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Case Report

# A case of severe movement disorder with *GNAO1* mutation responsive to topiramate

Saori Sakamoto [a], Yukifumi Monden [a,b,*], Ryoko Fukai [c,d], Noriko Miyake [c], Hiroshi Saito [a], Akihiko Miyauchi [a], Ayumi Matsumoto [a], Masako Nagashima [a], Hitoshi Osaka [a], Naomichi Matsumoto [c], Takanori Yamagata [a]

[a] *Department of Pediatrics, Jichi Medical University, Tochigi, Japan*
[b] *Department of Pediatrics, International University of Health and Welfare, 537-3 Iguchi, Shiobara, Tochigi 329-2763, Japan*
[c] *Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Japan*
[d] *Department of Neurology and Stroke Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan*

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**Abstract**

We report the case of a 19-year-old female patient who had progressive chorea associated with a *GNAO1* mutation. Chorea was refractory to multiple anticonvulsants, and the patient suffered from tiapride-induced neuroleptic malignant syndrome. After identification of a *GNAO1* missense mutation at the age of 18 years, topiramate treatment was initiated and the frequency of chorea decreased dramatically. The efficacy of topiramate may have been related to the inhibitory modulation of voltage-activated $Ca^{2+}$ channels. Given the side effects and complications associated with neuroleptics and deep brain stimulation, respectively, topiramate is recommended for the first-line management of severe chorea associated with a *GNAO1* mutation.


*Keywords:* Chorea; Pediatrics; *GNAO1*

## 1. Introduction

*GNAO1* (MIM 139311) encodes an alpha-subunit of heterotrimeric G-proteins (Gαo) abundantly expressed in brain tissue, especially neuronal synapses [1]. Since 1998, *GNAO1* mutations have been reported in a total of 22 patients. In 11 of these patients, the *GNAO1* mutation phenotype was characterized by early infantile epileptiform encephalopathy. The remaining 11 cases manifested as a progressive movement disorder [2–5]. Saitsu et al. [4] reported 4 of these cases, including our current case (*patient 4*), with severe involuntary movements.

A variety of medications have been used to treat pediatric patients with severe chorea, including antiepileptics, neuroleptics [2], and deep brain stimulation (DBS) [3,5]. These treatments have been reported to have varying levels of success; however, in most cases, patients

*Abbreviations:* DBS, deep brain stimulation; EEG, electroencephalography; GNAO1, G protein subunit alpha o1; MRI, magnetic resonance imaging

* Corresponding author at: Department of Pediatrics, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-city, Tochigi, Japan. Fax: +81 285 44 8329.
*E-mail address:* mon4441977319@jichi.ac.jp (Y. Monden).

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presenting with severe progressive chorea are resistant to even maximum doses of anticonvulsants.

Here, we report a young female case of a progressively developing chorea due to *GNAO1* mutation in whom topiramate therapy was clearly effective.

## 2. Case description

The clinical course from 0 to 18 years before initiating topiramate therapy was as previously described as *patient 4* by Saitsu et al. [4]. Hence, in this article, we describe the specific frequency of chorea episodes after different treatments, especially before and after administration of topiramate (Fig. 1).

At the time of this report, the patient was a 19-year-old female. Developmental milestones were normal until 7 months. From 11 months, the patient developed severe motor and developmental delays. Following a febrile generalized convulsive seizure at 4 years, the patient developed generalized chorea of the extremities. Her chorea presented as generalized movement occurring most frequently during infection or pain and disappearing during sleep. Although episodes occurred several times per day and usually lasted up to 30 min, the patient required continuous intravenous administration of midazolam for adequate symptom control when chorea persisted for more than a few hours. Laboratory data at 5 years were as follows: normal blood cell counts and biochemistry, normal lactic acid and pyruvate levels in the blood and spinal fluid, and the absence of anti-VGKC antibody.

