Clinical Observations

**Clinical Course of Six Children With GNAO1 Mutations Causing a Severe and Distinctive Movement Disorder**

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**ABSTRACT**

**OBJECTIVES:** Mutations in GNAO1 have been described in 11 patients to date. Although most of these individuals had epileptic encephalopathy, four patients had a severe movement disorder as the prominent feature. We describe the largest series of patients with de novo GNAO1 mutations who have severe chorea, developmental delay, and hypotonia in the absence of epilepsy. **METHODS:** Six patients with recurrent missense mutations in GNAO1 as detected by whole exome sequencing were identified at three institutions. We describe the presentation, clinical course, and response to treatment of these patients. **RESULTS:** All six patients exhibited global developmental delay and hypotonia from infancy. Chorea developed by age four years in all but one patient, who developed chorea at 14 years. Treatments with neuroleptics and tetrabenazine were most effective in the baseline management of chorea. The chorea became gradually progressive and marked by episodes of severe, refractory ballismus requiring intensive care unit admissions in four of six patients. Exacerbations indirectly led to the death of two patients. **CONCLUSIONS:** Patients with GNAO1 mutations can present with a severe, progressive movement disorder in the absence of epilepsy. Exacerbations may be refractory to treatment and can result in life-threatening secondary complications. Early and aggressive treatment of these exacerbations with direct admission to intensive care units for treatment with anesthetic drips may prevent some secondary complications. However the chorea and ballismus can be refractory to maximum medical therapy.

**Keywords:** GNAO1, chorea, ballismus, whole exome sequencing, movement disorder

**Introduction**

G alpha (G), is a heterotrimeric G protein expressed in neurons and implicated in the modulation of synaptic transmission.1 GNAO1 (MIM139311) mutations have been reported in 11 individuals.2-5 The initial series suggested that Ohtahara syndrome (early infantile epileptic encephalopathy with burst suppression) was the characteristic phenotype.2
However, two of the patients in a second series presented with movement disorder and intellectual disability; one of these two individuals later developed seizures. Recently, two siblings with a progressive movement disorder were described. We report six patients with de novo mutations of the GNAO1 gene who developed chorea, quadriplegia, global delay, and hypotonia without seizures. The movement disorder is severe, progressive, and in some cases life threatening. We detail the course of these six patients and their response to therapeutic measures.

Materials and Methods

Patients at three institutions with de novo GNAO1 mutations were identified by whole-exome sequencing. Clinical information was obtained via a medical record review. The project was reviewed by the Stanford Institutional Review Board, and informed consent was obtained from participating families.

Patient descriptions

Patients 1 and 2 are dizygotic twins (male and female) who initially presented at age three months with poor head control and motor delay. The results of their brain magnetic resonance imaging (MRI) at age 12 months were normal. At four years, they developed chorea and ballismus. Movements were initially intermittent with abatement during sleep but have since increased in frequency and severity. Beginning at age five years, Patient 2 has had exacerbations of chorea which require hospitalizations in the pediatric intensive care unit (ICU). Since age 5.5 years, Patient 2 has experienced daily exacerbations consisting of 5 to 30 minutes of chorea and ballismus with tachycardia, hyperthermia, and diaphoresis. Triggers include excitement and stress. At 5.5 years, both siblings are nonambulatory with no expressive language and receptive language abilities that outpace expressive language. Patient 1 has limited voluntary head movements, inaccurate attempts at voluntary movements of her arms, and is training to use a head switch communication device. Patient 2 does not have sufficient motor control to use a communication device. Both require gastrostomy tube feeding. Both have a heterozygous c.736G>A mutation (p.E246K) in GNAO1 which was not detected in either parent, suggesting germ-line mosaicism. This change is located in a highly conserved region and is predicted to be pathogenic. In addition, this mutation has been previously reported in an individual with severe chorea without seizures.

Patient 3 presented with hypotonia in the first month of life after an unremarkable perinatal course. Concurrent with a viral illness at 3 years and 10 months, she developed chorea involving all four extremities and face. At 4 years 5 months, she had an exacerbation of chorea with a urinary tract infection, necessitating hospitalization in the ICU. She died secondary to respiratory complications during this hospitalization. She had severe global developmental delay, never sitting independently, grasping objects, or combining syllables. Whole-exome sequencing revealed a heterozygous de novo c.625C>G (p.R209G) mutation in GNAO1. This change is located in a highly conserved region and predicted to be pathogenic. A c.625C>T change has been reported in the recent report of patients with a predominantly movement phenotype.

