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Case Report

Neuroimaging Findings in a Brain With Niemann–Pick Type C Disease

*Jei-Yie Huang,[1] Sing-Fung Peng,[2] Chih-Chao Yang,[3] Kuo-Yang Yen,[4] Kai-Yuan Tzen,[1] Ruoh-Fang Yen[1]**

Niemann-Pick type C disease (NPC) is a rare autosomal recessive lipid storage disorder caused by impaired cellular functions in processing and transporting low-density lipoprotein–cholesterol. In this report, we present magnetic resonance imaging (MRI), magnetic resonance spectrography (MRS) and 18-fluoro-2-deoxyglucose positron emission tomography (PET) imaging results for a 22-year-old male NPC patient. The patient's two MRI studies (at age 19 years and 22 years) demonstrated progressive changes of brain atrophy that were more prominent at the frontal lobes, and hyperintense signals in bilateral parietal–occipital periventricular white matter. MRS (at age 19 years) revealed no significant decrease in N-acetyl aspartate/choline ratio in the left frontal central white matter. PET (at age 22 years) showed significant bilateral hypometabolism in the prefrontal cortex and dorsomedial thalamus, and hypermetabolism in the parietal–occipital white matter, lenticular nucleus of the basal ganglia, cerebellum and pons. The imaging findings noted by MRI, MRS and 18-fluoro-2-deoxyglucose PET offered a possible supplementary explanation for the clinical neurological symptoms of this NPC patient.

Key Words: glucose metabolism, Niemann–Pick type C disease, magnetic resonance imaging, positron emission tomography

Niemann-Pick type C disease (NPC) is a rare autosomal recessive lipid storage disorder caused by impaired cellular functions in processing and transporting low-density lipoprotein–cholesterol.[1] Prevalence of this disease in western countries has been estimated to be approximately 1 in 100,000.[1] Fewer than 10 cases have been reported in Taiwan to date.[2–4]

In most NPC cases, the neurological defects begin to appear when patients are between 4 and 10 years old.[2] The symptoms are usually clumsiness and gait disturbance at the beginning, and include ataxia, mental disturbance, dystonia, dysarthria, dysphagia, seizures and vertical supranuclear gaze palsy during the disease course.[5–7] Death in NPC patients is usually

Departments of [1]Nuclear Medicine, [2]Medical Imaging and [3]Neurology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, and [4]Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan.

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***Correspondence to:** Dr Ruoh-Fang Yen, Department of Nuclear Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan.
E-mail: rfyen@ntu.edu.tw

caused by aspiration pneumonia.[8,9] For the minority of adult-onset NPC patients, the typical observed symptoms are psychiatric disorders such as dementia, depression, bipolar disease or schizophrenia.[10]

Mutations of the NPC1 gene, located on chromosome 18q11–12, are observed in 95% of NPC patients, whereas mutations of the NPC2 gene are noted in 5%.[1,2] It has been proposed that the mutations in the NPC genes cause blockage of cholesterol transport between lysosomes and the sterol regulator machinery, so that excessive cholesterol is accumulated and apoptosis of neurons occurs.[1,11] The intracellular accumulation of unesterified cholesterol in the lysosomal system can be detected from the fluorescence level around the nucleus, via filipin staining. To reach a conclusive diagnosis of NPC, both the abnormal accumulation of cholesterol and delayed low-density lipoprotein–cholesterol esterification in fibroblast cell culture should be observed.[12]

For NPC, brain magnetic resonance imaging (MRI) usually is not capable of detecting abnormality, except in the late stages.[6] Magnetic resonance spectroscopy (MRS) is a noninvasive neuroimaging technique for obtaining information about brain metabolism. In general, decreased N-acetyl aspartate indicates neuronal and axonal loss, whereas increased choline reflects demyelination or gliosis.[13,14] In addition, 18-fluoro-2-deoxyglucose (F-18 FDG) positron emission tomography (PET), based on glucose utilization in the brain, is known to be sensitive for the detection of metabolic derangements in patients with neurodegenerative disorders. In this report, we present the MRI, MRS and F-18 FDG PET imaging results for a 22-year-old male NPC patient.

Case Report

This patient was referred to our hospital when he was 19 years old because of speech and swallowing difficulty that had been progressing rapidly for the past 6 months. His birth and development history had been normal until age 11, when lower extremity stiffness with difficulty in squatting was noted. Since then, the patient's symptoms of dysarthria and dysphagia started and his school performance also began to deteriorate. His older brother suffered from the same neurological onset at age 13 years and died at age 19 years.