From 10 years, the patient suffered progressive developmental regression. Magnetic resonance imaging (MRI) at 10 years demonstrated diffuse brain atrophy in the cerebral cortex and basal ganglia. At 13 years, progressive atrophy of the cerebrum, cerebellum, and brain stem as well as thinning of the corpus callosum were observed. The MRI findings at 10 and 13 years old were previously described as *patient 4* by Saitsu et al. [4].

Despite the administration of diazepam, midazolam, and phenobarbital, chorea episodes increased to several

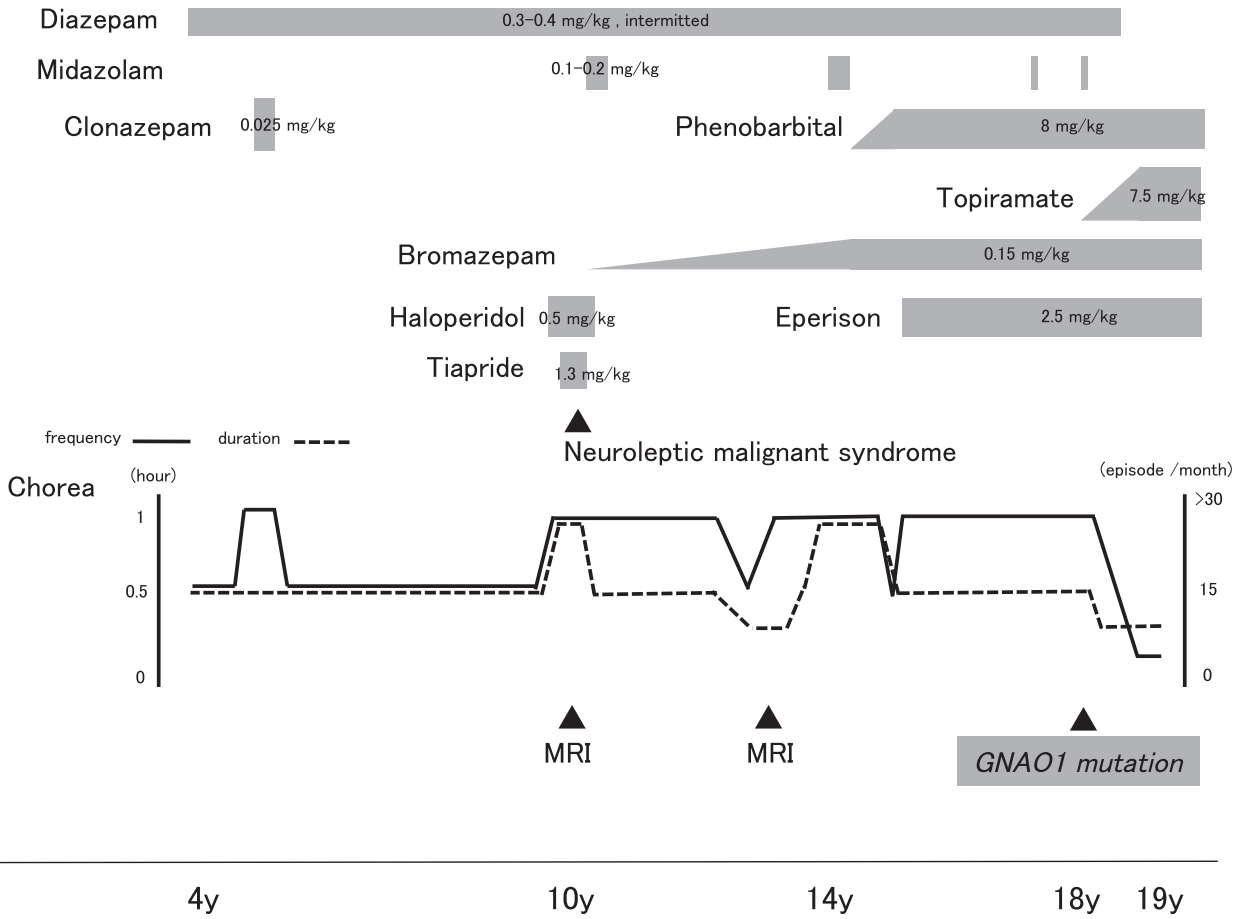


Fig. 1. Clinical course of treatment for chorea. When chorea episodes persisted or were frequent despite treatment with diazepam, the patient required continuous intravenous administration of midazolam. Haloperidol and tiapride therapy where discontinued due to the risk of neuroleptic malignant syndrome at 10 years. Although her episodes of chorea were frequent with these various pharmacological treatments, topiramate decreased the number of episodes, which led to a reduced need for diazepam and midazolam. *GNAO1*, G protein subunit alpha o1; MRI, magnetic resonance imaging.

Table 1
Clinical characteristics of patients with *GNAO1* mutations presenting with a movement disorder in the absence of epileptic encephalopathy [2–5]. FMDR, Fahn-Marsden Dystonia Rating Scale; MRI, magnetic resonance imaging; ICU, intensive care unit; mo, months; y, years.

| Case (reference) | Sex | Age | Age at initial presentation | Pattern of movement disorders | Age of onset of movement disorders | Effective treatment for movement disorders | Frequency or severity of movement disorders | Outcome of treatments | MRI findings | Mutation |
|---|---|---|---|---|---|---|---|---|---|---|
