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Case Report

Parkinsonism in Association with Dihydropteridine Reductase Deficiency

Yoshiaki Takahashi[a] Yasuhiro Manabe[a] Yumiko Nakano[a] Taijun Yunoki[a] Syoichiro Kono[a] Hisashi Narai[a] Mahoko Furujo[b] Koji Abe[c]

[a]Department of Neurology, National Hospital Organization Okayama Medical Center, Okayama, Japan; [b]Department of Pediatrics, National Hospital Organization Okayama Medical Center, Okayama, Japan; [c]Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan

Keywords
Dihydropteridine reductase deficiency · Levodopa · Parkinsonism · Hyperphenylalaninemia · SPECT · Dopamine transporter

Abstract
We report a 16-year-old man with disorders of tetrahydrobiopterin metabolism due to dihydropteridine reductase (DHPR) deficiency. He revealed moderate mental retardation, parkinsonism, and spastic paralysis with levodopa and 5-hydroxytryptophan (5-HTP) supplementation from the age of 2 months. Brain MRI showed high intensity areas in bilateral frontal and posterior deep white matter on fluid-attenuated inversion recovery (FLAIR). Coronal FLAIR image showed a high signal in bilateral pyramidal tracts. Single photon computed tomography (SPECT) imaging of the dopamine transporter was normal. This imaging indicates no dopaminergic cell loss. Our patient had no motor fluctuations or dyskinesias. Early diagnosis and replacement treatment might lead to a favorable outcome.

Yasuhiro Manabe, MD, PhD
Department of Neurology, National Hospital Organization Okayama Medical Center
1711-1 Tamasu Kita-ku
Okayama 701-1192 (Japan)
E-Mail ymanabe@okayamamc.jp

Introduction

Dihydropteridine reductase (DHPR) deficiency is a rare autosomal recessive inherited disease which affects the metabolism of tetrahydrobiopterin (BH_4), causing hyperphenylalaninemia and neurotransmitter deficiency [1]. Delayed neurological syndromes due to hypomyelination in the central nervous system are recognized and can include parkinsonism [1]. However, the clinical characteristics of parkinsonism and dopamine transporter (DAT) imaging have not been fully documented. Here, we report a case of levodopa-responsive parkinsonism with DHPR deficiency and demonstrate by means of dopamine transporter-single photon emission computed tomography (DAT-SPECT).

Case Report

A 16-year-old man was admitted to our hospital due to slowly progressive gait disturbance. He was found to have hyperphenylalaninemia on a routine Guthrie test for newborn screening. He was diagnosed as having DHPR deficiency based on a BH_4 loading test [2, 3]. Gene analysis revealed a compound heterozygous mutation of the *QDPR* gene (G18C/S59X, both are new mutations) [2, 3]. At the age of 2 months, treatment was started with BH_4 15–20 mg/kg/day, levodopa 15 mg/kg/day, and 5-hydroxytryptophan (5-HTP) 15 mg/kg/day. Entacapone 300 mg/day was added at the age of 10. He developed epileptic seizures at the age of 12. To avoid intracerebral folate deficiency, folic acid was added when he was 15 years of age. On admission, the general physical examination was normal. Neurological examinations revealed mental retardation, akinesia, rigidity of upper limbs, hand clumsiness, spastic paralysis, and clonus at the ankles. He had no daily motor fluctuations or dyskinesias. Deep tendon reflexes were hyperactive in all limbs. Babinski, Chaddock, Hoffman, and Trömner signs were positive on both sides. His gait was spastic. There were no obvious abnormalities of the sensory, cerebellar, and autonomic systems. The Mini-Mental State score was 18/30. At this time, the serum phenylalanine (Phe) value was 906 nmol/mL (normal, 42.6–75.5 nmol/mL). He was taking BH_4 8.4 g/day, levodopa 700 mg/day, 5-HTP 800 mg/day, entacapone 300 mg/day, folinic acid 15 mg/day, and levetiracetam 300 mg/day. Brain magnetic resonance imaging (MRI) showed high intensity areas in frontal and posterior deep white matter on fluid-attenuated inversion recovery (FLAIR) (Fig. 1a) and T2-weighted imaging. Coronal FLAIR image showed a high signal in bilateral pyramidal tracts (Fig. 1b). Dopaminergic striatal innervation was evaluated as dopamine reuptake transporter density by means of SPECT and [^{123}I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) tropane (^{123}I-FP-CIT). ^{123}I-FP-CIT SPECT was normal (Fig. 1c). Specific binding ratios were right 7.99 and left 8.13 (normal, >4.00). His spastic gait improved with an antispasmogenic agent.

