Short communication

Efficacy of idebenone for respiratory failure in a patient with Leigh syndrome: A long-term follow-up study

Kazuhiro Haginoya a,b,⁎, Shigeaki Miyabayashi c, Masahiro Kikuchi d, Akira Kojima e, Katsuya Yamamoto f, Kiyoshi Omura g, Mitsugu Uematsu b, Naomi Hino-Fukuyo h, Soichiro Tanaka a, Shigeru Tsuchiya b

a Department of Pediatric Neurology, Takuto Rehabilitation Center for Children, Sendai 982-0241, Japan
b Department of Pediatrics, Tohoku University School of Medicine, Sendai 980-8574, Japan
c Miyabayashi Kodomo Clinic, Sendai, Japan
d Department of Pediatrics, Hitachi General Hospital, Hitachi, Japan
e Kojima Pediatric Clinic, Adachi, Tokyo, Japan
f Nankodai Yamamoto Children's Clinic, Sendai, Japan
g Department of Pediatrics, National Nishitaga Hospital, Sendai, Japan

Abstract

Respiratory failure can be the direct cause of death in patients with Leigh syndrome. Unfortunately, no effective treatment strategy is available. Here, we report successful treatment of a patient with Leigh syndrome using idebenone, a derivative of coenzyme Q-10. The patient’s brainstem function, especially respiratory function, improved after idebenone treatment. Idebenone may be worth trying in patients with Leigh syndrome.

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1. Introduction

Leigh syndrome is a subacute necrotising encephalomyopathy frequently ascribed to mitochondrial respiratory chain deficiency. This condition is genetically heterogeneous, as mutations in both mitochondrial and nuclear genes have been reported [1,2]. However, specific molecular dysfunction could not be identified in 75% of patients [1,2]. Neuropathological findings of Leigh syndrome is characterized by spongiosis, neuronal loss, and capillary proliferation in central nervous system including striatum, thalamus, brain stem and cerebellum [3]. Respiratory failure can be the direct cause of death in patients with Leigh syndrome. Unfortunately, no effective treatment strategy is available. Here, we report successful treatment of a patient with Leigh syndrome using idebenone, a derivative of coenzyme Q-10 (CoQ-10).

2. Case report

A 17-year-old boy had nystagmus, ataxia, and gait instability since 5 years of age. These symptoms worsened during a febrile illness, and improved gradually after the febrile episode had abated. His gait ataxia deteriorated gradually at 8 years of age, when he first visited our hospital. The patient was diagnosed with Leigh's encephalopathy because of elevated lactate and pyruvate levels in his cerebrospinal fluid (CSF) and high signal intensity lesions on T2-weighted magnetic resonance imaging (MRI) in the putamen bilaterally. Cytochrome c oxidase activity was 30% of the normal value in biopsied muscle and cultured skin fibroblasts [4]. Mitochondrial gene analysis failed to find the mutation specific for Leigh syndrome. The patient’s younger brother died of the same disease at the age of 10 months due to respiratory insufficiency and his autopsy revealed the characteristic neuropathological findings of Leigh syndrome. Our patient was admitted at the age of 11 years because of respiratory failure, when his PaCO2 was 78 mm Hg and PaO2 was 30 mm Hg. After 6 days of ventilator care, his blood gases improved and he was discharged on CoQ-10 (120 mg/day, subsequently increased to 240 mg/day). He was readmitted 5 months later because of respiratory failure with a PaCO2 of 75 mm Hg and PaO2 of 46 mm Hg.

On admission, he had ataxic respiration, scanning speech, exaggerated deep tendon reflexes, slow eye movement, limited upper gaze, and was mentally deficient with an IQ of 38. Idebenone (90 mg/day) was started after receiving informed consent and ethics committee approval. His clinical findings and laboratory data were evaluated before and 6 months after starting idebenone.