| Present case | F | 18 y | 7 mo | Chorea | 4 y | Topiramate | More than once a day | Once a month | Global atrophy, thin corpus callosum (11 y, 14 y) | c.625C>T |
| 1 (4) | F | 13 y | 4 mo | Athetosis, dystonicus | 4 y | Not indicated | Multiple times to ICU | Not indicated | Normal (4 y, 12 y) | c.736G>A |
| 2 (2) | M | 5 y | 3 mo | Chorea, ballismus | 4 y | No treatment | Intermitted | Intermittent | Normal (12 mo) | c.736G>A |
| 3 (2) | F | 5 y | 3 mo | Chorea, ballismus | 4 y | Tetrabenazine | Multiple time to ICU | Effectively controlled | Normal (12 mo), global atrophy (5 y) | c.736G>A |
| 4 (2) | F | 4 y | 1 mo | Chorea | 3 y 10 mo | None | Multiple time to ICU | Died of respiratory complications at 4 y | Normal (13 mo) | c.625C>G |
| 5 (2) | F | 10 y | 6 mo | Chorea, ballismus | 6 mo | Baclofen, clobazam, tetrabenazine, haloperidol, diazepam | Daily, multiple time to ICU | Died of sepsis at 10 y | Normal (4 y), global atrophy and T2 hypointensity in globus pallidi (9 y) | c.736G>A |
| 6 (2) | M | 16 y | 6 mo | Chorea | 3 y | Risperidone, benzodiazepines | Multiple time to ICU | Shorter length of hospitalization | Normal (3 y), global atrophy (15 y) | c.626G>A |
| 7 (2) | M | 15 y | 5 mo | Chorea | Mild dyskinesia (5 mo), generalized chorea(14 y) | Tetrabenazine, diazepam | Lost functional movement | Improved | T2 hypointensity in globus pallidi (14 y) | c.736G>A |
| 8 (3) | M | 8 y | 18 mo | Chorea | 17 mo | Deep brain stimulation | Multiple time to ICU | No admissions required | Normal | c.626G>A |
| 9 (3) | M | 6 y | 2 y | Chorea | 2 y | Deep brain stimulation | Multiple time to ICU | FMDRS dropped from 65.5 to 34.0 | Normal | c.626G>A |
| 10 (5) | F | 5 y | 13 mo | Choreo-athetosis | 2 y | Deep brain stimulation | Multiple time to ICU | FMDRS dropped from 89.0 to 9.0 | Normal | c.698A>C |