During the patient's first admittance to our hospital, his neurological examination revealed diffuse spasticity, dystonia, limb and trunk ataxia, vertical supranuclear gaze palsy, facial grimace, mild rigidity in limbs, hyperactive deep tendon reflexes, and limb dysmetria. No retinal pigmentation abnormality was noted by the consulting ophthalmologist. All other physical examination results were normal.

The patient's first brain MRI showed slightly increased signal intensity in bilateral parietal–occipital periventricular white matter (Figure 1A). Single voxel proton MRS of the left frontal central white matter (TR/TE = 1500/270 milliseconds) showed no significant decrease in N-acetyl aspartate/choline ratio (Figure 1B and 1C).

Cerebrospinal fluid analysis showed absence of pleocytosis and normal protein and sugar levels. Aspirates of bone marrow biopsy demonstrated a significant increase in foamy cells. The diagnostic result of NPC for this patient was confirmed by filipin staining and cholesterol esterification assay of skin fibroblasts performed by the National Referral Laboratory, Adelaide, Australia. The results showed the presence of perinuclear nonesterified cholesterol deposits and a significantly reduced rate of cholesterol esterification (1.4 pmol/hr/mg protein, normal range: > 3 pmol/hr/mg protein) in cultured fibroblasts.

Although empirical treatment using lavostatin (a hypolipidemic agent) for this patient was given, his NPC symptoms still deteriorated gradually. His worsening dysphagia eventually resulted in frequent choking such that he was readmitted for percutaneous gastrostomy with feeding tube placement, at age 22 years; 3 years after initial diagnosis. The follow-up brain MRI revealed more prominent brain atrophy, especially in the frontal

