

# Childhood-Onset Progressive Dystonia With Mitochondrial DNA G14459A Mutation: Efficacy of Long-Term Sodium Succinate Treatment

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## Abstract

This article reports the case of an 11-year-old boy with progressive dystonia caused by the homoplasmic G14459A mitochondrial DNA mutation. The patient presented with focal dystonia in the right upper limb at 3 years of age, which progressed over 4 years to exhibit dystonia in both the upper and lower limbs. At 7 years of age, high signal intensity lesions in the bilateral striata and the mid-brain were observed on fluid-attenuated inversion recovery images. It was observed on diffusion-weighted images that with time, these high signal intensity lesions migrated from the putamen to the caudate nuclei, which closely correlated with disease progression. Because his symptoms and abnormal magnetic resonance imaging findings progressed despite treatment with coenzyme Q10 and L-carnitine, at 7 years of age he was then started on sodium succinate, hoping to improve his complex I deficiency. After treatment, progression of MRI abnormalities appeared to have been suppressed for 4 years, although no improvement was observed in dystonia.

## Keywords

mitochondrial DNA, Leber hereditary optic neuropathy, dystonia

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Mitochondrial disorders have been associated with various clinical manifestations ranging from myopathies to multisystem disorders. Recently, there have been several reports of cases of patients with G14459A mitochondrial DNA mutation in the reduced nicotinamide adenine dinucleotide dehydrogenase subunit 6 gene.<sup>1-9</sup> A G>A transition mutation at nucleotide position 14 459 leads to alanine-to-valine amino acid substitution at position 72 of the reduced nicotinamide adenine dinucleotide dehydrogenase subunit 6 of complex I. Patients with G14459A mitochondrial DNA mutation present as 5 different phenotypes, namely Leber hereditary optic neuropathy,<sup>4,6</sup> Leber hereditary optic neuropathy plus dystonia,<sup>2,5</sup> childhood-onset dystonia,<sup>1,3-6</sup> Leigh or Leigh-like syndrome,<sup>7,9</sup> and clinically asymptomatic.<sup>1,3-5</sup> The childhood-onset phenotype associated with the G14459A mitochondrial DNA mutation has characteristics of dystonia, short stature, bulbar and corticospinal tract dysfunction, and striatal necrosis on brain magnetic resonance imaging (MRI). The Leigh phenotype shows developmental delay and brain stem lesions on MRI. The case of a patient presenting with childhood-onset, progressive dystonia, and rigospasticity with

the homoplasmic G14459A mitochondrial DNA mutation showing interesting manifestations on MRI is described. This patient was treated with sodium succinate to improve complex I deficiency because his symptoms and MRI abnormalities progressed, despite treatment with coenzyme Q10 and L-carnitine.

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## Case Report

The patient was an 11-year-old boy with no family history of optic neuropathy or dystonia. He presented with focal dystonia in the right upper limb at 3 years of age, and his disease progressed over 4 years to dystonia in both the upper and the lower limbs on his dominant right side. At 5 years of age, he was able to walk slowly without holding a handrail. However, at 7 years of age, he had severe dysarthria and was unable to walk without support owing to dystonia and spasticity. He had neither mental retardation (verbal IQ, 129; performance IQ, 97; full-scale IQ, 115 by the Weschler Intelligence Scale for Children) nor short stature. Ophthalmologic examination showed no remarkable findings indicative of optic neuropathy. Magnetic resonance imaging findings at 3 years of age showed high signal intensity lesions in bilateral putamina on fluid-attenuated inversion recovery images (Figure 1A-C) and diffusion-weighted images (Figure 1D). With time, the high signal intensity lesions on diffusion-weighted images migrated from the putamina to the caudate nuclei (Figure 1E-L). The MRI findings obtained at 6 years of age showed that the high signal intensity lesions had spread to the bilateral caudate nuclei and the midbrain on fluid-attenuated inversion recovery images (Figure 1I-K) and diffusion-weighted images (Figure 1L). On laboratory examination at 7 years of age, blood cell counts were normal, and the concentrations of lactate and pyruvate were not elevated in serum and cerebrospinal fluid. The serum concentrations of copper and ceruloplasmin were normal. In the serum Amino acid analysis, organic acid level in urine, and levels of lysosomal enzyme in white blood cells were found to be normal. Sequence analysis of the white blood cell mitochondrial DNA from this patient showed the presence of a homoplasmic G>A transition mutation at nucleotide position 14 459 in the reduced nicotinamide adenine dinucleotide dehydrogenase subunit 6 gene (Figure 2).

The patient had been treated with coenzyme Q10 (2 mg/kg/d), L-carnitine (90 mg/kg/day), and vitamins since the age of 4 years. However, his symptoms and MRI abnormalities progressed gradually despite treatment. Therefore, oral administration of sodium succinate (250 mg/kg/d) was started from the age of 7 years, on the basis of the presence of G14459A mitochondrial DNA mutation (which can cause complex I deficiency) and a previous case report of a patient with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS).<sup>10</sup>

On the follow-up MRI examinations over the subsequent 4 years, progression of MRI abnormalities appeared suppressed, but there was no improvement in dystonia (Figure 1M-T).