times a month. Therefore, haloperidol and tiapride therapies were initiated in response to an increased frequency of episodes. However, the patient suffered from hyperthermia and elevated creatine kinase levels, and these medications had to be discontinued due to the development of neuroleptic malignant syndrome. The frequency of chorea episodes increased under normal conditions as well as during pyrexia, infection, and pain. When chorea persisted for more than a few hours, the patient required continuous intravenous administration of midazolam for adequate symptom control. Despite the administration of diazepam, midazolam, bromazepam and phenobarbital, chorea episodes occurred once a day or more.

At 18 years, a molecular genetic analysis revealed a *de novo* missense mutation in exon 6 of *GNAO1*(c.625C>T, p.Arg209Cys) as previously described [4]. Based on this evidence, topiramate administration was initiated and significantly reduced the frequency of chorea episodes to about two per month. Although a few episodes of chorea occurred during infection, just single injection of midazolam effectively controlled them. At 19 years, episodes occurred primarily during infection and menstruation, but usually lasted no more than ten minutes. The frequency of chorea decreased to about once per month, and no additional administration was required for exacerbations of chorea (Fig. 1).

## 3. Discussion

Here, we have described the case of a female patient with a *GNAO1* mutation who progressively developed chorea, quadriplegia, and global delay with the absence of severe seizures. The patient's chorea demonstrated complete resistance to antiepileptics. Furthermore, the patient suffered from tiapride-induced neuroleptic malignant syndrome. At 18 years, we identified a *de novo* missense mutation in exon 6 of *GNAO1*. The clinical features of patients reported in the literature with *GNAO1* mutations causing a distinctive movement disorder (including the current case) are summarized in Table 1 [2–5].

A variety of medications have been used to treat severe chorea in pediatric patients. Some reported cases of chorea due to a *GNAO1* mutation were effectively managed using neuroleptics or DBS [2,3,5]. However, in most cases, patients presenting with severe progressive chorea are resistant to anticonvulsant therapy. Yet, in the current case, baseline chorea was dramatically improved by topiramate.

In previous studies, topiramate was also reported as effective in the control of hemichorea and essential tremor via enhancement of GABA-ergic neurotransmission [6,7]. On the other hand, the ability of topiramate to modulate high voltage-activated $Ca^{2+}$ channels was hypothesized as the mechanism of action for its beneficial effects on chorea associated with *GNAO1* mutations; indeed, *GNAO1* mutations have been reported to alter central nervous system (CNS) $Ca^{2+}$ channel modulation [8]. The association of Gαo with $Ca^{2+}$ currents in the CNS is likely responsible for alterations of $Ca^{2+}$ channel modulation with *GNAO1* mutations. In the hippocampal CA3 region, activation of G-protein coupled A2 adrenergic receptors by norepinephrine attenuates epileptiform activity through a mechanism involving the inhibitory effect of Gαo-mediated signaling on voltage-dependent $Ca^{2+}$ channels [9]. Therefore, it can be hypothesized that certain mutations of *GNAO1* impair the inhibition of $Ca^{2+}$ channel currents, resulting in a form of epilepsy that is sensitive to topiramate.

Furthermore, while the function of Gαo in the basal ganglia is unknown, Gαo-deficient mice demonstrate severe impairments in motor control [9,10]. Moreover, brain MRIs in the current case and in cases 5 and 7 (Table 1) showed atrophy or T2 hypointensity in the basal ganglia. These findings lead us to speculate that the inhibitory effect of topiramate on voltage-activated $Ca^{2+}$ currents also underlies the observed improvements in chorea.

