Journal of Bangladesh College of Physicians and Surgeons
Vol. 43, No. 3, July 2025

GNOA1 Gene Mutation in Children: A Case Report

HA KHAN[a], J PARVIN[b], D SAHA[c], S HOSSAIN[d], MM HOSSAIN[e], MSA BEGUM[f], NC SAHA[g]

Abstract:

GNOA1 gene mutations are rare genetic disorders linked to neurodevelopmental disorders in children. This case report describes the variable clinical manifestations of two unrelated children with GNOA1 gene mutations who were evaluated at a tertiary care hospital in Bangladesh. The first case presented with early-onset epilepsy along with movement disorders, while in the second case, movement disorders were observed without seizures. Both cases exhibited common features of global developmental delay. GNOA1 gene mutation was found in both cases using whole-exome sequencing. To our knowledge, these are indeed the first case report from Bangladesh..The findings from this case report contribute to the understanding of the diverse clinical spectrum of GNOA1 gene mutations and awareness of this variability is essential for accurate diagnosis, prognosis, and management.

Keywords: GNOA1 gene mutation, Children, Developmental delay, Early onset epilepsy, Movement disorders

(J Bangladesh Coll Phys Surg 2025; 43: 250-252)
DOI: https://doi.org/10.3329/jbcps.v43i3.82880

Introduction:

GNAO1(guanine nucleotide-binding protein, alpha-activity polypeptide O) disorder is a rare neurodevelopmental disorder that is inherited in an autosomal dominant fashion. Over 200 individuals with GNAO1-related disorders have been documented and published to date.[8] Variable phenotypes have been reported among individuals with this disorder. The clinical phenotypes of GNAO1 disorder are developmental delay, epilepsy, and movement disorders. Epilepsy presents in different forms, including early onset epileptic encephalopathy such as Ohtahara syndrome, as well as generalized and focal epilepsies that occur at various ages.[9] [10] Movement phenotypes associated with GNAO1 include chorea, dystonia, orofacial dyskinesia, and stereotyped hand movements.[2] [11] [12] Developmental milestones are also delayed in most patients with GNAO1 variants.[4] Interestingly, most patients mainly present phenotypes between epilepsy or movement disorder, whereas a small number of patients showed both epilepsy and movement phenotypes equally.[13] Patients with marked movement disorders without epilepsy have also been reported.[2] [4] Due to its rarity and phenotypic variability, diagnosis can be delayed or missed.

Here, we report 2 pediatric patients who carried GNAO1 variants with different clinical phenotypes. The aim of this case report is to contribute to the understanding of this rare genetic condition in children.

Case History:

Case -1

A 10-month-old girl , fourth issue and second twin of non-consanguineous parents came to our hospital , National Institute of Neurosciences (NINS) with complaints of recurrent seizures since the neonatal period, abnormal twisting movement since 7 months of age, and developmental delay (no neck control, bubbling and poor vision with no follow and fixation). Her perinatal course was uneventful. Her first twin has been

a. Dr. Husnea Ara Khan, Assistant Professor, Department of Pediatric Neurology, National Institute of Neurosciences & Hospital, Dhaka, Bangladesh.
b. Dr. Jobaida Parvin, Assistant Professor, Department of Pediatric Neurology, National Institute of Neurosciences & Hospital, Dhaka, Bangladesh.
c. Dr. Dipa Saha, Associate Professor, Department of Pediatric Neurology, Ad-din Women's Medical college, Dhaka, Bangladesh.
d. Dr. Sharmin Hossain, Junior Consultant, Department of Pediatric Neurology, National Institute of Neurosciences & Hospital, Dhaka, Bangladesh.
e. Dr. Mohammed Monir Hossain, Assistant Professor, Department of Pediatric Neurology, National Institute of Neurosciences & Hospital, Dhaka, Bangladesh.
f. Dr. Mst Shameem Ara Begum, Assistant Professor, Department of Pediatric Neurology, National Institute of Neurosciences & Hospital, Dhaka, Bangladesh.
g. Prof. Narayan Chandra Saha, Professor & Head, Department of Pediatric Neurology, National Institute of Neurosciences & Hospital, Dhaka, Bangladesh.