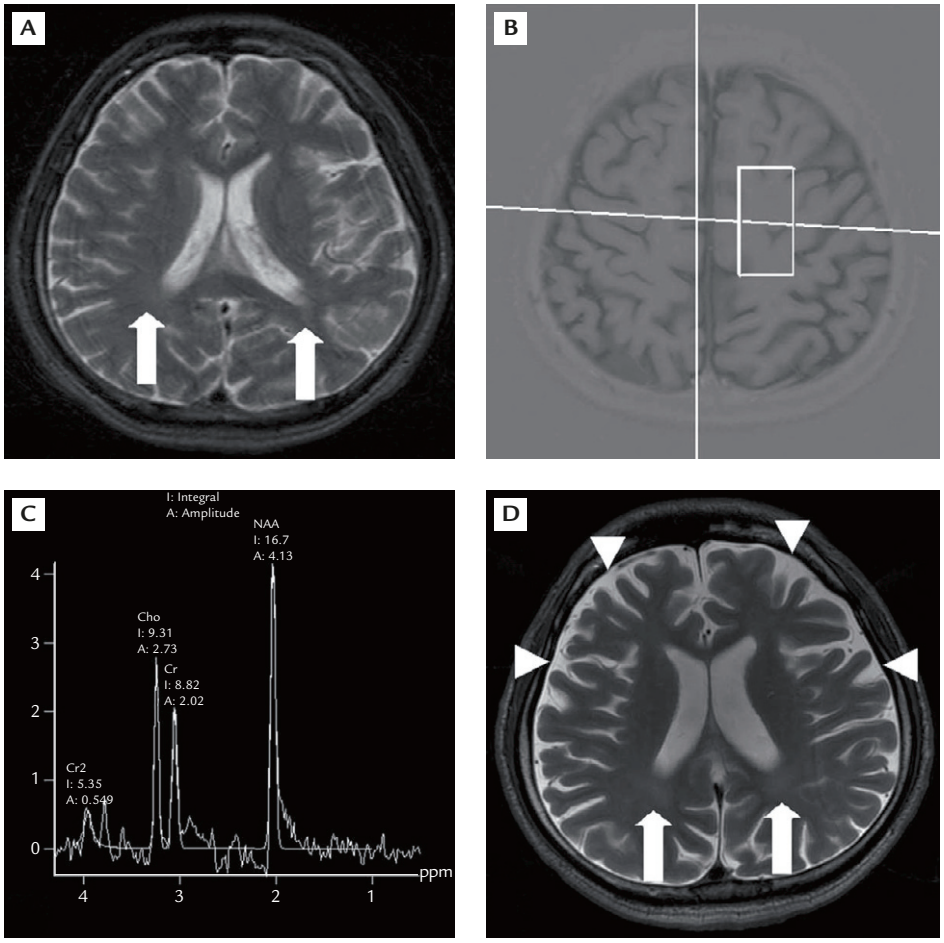

Figure 1. (A) At age 19, fast-spin echo T2-weighted images (effective TR/effective TE = 4700/93 milliseconds, echo train length 90) in the axial plane at the level of both lateral ventricular bodies showed slightly increased signal intensity in bilateral in parietal–occipital periventricular white matter (arrows). (B) At age 19, single-voxel, point-resolved spectroscopy (TR/TE = 1500/270 milliseconds) sampled at the left frontal central white matter. (C) Magnetic resonance spectroscopy showed no significant decrease in N-acetyl aspartate/choline. (D) Follow-up fast-spin echo T2-weighted images at the similar level at age 22 showed more prominent sulci of both cerebral convexities, especially in the frontal lobes (arrowheads), and more increased signal intensity in bilateral parietal–occipital periventricular white matter (arrows).

lobes and more increased signal intensity in bilateral parietal–occipital periventricular white matter (Figure 1D).

Brain F-18 FDG PET was subsequently performed and the axial views of PET images are shown in Figure 2A, which reveals obvious hypometabolism in the prefrontal cortex and thalamus. Figure 2B and 2C shows the statistical parametric mapping (SPM99, Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London) results for the patient, compared with 10 age-matched healthy controls with a height threshold of $p = 0.001$ ($T = 4.30$), extent size threshold of $p = 0.005$ (210 voxels), and uncorrected for multiple comparisons. The statistical parametric mapping results showed significant hypometabolism in the prefrontal cortex and dorsomedial nucleus of the thalamus (Figure 2B); and hypermetabolism in the parietal–occipital white matter, lenticular nucleus of the basal ganglia, cerebellum, and pons (Figure 2C).

Discussion

Our findings demonstrate progressive changes in the patient's two MR images and consistent