According to the above studies, topiramate may be superior to other antiepileptics for the treatment of progressive chorea related to a *GNAO1* mutation. As per Table 1, chorea in cases 3, 5, 6, and 7 was responsive to tetrabenazine [2]; however, tetrabenazine can trigger acute dystonic reactions and/or neuroleptic malignant syndrome [11]. Chorea in cases 8, 9, and 10 responded well to DBS [3,5], and it was concluded that DBS was a preferable option in patients refractory to pharmacological treatment [3] (e.g., as in case 4 [2]). However, surgical complications have been associated with DBS, including intracranial hemorrhage, infection, and death, in more than 2% of cases, respectively [12].

Our report has several limitations. First, it was a single case report, and the efficacy of topiramate should be studied in more patients. Second, we did not evaluated the patient's chorea with quantified scales, and will examine further with Unified Huntington's Disease Rating Scale [13].

## 4. Conclusions

Considering the hypothesized mechanism by which *GNAO1* mutations mediate movement disorders and the known side effects of neuroleptics, topiramate is a promising option for the management of *GNAO1*-mutation-related chorea and should be considered prior to DBS.

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## References


[1] Jiang M, Bajpayee NS. Molecular mechanisms of go signaling. Neurosignals 2009;17:23–41.

[2] Ananth AL, Robichaux-Viehoever A, Kim YM, Hanson-Kahn A, Cox R, Enns GM, et al. Clinical course of six children with *GNAO1* mutations causing a severe and distinctive movement disorder. Pediatr Neurol 2016;59:81–4.

[3] Kulkarni N, Tang S, Bhardwaj R, Bernes S, Grebe TA. Progressive movement disorder in brothers carrying a *GNAO1* mutation responsive to deep brain stimulation. J Child Neurol 2016;31:211–4.

[4] Saitsu H, Fukai R, Ben-Zeev B, Sakai Y, Mimaki M, Okamoto N, et al. Phenotypic spectrum of *GNAO1* variants: epileptic encephalopathy to involuntary movements with severe developmental delay. Eur J Hum Genet 2016;24:129–34.

[5] Yilmaz S, Turhan T, Ceylaner S, Gökben S, Tekgul H, Serdaroglu G. Excellent response to deep brain stimulation in a young girl with *GNAO1*-related progressive choreoathetosis. Childs Nerv Syst 2016;32:1567–8.

[6] Nakamura K, Kodera H, Akita T, Shiina M, Kato M, Hoshino H, et al. De Novo mutations in *GNAO1*, encoding a Gαo subunit of heterotrimeric G proteins, cause epileptic encephalopathy. Am J Hum Genet 2013;93:496–505.

[7] Chang KH, Wang SH, Chi CC. Efficacy and safety of topiramate for essential tremor: a meta-analysis of randomized controlled trials. Medicine (Baltimore) 2015;94:e1809.

[8] Kim JA, Jung S, Kim MJ, Kwon SB, Hwang SH, Kwon KH. A case of vascular hemichorea responding to topiramate. J Mov Disord 2009;2:80–1.

[9] Goldenstein BL, Nelson BW, Xu K, Luger EJ, Pribula JA, Wald JM, et al. Regulator of G protein signaling protein suppression of Galphao protein-mediated alpha2A adrenergic receptor inhibition of mouse hippocampal CA3 epileptiform activity. Mol Pharmacol 2009;75:1222–30.

[10] Jiang M, Gold MS, Boulay G, Spicher K, Peyton M, Brabet P, et al. Multiple neurological abnormalities in mice deficient in the G protein Go. Proc Natl Acad Sci USA 1998;95:3269–74.

[11] Burke RE, Reches A, Traub MM, Ilson J, Swash M, Fahn S. Tetrabenazine induces acute dystonic reactions. Ann Neurol 1985;17:200–2.

[12] Bronstein JM, Tagliati M, Alterman RL, Lozano AM, Volkmann J, Stefani A, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. Arch Neurol 2011;68:165.

[13] Huntington Study Group. Unified Huntington's disease rating scale: reliability and consistency. Mov Disord 1996;11:136–42.