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Case Report
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The Neuroimaging Studies of a Patient of 16q12.2q21 Deletion Involving *GNAO1* Gene with Non-Progressive Dystonia

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Abstract

We report a patient with late onset non-progressive dystonia which developed at the age of 12 years associated with 16q12 deletions involving *GNAO1*. This patient showed unique neuroimaging findings; narrowed bilateral carotid artery, high T2WI and flair signal intensity of periventricular white matter, and cerebral hypoperfusion of bilateral periventricular white matter, basal ganglia, and frontal cortices. It remains to be clarified if these findings are related to the deletion of *GNOA1* or other genes.

Keywords: *GNAO1*; Dystonia; 16q12 Deletion; Neuroimaging; SPECT; MRI angiography

Introduction

The heterozygous *GNAO1* variants have been known to cause Developmental Epileptic Encephalopathy (DEE) [1] and early onset severe movement disorder [2]. It has been revealed that loss-of-function variants cause DEE, while gain of function variants can cause early onset mainly dystonic movement disorder [3,4]. Recently, late-onset dystonia has been reported as a milder form of *GNAO1* encephalopathy [5,6], most of which revealed missense variants except for one case of deletion.

16q12.2q21 deletion is a rare disorder associated with developmental delays, intellectual disabilities, and dysmorphic facial features [7]. Recently, late onset non-progressive dystonia associated with 16q12 deletions including *GNAO1* has been reported in three patients [8,9,5], whose dystonia developed at the ages of 9, 20 and 9 years each. Here, we present the first Japanese case of 16q12 deletion syndrome with non-progressive dystonia, who had unique neuroimaging findings.

Case Presentation

The patient is a 41-year-old woman born at 39 weeks gestation to healthy, non-consanguineous parents. There was no family history of neurological disorders, and her birth weight, height, and head circumference were within normal ranges. Shortly after birth, she exhibited feeding difficulties, hypotonia, molar dysplasia, and developmental delays. Her facial features included low-set ears, a low nasal bridge, a slightly thick upper lip, and a short neck. She achieved head control at 1 year and 2 months and was able to walk independently at 3 years and 8 months. Her speech development included a few words by 2 years and 6 months and two-word sentences by 6 years. At 12 years old, she exhibited dystonia in her right leg, which worsened, leading to walking difficulties by 14 years. The brain MRI at 13 years old showed disseminated high intensity signal of the white matter around the lateral ventricle on T2WI and FLAIR (Figure 1a and 1b) and MR angiography showed stenosis of the bilateral internal carotid arteries (Figure 1c). At 25 years, dystonia extended to her neck and right upper limb girdle, and she suffered from dysphagia, frequent choking, and muscle weakness in both lower limbs, but no intellectual regression. The examination at 25 years old showed reduced deep tendon reflexes of the lower extremities and reduced rage of movement of the ankle. There were no pyramidal symptoms, but dystonic hypertonus was evident in the neck muscles and the right upper limb girdle with twisted dystonic posture of the neck and upper trunk. She could walk

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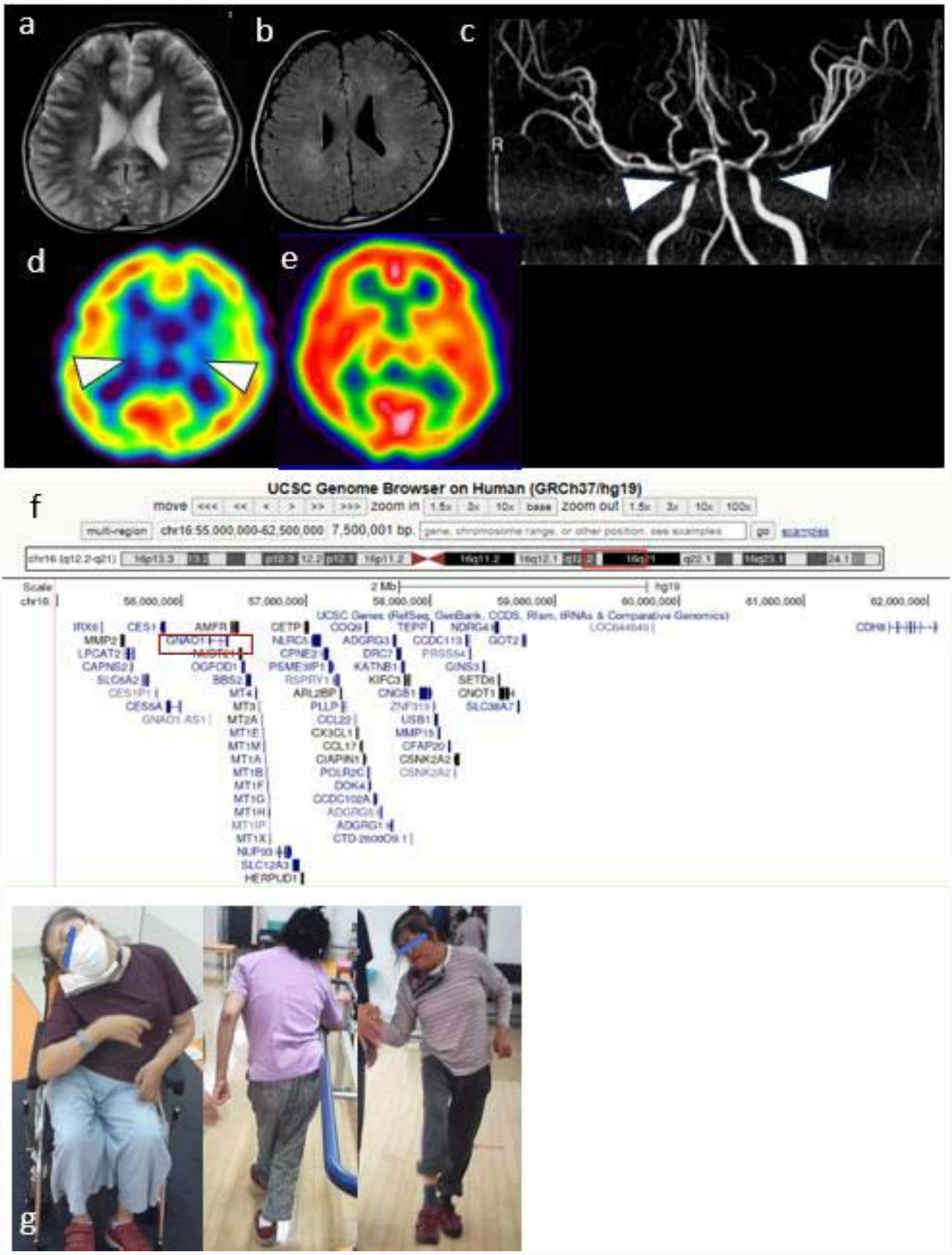

