euphoria, uninhibited behavior and personality alterations that are major features of NHD.



A



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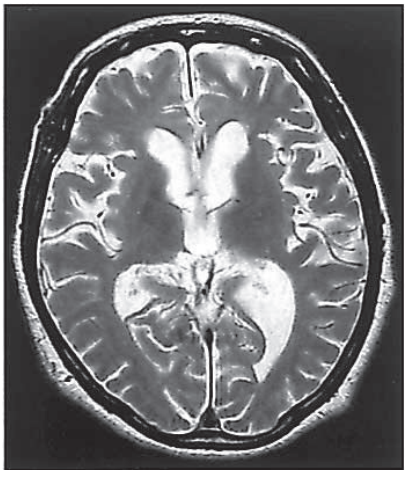

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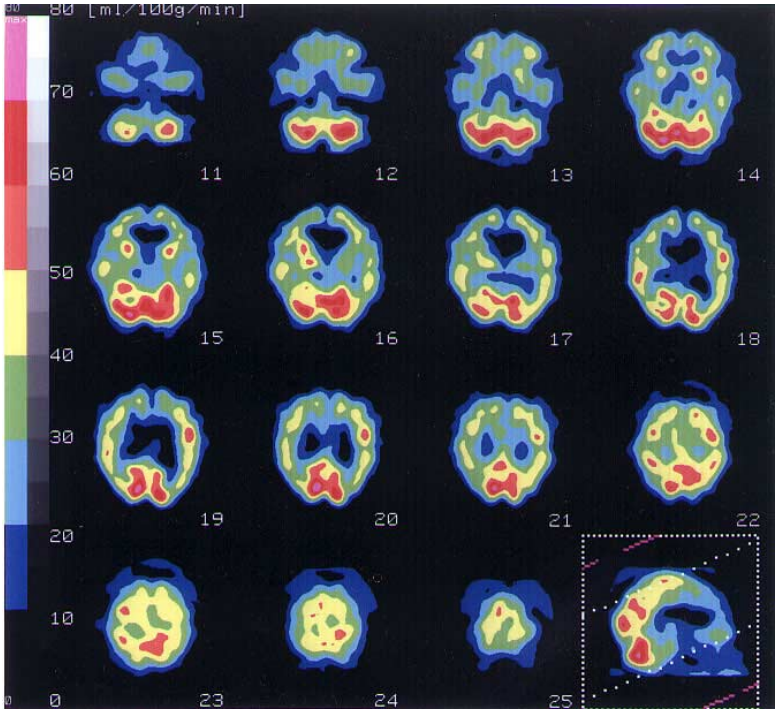

D

Fig. 1 Images of a 43-year-old woman with Nasu-Hakola disease. A: Biospy specimen of the bone marrow obtained from the left proximal tibia. (original magnification, × 80; hematoxylin-eosin stain) B: X-ray film of the right knee joint shows multilocular cystic radiolucent areas in the right femur, tibia, and fibula. C: Axial T2-weighted MR image (TR/effective TE: 4000/83.5 msec). D: ^{99m}Tc-ECD brain SPECT (axial images). The colored bar demonstrates the quantitative rCBF counts (maximum, 80 ml/ 100 g per min; minimum, 0 ml/100 g per min).

Our brain SPECT study using ^{99m}Tc-ECD showed a decrease of rCBF in the bilateral frontal lobes and thalamus. This finding supports the presence of hypoperfusion/hypometabolism in bilateral frontal lobes and thalamus in patients with NHD, and is consistent with the known underlying neuropathology of NHD. Brain SPECT is useful for demonstrating the pathophysiologic brain region in patients with NHD.

From the standpoint of the SPECT and PET findings, the differential diagnosis of frontal hypoperfusion/hypometabolism includes frontotemporal dementia (FTD). Ishii et al. and Miller et al. reported hypoperfusion/hypometabolism in the frontal and anterior temporal lobes and the subcortical structures including the basal ganglia and thalamus in FTD patients.[12,13] The SPECT and PET findings of NHD are similar and indistinguishable from those of FTD. However, the combination of frontal-type hypoperfusion and radiologically demonstrable polycystic osseous lesions is characteristic and makes it possible to distinguish NHD from FTD clinically.

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