Patient 4 presented in early infancy with a weak suck, poor head control, poor weight gain, and a few spontaneous movements. By age 6 months, she developed irregular, spastic movements of the head, neck, trunk, and her extremities. At four years of age, she developed generalized chorea, abating with sleep. Her brain MRI at age four years was normal. Until age eight years, she made small improvements in motor development with limited purposeful movements of her extremities and communication through eye movements and vocalizations. However, she remained wheelchair bound and required a mechanical ventilator. Her movements include a change in a highly conserved region and is predicted to be pathogenic. This change is located in a highly conserved region and is predicted to be pathogenic. A c.625C>T change has been reported in the recent report of patients with a predominantly movement phenotype. A de novo mutation (p.E246K) in GNAO1 was found in Patient 4, which was not detected in either parent, suggesting germ-line mosaicism. This change is located in a highly conserved region and is predicted to be pathogenic. In addition, this mutation has been previously reported in an individual with severe chorea without seizures.

Clinical Characteristics of Patients With GNAO1 Movement Disorder

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Presenting feature</td>
<td>Hypotonia, motor delay</td>
<td>Hypotonia, Motor delay</td>
<td>Hypotonia, Motor delay</td>
<td>Hypotonia, motor delay</td>
<td>Hypotonia, Motor delay</td>
<td>Hypotonia, motor delay</td>
</tr>
<tr>
<td>Age at initial presentation</td>
<td>3 mo</td>
<td>3 mo</td>
<td>1 mo</td>
<td>6 mo</td>
<td>6 mo</td>
<td>5 mo</td>
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<tr>
<td>Dysmorphic features</td>
<td>None</td>
<td>Microcephaly</td>
<td>None</td>
<td>None</td>
<td>Hypertelorism</td>
<td>None</td>
</tr>
<tr>
<td>Chorea onset</td>
<td>12 mo</td>
<td>12 mo</td>
<td>13 mo</td>
<td>13 mo</td>
<td>13 mo</td>
<td>14 yr</td>
</tr>
<tr>
<td>Magnetic resonance imaging (MRI)brain</td>
<td>Normal at 12 mo</td>
<td>Normal at 12 mo, global atrophy at age 5.5 yr</td>
<td>Normal at 13 mo, global atrophy at age 5.5 yr</td>
<td>Normal at 13 mo, global atrophy and T2 hypointensity in globus pallidi at age 9 yr</td>
<td>Normal at 13 mo, global atrophy and T2 hypointensity in globus pallidi at age 15 yr</td>
<td>Normal at 13 mo, global atrophy and T2 hypointensity in globus pallidi at age 14 yr</td>
</tr>
<tr>
<td>Motor milestones achieved</td>
<td>Head control, voluntary arm movements</td>
<td>Head control</td>
<td>None</td>
<td>Head control, voluntary arm movements</td>
<td>Limited ambulation with walker, manually operates communication board</td>
<td>None</td>
</tr>
<tr>
<td>Expressive speech milestone</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Monosyllable words</td>
<td>None</td>
</tr>
<tr>
<td>achieved</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Intensive care unit (ICU) admission for chorea</td>
<td>Alive at 5.5 yr</td>
<td>Alive at 5.5 yr</td>
<td>Deceased at 4 yr</td>
<td>Alive at 16 yr</td>
<td>Alive at 15 yr</td>
<td>Alive at 15 yr</td>
</tr>
<tr>
<td>Mutation</td>
<td>De novo heterozygous c.736G&gt;A</td>
<td>De novo heterozygous c.736G&gt;A</td>
<td>De novo heterozygous c.625C&gt;G</td>
<td>De novo heterozygous c.736G&gt;A</td>
<td>De novo heterozygous c.626G&gt;A</td>
<td>De novo heterozygous c.736G&gt;A</td>
</tr>
</tbody>
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gastrostomy tube feedings. After age seven years, she developed exacerbations of chorea and ballismus associated with tachycardia, fever, and diaphoresis. These episodes occurred daily, lasted minutes to hours, and were triggered by infection, excitement, bowel movements, and emotional stress. Her baseline chorea became nearly continuous. She had a series of ICU admissions with each becoming more prolonged and requiring higher levels of intervention to control movements. Complications included pressure ulcers and femur fractures requiring pharmacologic paralysis for six weeks to allow healing, during which time she continued to have spells of autonomic instability with tachycardia, hypertension, and hyperthermia. At nine years, her repeat brain MRI that revealed mild generalized atrophy and subtle T2 hypointensities in globus pallidi. At age 10 years, she developed a severe exacerbation of ballismus in the setting of a *Clostridium difficile* infection and ultimately died of sepsis. A limited postmortem examination was performed, and brain pathology revealed decreased brain volume and chronic periventricular gliosis. Whole-exome testing revealed a *de novo* heterozygous missense mutation (c.736G>A) in the *GNAO1* gene, the same mutation that was identified in Patients 1, 2, and 6.