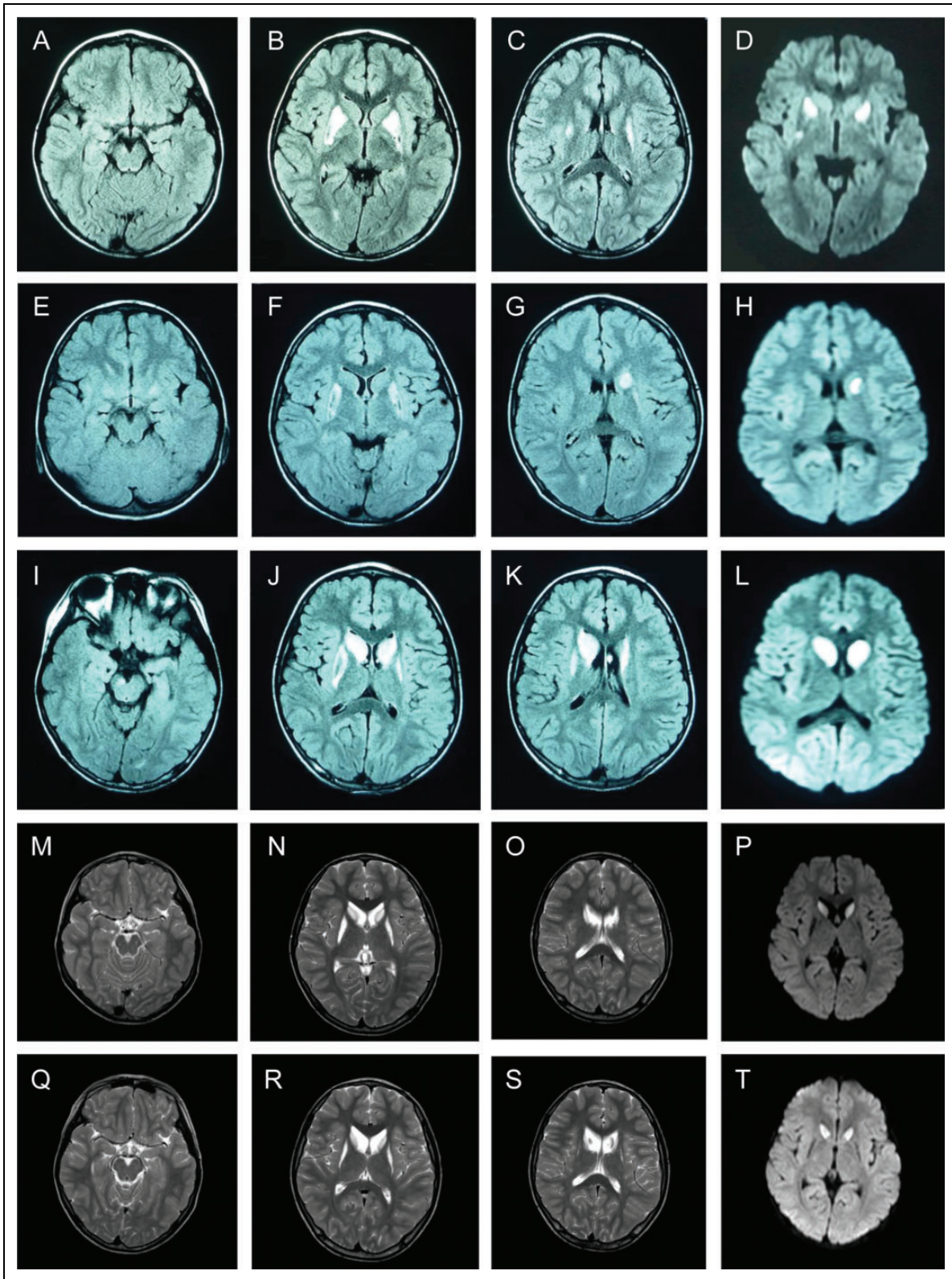
## Discussion

In the present case, mitochondrial DNA analysis of the entire region revealed a G>A transition mutation at nucleotide position 14 459, leading to alanine-to-valine amino acid substitution at position 72 of the reduced nicotinamide adenine dinucleotide dehydrogenase subunit 6 of complex I. The