Discussion

Our patient revealed normal DAT-SPECT. Levodopa-responsive dystonia is suggestive to our patient. Levodopa-responsive dystonia is due to heterozygote mutations in the GTP cy-

clohydrolase 1 gene, where an endogenous synthesis of monoamines remains. GTP cyclohydrolase 1, encoded by the *GCH1* gene, is an essential enzyme for dopamine production in nigrostriatal cells. Loss-of-function mutations in *GCH1* result in severe reduction of dopamine synthesis in nigrostriatal cells and are the most common cause of dopa-responsive dystonia, a rare disease that classically presents in childhood with generalized dystonia and a dramatic long-lasting response to levodopa [4]. The childhood-onset dystonia subtype has normal DAT imaging; however, DAT imaging was reduced in the adult-onset parkinsonian subtype, indicating Parkinson disease-like nigrostriatal dopaminergic denervation [4]. GCH 1 deficiency and consequent chronic dopamine deficiency with the adult-onset parkinsonian subtype might directly predispose to nigral cell death [4]. Our patient had no signs of monoamine deficiency under long-term replacement therapy despite the severe enzymatic deficiency and the long duration of the disease. This would suggest that a normal level of dopamine exhibits a protective role on the survival of nigral neurons. Findings of parkinsonism in disorders of tetrahydrobiopterin metabolism on DAT imaging have rarely been reported (Table 1). Evans et al. [5] reported a patient who had received a delayed diagnosis of phenylketonuria as an infant and developed motor fluctuations without dyskinesias. Sedel et al. [6] reported a patient who had no daily motor fluctuations or dyskinesias after long-term replacement treatment. Our patient also had no daily motor fluctuations or dyskinesias after long-term replacement treatment. These findings suggest that early diagnosis and treatment with levodopa and 5-HTP might lead to a favorable outcome.

Levodopa-induced motor complications most likely resulted from dopamine neuron loss. Normal DAT imaging implies a good storage capacity of dopaminergic nerve terminals [6]. In addition to our case, 1 adult patient with the use of levodopa from the age of 3 months, despite the severe DHPR deficiency, exhibited no dyskinesia or dopaminergic cell loss, as suggested by normal positron emission tomography (PET) imaging of the dopamine transporter [6]. Although it is still under discussion whether the long-term use of levodopa is toxic for dopaminergic neurons, this observation and our case report suggest that early diagnosis and replacement therapy with levodopa and 5-HTP might have protective effects on brain neurons during development. The accumulation of further clinical cases is needed.

Statement of Ethics

Informed consent was obtained from the patient for his participation in this case report.

Disclosure Statement

The authors state that they have no conflicts of interest. They have no financial disclosure to make.

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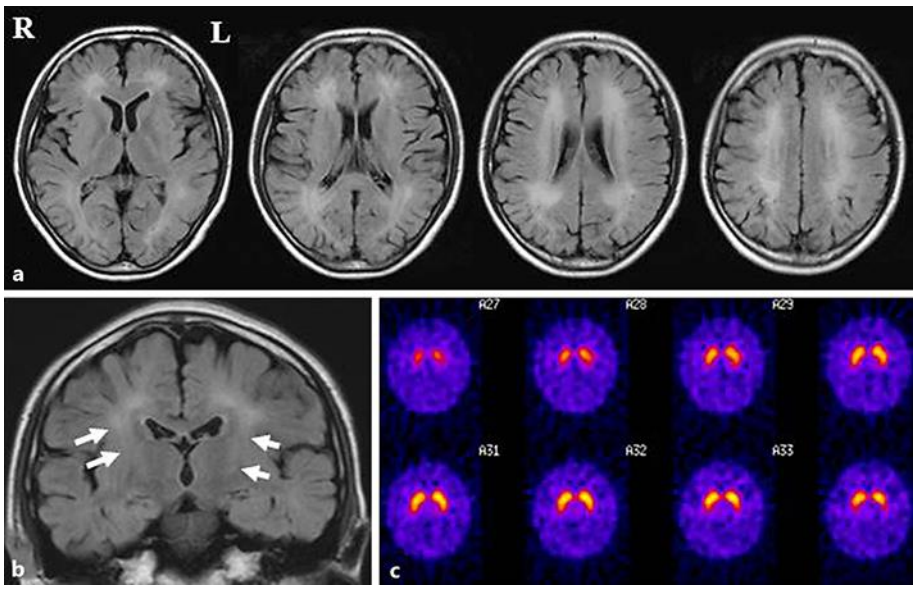

Fig. 1. **a** FLAIR MRI showing high signal in bilateral frontal and posterior deep white matter. **b** Coronal FLAIR image showing high signal in bilateral pyramidal tracts (arrows). **c** [^{123}I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) tropane single photon computed tomography (^{123}I-FP-CIT SPECT) was normal.

Table 1. Clinical features of patients with disorders of tetrahydrobiopterin metabolism on DAT imaging

Case	Age/ sex	Age at diagnosis	Age at replacement treatment	Symptoms	Deficiency enzyme	Dopamine transporter	Prognosis	Authors, year [Ref.]
1	37/F	2 years	33 years	gait disturbance, bilateral postural hand tremor, hand clumsiness	phenylalanine 4-hydrolase (PAH)	normal	slowly progressive	Evans et al., 2004 [5]
2	29/M	newborn screening	3 months	akinesia, rest tremor, bilateral ptosis, hypersalivation	dihydropteridine reductase (DHPR)	normal	slowly progressive	Sedel et al., 2006 [6]
3	16 /M	newborn screening	2 months	akinesia, rigidity, hand clumsiness, spastic paralysis, clonus at ankles	dihydropteridine reductase (DHPR)	normal	slowly progressive	Our case, 2016