Patient 5 presented with hypotonia and motor delay from early infancy after an uneventful perinatal course. He developed chorea at age three years; at that time the MRI brain and spectroscopy were unremarkable. At age six years, he had multiple admissions for exacerbations of chorea, including one requiring intubation and sedation. For the next eight years, he had chorea at baseline and no hospitalizations. During this interval, he was wheelchair bound but was able to access a communication device with limited voluntary movements of his arms. Starting at age 15 years, he required numerous ICU admissions for chorea and ballismus. The exacerbations were characterized by tachycardia, fever, and diaphoresis leading to rhabdomyolysis. Since age 16 years, he has experienced motor regression, remaining wheelchair bound with gastrostomy tube feedings. He has effortful vocalizations that his family can recognize as words. Repeat brain MRI at age 15 years indicated volume loss and abnormally prominent ventricles. Whole-exome sequencing revealed a *de novo* heterozygous mutation in *GNAO1* (c.626G>A) (p. R209H). This amino acid is highly conserved, and the same amino acid is affected in Patient 3.

Patient 6 first presented in infancy with hypotonia, global developmental delay, and mild dyskinesia. He was stable until age 14 years, when he was able to stand and ambulate briefly using a walker and manually operate a communication board. He participated in school and had relatively spared receptive language and ability to engage socially. He required assistance with all activities of daily living. At 14.5 years, he developed generalized chorea that progressed over four months. He subsequently lost functional use of his hands and truncal control due to chorea. He also had weight loss and became newly dependent on gastrostomy tube feeds. Brain MRI showed subtle T2 hypointensity in the globus pallidi. Whole-exome sequencing revealed a *de novo* heterozygous missense mutation (c.736G>A) in the *GNAO1* gene, the same mutation identified in Patients 1, 2, and 4.

**Treatments for chorea**

Patient 1 has intermittent chorea not requiring treatment. Patient 2 has been admitted multiple times to the ICU for chorea/ballismus. Increasing doses of clonazepam, clonidine, and trazodone had no clear benefit. Midazolam drip that was titrated as high as 0.12 mg/kg/hr, and risperidone at 0.5 mg twice daily initially dramatically improved her signs; however, on subsequent admissions, risperidone at 9 mg/day was ineffective. During her most recent admission, tetrabenazine at 37.5 mg three times daily effectively controlled the movements, and risperidone and midazolam were withdrawn.

Patient 3 was treated unsuccessfully as an outpatient on a regimen of clonidine, valproic acid, clonazepam, and bethanechol. On initial presentation to the ICU, she was given intravenous lorazepam, and trihexyphenidyl was added to the regimen. When movements continued, she was intubated and started on sedative drips initially with dexmedetomidine, then with propofol, and later midazolam. Patient 4 underwent multiple medication trials throughout her life. Until age seven years, clonazepam and cllobazam provided modest relief, but chorea became persistent in spite of 50 mg of cllobazam per day. Other medications that were ineffective included topiramate, levetiracetam, valproic acid, and clonidine. The medication regimen which ultimately controlled her baseline chorea before her death was baclofen 20 mg three time per day, cllobazam 20 mg three times daily, tetrabenazine 150 mg twice daily, haloperidol 6 mg twice daily, and diazepam 14 mg every four hours. While in the ICU, diazepam was the most effective medication for treating the storms of chorea and ballismus, at a maximum dosage of 27 mg every 2 hours. Continuous intravenous infusions of pentobarbital, propofol, versed, fentanyl, and dexmedetomidine were all used in the ICU setting. Paralysis with a continuous vecuronium infusion was used for six weeks to allow femur fractures to heal.

Patient 5 initially received minimal to no home medications for chorea. During ICU admissions, his storms of chorea were treated with high doses of continuous dexmedetomidine, opioids, and benzodiazepines. Vecuronium infusion was also required on several occasions to control his movements and prevent lactic acidosis. During his most recent ICU admission, risperidone 0.75 mg twice daily resulted in a dramatic improvement in his movements and a shorter length of hospitalization compared with previous episodes.