Figure 1: The results of neuroimaging, genetic studies, and clinical presentation.
The brain MRI at 13 years old showed high signal intensity of periventricular white matter on T2WI (a) and FLAIR (b), which was persistent on the repeat imaging at 18 and 35 years old. MR angiography at age 13 showed stenotic bilateral carotid artery (arrow heads) without Moyamoya vessels (c). ECD-SPECT at 35 years old showed relative hypoperfusion of the bilateral periventricular white matter, basal ganglia, and thalami (arrow heads) (d) as compared with normal study (e). The genetic study revealed 16q12 deletion, among which *GNAO1* gene was included (f). At age 41, the patient exhibited segmental dystonia in the neck and upper limb girdle while sitting on the wheel chair and assistance is required on walking (g). The patient and her family gave permission on the photo presentation.

10 steps using both hands supported and could read and write in Hiragana, as well as create and send emails on her cell phone. The nerve conduction study showed reduced CMAP of the tibial nerve, but MCV was normal, suggesting axonal neuropathy. Blood tests showed no abnormalities, and amino acid analysis and tandem mass spectrometry were unremarkable. 99mTc-Ethyl Cysteinate Dimmer (ECD)-SPECT at 25 years old showed relative hypoperfusion of the bilateral periventricular white matter, basal ganglia, and frontal cortices (Figure 1d), which was evident as compared with normal study (figure 1e). The repeat MRI at 18 and 35 years old showed the same high intensity signal around bilateral lateral ventricles and no atrophy of the basal ganglia. The MR angiography at 35 years old confirmed narrowing of the bilateral internal carotid artery.

Family-based whole-exome sequencing, conducted as previously reported [10], identified a heterozygous de novo pathogenic deletion of 16q12.2q21 (Chr16: 55,400,000-59,800,000, GRCh37/hg19), involved *GNAO1* (Figure 1f). The patient and her family provided informed consent for next-generation sequencing and publication of this case report. The study was approved by the Ethics Review Boards of Miyagi Children's Hospital.

Rehabilitation therapy and botulinum toxin injection on the neck and shoulder muscles were initiated for dystonia. Since the age of 27, oral treatments including levodopa, dantrolene sodium, diazepam, tizanidine hydrochloride, and gabapentin were started, leading to some improvement in walking. However, segmental dystonia of the neck and the right upper limb girdle persisted. Currently, she suffered from no worsening of dystonia, and the condition remains non-progressive with assisted walk (Figure 1g).

Discussion

This case shares other features of 16q12 deletion syndrome, including developmental delay, intellectual disability and dysmorphic facial features. The patient exhibited with non-progressive childhood-onset dystonia. No significant genetic abnormalities other than the 16q12 deletion were found in this case. It remains to be clarified why haploinsufficiency of *GNAO1* gene can lead to late-onset dystonia [5,8].

Dystonia due to *GNAO1* gene abnormalities is reported to be difficult to treat [11], but there have been successful cases of Deep Brain Stimulation (DBS) therapy [8,12,11] and medication [9] in patients with 16q12 deletion-associated dystonia. In this case, oral treatments have been partially successful, but DBS has not yet been attempted, suggesting there may still be potential for further symptom improvement.

Interestingly, she presented narrowed bilateral carotid artery, but no sign of Moyamoya disease or infarction of the basal ganglia. It remains to be clarified if these findings are related to the deletion of *GNOA1* or other genes. The present patient showed high T2WI and FLAIR signal intensity of periventricular white matter. Furthermore, cerebral hypoperfusion was revealed in the same region, bilateral basal ganglia, and frontal cortices. These findings are first noted in the literature and may be related to the dystonia of this patient. However, further examination is required in other patients before drawing any conclusions.

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