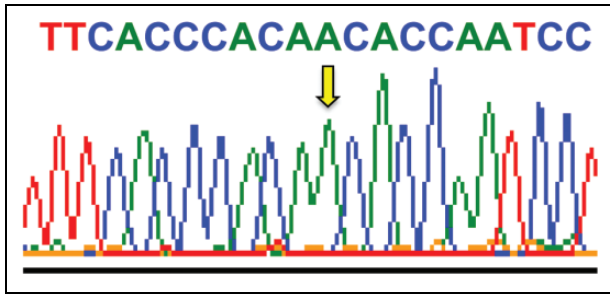
G14459A mitochondrial DNA mutation has been reported in the following patients: 9 with childhood-onset dystonia, 6 with Leber hereditary optic neuropathy, 4 with Leber hereditary optic neuropathy plus dystonia, 4 with Leigh or Leigh-like syndrome, and 4 who were clinically asymptomatic. The general features of cases reported to be of the dystonia phenotype were progressive generalized dystonia and/or optic neuropathy. The common finding on brain MRI was striatal necrosis without brain stem lesions. The clinical findings of Leigh disease are optic involvement, early developmental delay, and hypotonia. The patients with Leigh-like encephalopathy showed visual dysfunction, ataxia, and hearing loss. T2-weighted magnetic resonance images showed high signal intensity lesions in the medial thalamic nuclei, anterior pons, and cerebral peduncles in one patient and in the dorsal midbrain and red nucleus in other patients, in addition to a basal ganglia lesion. The patient reported in our study presented with the dystonic phenotype and Leigh-like findings on neuroimaging, showing degeneration in the bilateral striata and right substantia nigra. The variation in clinical expression indicates that modifying nuclear factors are likely involved, playing a role in the clinical expression of mitochondrial diseases.

The diffusion-weighted MRI findings in our patient are characteristic. With time, high signal intensity lesions on diffusion-weighted images migrated from the putamina to the caudate nuclei, which closely correlated with his disease progression. Diffusion-weighted images enhance the restricted mobility of water molecules in the brain, and it is a useful tool for detecting acute ischemic lesions in patients with stroke. The pathophysiology of the diffusion abnormalities associated with mitochondrial diseases remains unclear, although it has been reported in some patients with Leigh disease.<sup>11</sup> Considering the finding that diffusion abnormalities migrated from the putamina to the caudate nuclei in parallel with the disease progression in this patient, diffusion abnormalities might be caused by the chronic mitochondrial respiratory dysfunction due to the mutation of the reduced nicotinamide adenine dinucleotide dehydrogenase subunit 6 gene.

Several drugs for mitochondrial encephalopathy have been reported. They include coenzyme Q10, cytochrome c nicotinamide, dichloroacetate, L-arginine, and succinate. These drugs (except for L-arginine) are mitochondrial respiratory chain enzymes or its substrates and are considered to compensate for the defects in the corresponding pathways. Because the G14459A mitochondrial DNA mutation could cause complex I deficiency, oral administration of sodium succinate was started on the basis of a previous case report of a patient with MELAS.<sup>10</sup> The proposed pharmacological mechanism is that the respiratory capacity with the defect in complex I can be improved or restored by succinate administration through the activation of the complex II system. It has been reported that succinate enhances electron flow from complex II to complex III (coenzyme Q cytochrome c reductase) and to complex IV (cytochrome c oxidase), enabling these 2 energy coupling sites to operate normally. In the present case, progression of MRI abnormalities appears to have been suppressed for 4 years after



**Figure 1.** A-D, Brain magnetic resonance imaging (MRI) obtained at 3 years 2 months of age shows high signal intensity lesions with partially cystic lesions in the bilateral putamina on fluid-attenuated inversion recovery images (A-C) and diffusion diffusion-weighted imaging (D). E-H, Brain MRI obtained at 5 years 2 months of age show a high signal intensity lesion that is newly detected in the left caudate nucleus on fluid-attenuated inversion recovery images (E-G). Diffusion-weighted imaging shows that the bilateral putamina are iso- or hypointense and the left caudate nucleus is hyperintense (H). I-L, Brain MRI obtained at 6 years 11 months of age shows high signal intensity lesions spread to bilateral caudate nuclei and the midbrain (right substantia nigra) on fluid-attenuated inversion recovery images (I-K) and diffusion-weighted imaging (L), in addition to the putaminal hyperintensities. M-O, Brain MRI obtained at 8 years 6 months of age shows high signal intensity lesions in the bilateral putamina and caudate nuclei on T2-weighted (M-O) and diffusion-weighted imaging (P). Q-T, Brain MRI obtained at 10 years 5 months of age shows high signal intensity lesions in the bilateral putamina and caudate nuclei on T2-weighted (Q-S) and diffusion-weighted imaging (T). There is a trend for decrease in striatal volume. A-C, E-G, I-K: fluid-attenuated inversion recovery images; M-O, Q-S: T2-weighted images; and D, H, L, P, T: diffusion-weighted images.



**Figure 2.** Sequence analysis of the white blood cell mitochondrial DNA from this patient shows the presence of a homoplasmic G>A transition mutation at nucleotide position 14 459 in the reduced nicotinamide adenine dinucleotide dehydrogenase subunit 6 gene.

treatment with sodium succinate. There is a possibility that treatment with sodium succinate is helpful in patients with G14459A mitochondrial DNA mutation, although further investigation is necessary.

#### Authors' Note

This work was done at Tokyo Metropolitan Children's Medical Center. This case has not been presented elsewhere.

#### Author Contribution

AK wrote the manuscript, reviewed the literature, and prepared the manuscript for submission. HO and MK reviewed the article. YG performed genetic analysis.

#### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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#### Ethical Approval

This study was done in accordance with the rules set by Tokyo Metropolitan Children's Medical Center review board.

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