Patient 6 was treated unsuccessfully on an outpatient regimen of oxcarbazepine and clonazepam. He was admitted for excessive chorea and dehydration, and a rapid titration of risperidone was also ineffective. He improved and stabilized on high-dose oral diazepam, up to 40 mg three times per day, which was lowered subsequently to 20 mg three times per day after the addition of tetrabenazine (titrated to 125 mg/day).

**Discussion**

We describe six patients with global developmental delay, hypotonia, quadriplegia, and severe movement disorder attributed to mutations in the *GNAO1* gene. None of our patients has had seizures.3 Our patients all presented in early infancy with hypotonia and global developmental delay but typically developed a severe movement disorder with chorea and ballismus by age 4 years. Four of the six individuals had movements that were severe enough to require ICU hospitalization. Refractory movements were an indirect cause of death in two patients. Our cohort of patients supports the notion that *GNAO1* mutations can cause neurological signs in the absence of epilepsy and that movement disorder can represent the major source of morbidity in *GNAO1*-associated encephalopathy.

Four of our patients have the same c.736G>A mutation of *GNAO1* which results in substitution of a highly evolutionarily conserved glutamine residue at position 246. This change has also recently been reported by Saitou et al.6 in a patient with movement disorder and intellectual disability without epilepsy. The other two patients in our series have a missense mutation involving a highly conserved arginine at position 209. Saitou et al.6 along with Kulkarni et al.4 report patients with mutations involving the same residue. These patients also have a phenotype that consists primarily of movement disorder and static encephalopathy. Therefore, the mutations reported in our series appear relatively specific to the movement disorder phenotype as opposed to epileptic encephalopathy.

The baseline movement disorder in these patients is characterized by chorea. Patients develop severe exacerbations that can last hours to days and have a prominent autonomic component with tachycardia, hyperthermia, hypertension, and diaphoresis. Triggers include infection, excitement, anxiety, emotional stress, and bowel...
movements, although they frequently occur without an obvious trigger. The autonomic component cannot solely be accounted for by the intensity of the movement, because these paroxysmal changes continued to occur in Patient 4 even while paralyzed. The pathophysiology behind this dysautonomia is unclear. Paroxysmal sympathetic activity has been reported after a variety of acquired neurological insults, and autonomic instability is commonly reported in adult neurodegenerative movement disorders such as Parkinson disease.\(^7,8\)

Treatment of the movement disorder has been challenging. The severity of the chorea and ballismus in our patients is greater than in other disorders causing chorea in childhood. Baseline chorea has responded to tetrabenazine and neuroleptics, while the exacerbations appear to respond best to high dosages of benzodiazepines and neuroleptics. Tetrabenazine has been the most successful medication in controlling chorea in Patients 2, 4, and 6, but in Patient 4, no effect was observed until total daily dose exceeded 200 mg per day; she eventually was treated with a total daily dose of 300 mg, which is higher than doses previously reported for treating severe chorea in children.\(^9\) A recent report documents the success of deep brain stimulation in siblings with GNAO1 mutations.\(^9\)

The result of clinical brain MRI and MR spectroscopy was normal in all patients who were imaged under age five years. Patients 2, 4, and 5 later exhibited global volume loss with abnormally prominent ventricular size. This in combination with the findings of periventricular gliosis on postmortem examination in Patient 4 and clinical course with worsening movement disorder suggests a chronic neurodegenerative process.

G\(_0\) is the most abundant G protein in neurons, suggesting the importance of this protein in brain function.\(^1\) Mice null for the G\(_0\) protein have a movement phenotype with a generalized tremor and poor motor control as well as a shortened life span.\(^10\) The G\(_{10}\) subunits have been depicted to function in the regulation of ion channels.\(^11\) Further understanding of the mechanism by which G\(_{10}\) mutations lead to abnormal movements and autonomic dysfunction may lead to potential therapeutic targets for disabling signs.

We report six patients with developmental delay, quadriplegia, hypotonia, and severe chorea due to GNAO1 mutations. None have had seizures, which are the prominent feature reported in the initial series of patients with this mutation. Clinicians should consider this entity in the evaluation of patients with global developmental delay, hypotonia, and movement disorder, especially in the setting of chorea and ballismus. The severity of the movement disorder frequently requires hospitalization in the ICU. Movements appear to respond to tetrabenazine, benzodiazepines and neuroleptics. However, at times, maximal medical treatment has been insufficient to prevent life-threatening complications.

References