All-night polysomnography showed sleep cycle abnormalities consisting of rapid eye movement (REM) seen during stage 1 non-
REM sleep and paucity of sleep spindles, which remained after idebenone. Central and mixed type sleep apnea were observed frequently, although the apnea index decreased from 6.3 to 3.8 after administration of idebenone. His rib cage and abdominal movements on respiration during both sleep and wakefulness were irregular, small, and atactic before, but became regular and larger after idebenone administration, and his tidal volume improved markedly. Percutaneous arterial oxygen saturation levels after idebenone administration changed from 90 to 95% during wakefulness and from 80–90 to 95% during sleep (Fig. 1). The auditory brainstem responses (ABR) showed no reproducible wave form of Waves III–V, which remained after idebenone. His cerebrospinal fluid lactate levels ranged from 26–28 mg/ml before and after idebenone treatment, and the PaO₂ and PaCO₂ ranged from 57–68 mm Hg and from 60–70 mm Hg, respectively, before idebenone treatment. After idebenone, these improved to 75–80 mm Hg and 45–60 mm Hg, respectively. He has been well for the last 4 years 8 months after idebenone treatment with no respiratory failure or side effects, and his PaO₂ and PaCO₂ levels remain stable, as shown in Fig. 2, although recent data showed some decrement in PaO₂ level.

3. Discussion

The therapeutic application of CoQ-10 to patients with Kearns–Sayre syndrome and MELAS syndrome ameliorated their clinical symptoms, although the neurological improvement was mixed, and ranged from favorable to poor [5–7]. As CoQ-10 has been reported to have good cardiac muscle tissue penetration, improved energy metabolism has been reported in patients with ischemic heart disease [8]. However, its pharmacological effects on the brain are not fully understood.

Idebenone, a short-chain analog of CoQ-10, crosses the blood–brain barrier [9], and has been reported to be a relatively good antioxidant [10] and to improve mitochondrial ATP production in the

![Fig. 1. Respiratory movements of the rib cage and abdomen with percutaneous arterial oxygen saturation monitoring.](image-url)
and brain stem of rats [17]. Recent studies have revealed that free radical scavenger activity, idebenone has an enhancing effect on metabolism [17,18]. In addition to the action on the energy system and the central ventilatory response through modifying monoamines mechanisms of its effect, idebenone itself may also have an effect on function, improved after idebenone treatment. In terms of potential obvious, our patient's brainstem function, especially respiratory nervous system. Although other neurological improvements were not idebenone enters the brain easily and improves the energy state of the last 4 years 8 months after idebenone treatment with no respiratory failure or side effects, and his PaO2 and PaCO2 levels remain stable.

Fig. 2. Clinical course and arterial gas analyses along with idebenone treatment. The PaO2 and PaCO2, these improved after idebenone administration. He has been well for the last 4 years 8 months after idebenone treatment with no respiratory failure or side effects, and his PaO2 and PaCO2 levels remain stable.

brain [11]. A recent study showed that idebenone is effective in improving the cardiac deficiency and cerebellar symptoms in patients with Friedreich's ataxia [12], which gene product is localized in the mitochondria. Idebenone has been given to three patients with MELAs [13–15] and reported to improve their clinical symptoms and cerebral functions, including electroencephalogram (EEG), IQ, and cerebral metabolic ratio of oxygen. However, its use in Leigh syndrome has not been reported previously. In the present case, high-dose CoQ-10 had no effect on respiratory function in spite of the previous report [16].

Initially, we used CoQ-10 and idebenone simultaneously; however, after discontinuing the CoQ-10, the patient's respiratory condition has been stable for more than 4 years. These observations suggest that idebenone enters the brain easily and improves the energy state of the nervous system. Although other neurological improvements were not as obvious, our patient's brainstem function, especially respiratory function, improved after idebenone treatment. In terms of potential mechanisms of its effect, idebenone itself may also have an effect on the central ventilatory response through modifying monoamines metabolism [17,18]. In addition to the action on the energy system and free radical scavenger activity, idebenone has an enhancing effect on the turnover of serotonin (5-HT) in the hippocampus, diencephalon and brain stem of rats [17]. Recent studies have revealed that medullary 5-HT neurons are of special importance in central chemoreception [19]. 5-HT abnormalities are present in many cases with the sudden infantile death syndrome [20] and serotonin transporter knockout mice have a reduced ventilatory response to hypercapnia [21]. In conclusion, treatment with idebenone may be worth trying in patients with Leigh syndrome, especially patients associated with cytochrome c oxidase deficiency.

References