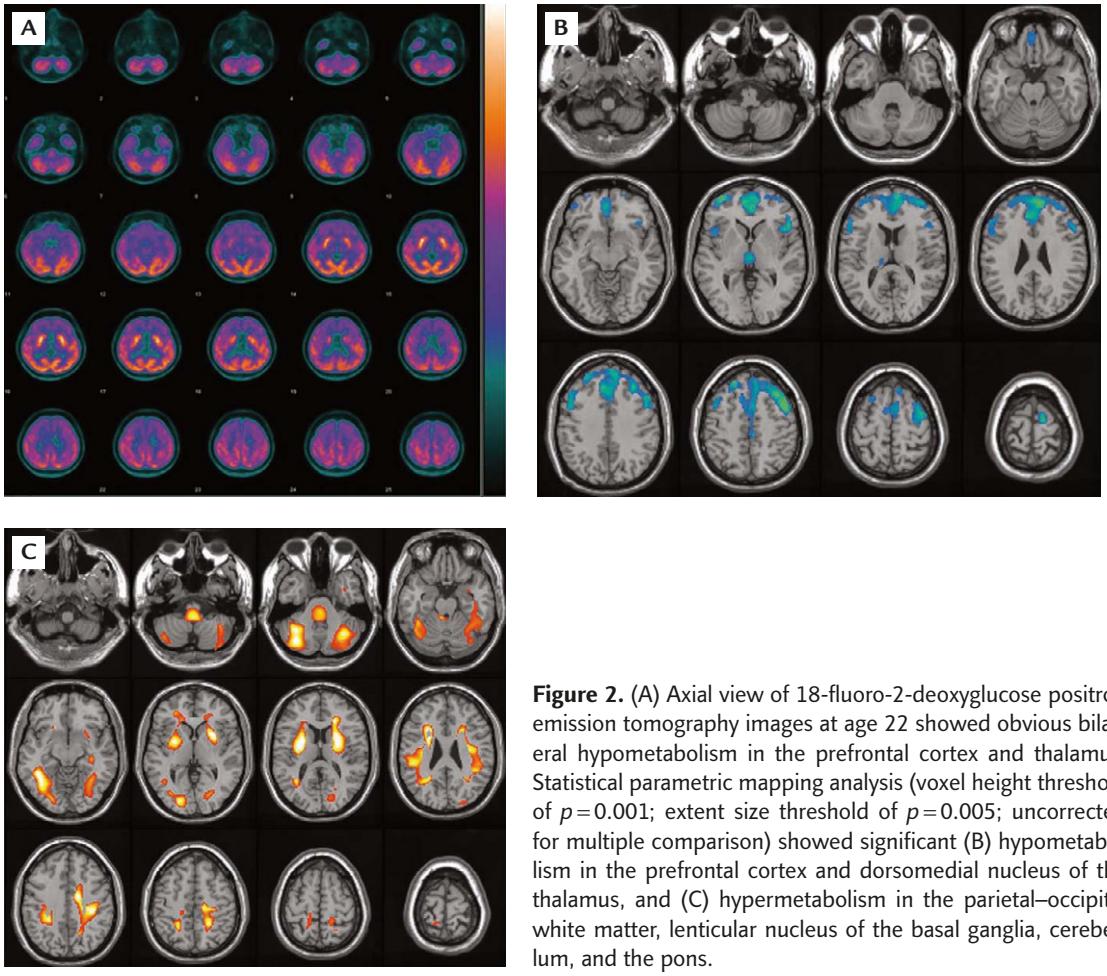

Figure 2. (A) Axial view of 18-fluoro-2-deoxyglucose positron emission tomography images at age 22 showed obvious bilateral hypometabolism in the prefrontal cortex and thalamus. Statistical parametric mapping analysis (voxel height threshold of $p = 0.001$; extent size threshold of $p = 0.005$; uncorrected for multiple comparison) showed significant (B) hypometabolism in the prefrontal cortex and dorsomedial nucleus of the thalamus, and (C) hypermetabolism in the parietal–occipital white matter, lenticular nucleus of the basal ganglia, cerebellum, and the pons.

findings in his MRI and F-18 FDG PET. These imaging results may be related to the clinical manifestations and neuropathology of this NPC patient. To the best of our knowledge, there are only two previous reports with regard to the F-18 FDG PET findings in NPC patients.[15,16]

At age 22 years, MRI revealed brain atrophy, especially in the frontal lobes, and F-18 FDG PET showed hypometabolism in the frontal cortex. The neuronal dysfunction of the frontal lobe in this patient might have been responsible for the imaging results. Hypometabolism in the prefrontal cortex[15,16] and thalamus[15] has been reported and is similar to the PET and MRS findings in this case. Hypometabolism in the prefrontal cortex and dorsomedial nucleus of the thalamus might be related to cognition and intelligence impairment. The dorsomedial nucleus is interconnected with the prefrontal cortex and is known to play important roles in prefrontal functions such as affect and foresight.[17] It has been reported that most adult-onset NPC patients are referred to clinicians due to behavior and mood changes or some major psychiatric problems,[9,10] and cognitive impairment is one of the common initial deficiencies of NPC patients.[6] These clinical manifestations have been confirmed in a postmortem analysis of NPC patients.[16] This postmortem neuropathological study showed non-amyloid neurofibrillary tangles predominantly in the frontal lobe and thalamus. It has been suggested that perturbed cholesterol metabolism or lysosomal membrane trafficking might affect the formation of neurofibrillary tangles in NPC patients.[18]

Battisti et al[15] have reported hypometabolism in the cerebellum, whereas PET in our case revealed hypermetabolism in the lenticular nucleus of the basal ganglia, pons, and cerebellum.

Hypermetabolism was not reported in either of the two previous studies. In our opinion, this discrepancy may be attributed to the different types or stages of NPC. In the study by Battisti et al, the onset was at age 25 years (compared with 11 years in our patient), F-18 FDG PET was performed at 33 years (22 years in our patient), and MRI showed severe cerebellar atrophy (MRI did not reveal this in our patient).

Hypermetabolism in the basal ganglia, mid brain and cerebellum may be related to dystonia. It has been observed that hyperperfusion in the putamen is associated with dystonic posturing in patients with temporal lobe epilepsy.[19] Cerebellar and pontine metabolic increases have been observed in patients with essential blepharospasm,[20] which is a focal dystonia. The patient's peculiar grimace is also a form of facial dystonia. These types of hypermetabolic phenomena may be attributed to the abnormal metabolic networks, as occur in patients with DYT1 dystonia.[21]

Significant hypermetabolism in the parietal–occipital white matter in the present case report was another PET finding that has not been noted before. MRI also showed increased signal intensity in the same areas. White matter degeneration in NPC patients has been documented.[22] In an animal model using NPC mice, demyelination has been observed in the early disease course and is accompanied by marked gliosis and reduced axon number.[23] Using diffusion tensor imaging, significant reduction in brain water diffusion has also been observed in white matter in an NPC patient.[24] We suspect that the white matter hyperintensity with MRI and hypermetabolism with PET in our case brings forth possible evidence for active demyelination in NPC.

Our results suggest that brain imaging offers a possible supplementary explanation of the clinical neurological symptoms in NPC patients. In our opinion, these neuroimaging modalities could provide an avenue to non-invasively study correlation of NPC with its neuropathological aspects. Further studies in more NPC patients are needed to verify our assumptions.

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