Address of Correspondence: Dr. Husnea Ara Khan, Assistant Professor, Department of Paediatric Neurology, National Institute of Neurosciences & Hospital, Sher-E-Bangla Nagar, Dhaka, Bangladesh. E-mail: kona5415@yahoo.com, Mob:01769111097

Received: 22 February, 2025 **Accepted:** 06 May, 2025

suffering from similar type of illness. Her seizure was multifocal clonic, occasional myoclonic. During the physical examination , it was observed that she had no interest to her surroundings, hypertonia with brisk deep tendon reflexes. She was treated with multiple antiseizure medications like levetiracetam, sodium valproate, and clobazam. Additionally, inj Vitamin B6, oral folinic acid, biotin were also added in suspicion of vitamin-responsive epilepsy but no response was found. Her epilepsy was lebelled as refractory. We considered developmental epileptic encephalopathy, GLUT-1 deficiency, and metabolic epilepsy as our differential diagnoses. Diagnostic workup that included serum metabolic screening, electroencephalography, and magnetic resonance imaging of the brain revealed no abnormalities. Cerebrospinal fluid (CSF) and serum glucose ratio was within normal limits. Finally, whole-exome sequencing with mitochondrial genome was sent to a genetic laboratory in a neigbouring country, which detected a likely pathogenic heterozygous missense mutation of the GNAO1 gene (c.520G>A, p.Asp174Asn)

Case -2

A 5-year-old boy, the second issue of nonconsanguineous parents, presented with developmental delay (motor, speech and cognition) and abnormal movement since 1.5 years of age. His movements were dyskinetic, sometimes choreoform involving both upper and lower limbs, intermittent in nature, persisted few minutes to few days, disappeared during sleep, and was aggravated by febrile illness, crying, and sound. He had no history of seizures. No family history of such types of illness. His perinatal period was uneventful. He could not walk but could stand briefly with support. On examination, he was alert and active, could follow simple commands, and had no focal neurological deficit, with normal tone and deep tendon reflexes.Initial differential diagnoses were organic aciduria, mitochondrial disorders, and genetic dystonia. His MRI of the brain and basic metabolic screening showed no abnormalities. Hence, Blood for whole exome sequencing was sent to a genetic lab in abroad. A likely pathogenic heterozygous missense mutation of the GNAO1 gene (c.626G>A,p.Arg209His) was found.

Discussion:

The GNAO1 gene encodes an alpha-subunit of heterotrimeric G-proteins (Gáo), which is most commonly expressed in the central nervous system and exhibits variable phenotypes. The main GNAO1-associated phenotypes are epilepsy, movement disorders, and global developmental delay. Variability in phenotypic expression complicates early diagnosis.

The cases presented in this report highlight the clinical heterogeneity associated with GNOA1 gene mutations in children. Genetic testing was crucial in identifying GNOA1 gene mutations as the underlying cause.

In this case report, both cases had some similarities and differences in clinical characteristics. The first case presented with a combination of epilepsy and movement disorders, where epilepsy was a prominent feature. On the other hand, in the second case, movement disorders were core features, and had no epilepsy. These phenotypic variabilities were reported in previous studies.[4 14] Amitha L et al reported six patients with mutations of the GNAO1 gene who developed movement disorder without seizures which is consistent with our second case.[4] The first case presented in early infancy with epilepsy but the second case typically developed movement disorder by age 1.5 years. Both cases were resistant to drug intervention. Global developmental delay was common in both cases.

Neuroimaging findings in this case series were normal, which is consistent with the study done by Schirinzi et al.[7] However, some previous studies have demonstrated variable brain abnormalities associated with GNOA1 gene mutations. These may include structural brain anomalies, such as cortical malformations or ventriculomegaly, as well as white matter changes.[4 15]

The first patient presented a novel variant c.502G>A (p.Asp17Asn), which has not been previously reported. However, Nakamura et al.[2] documented the p.Asp17Gly variant, affecting the same amino acid and leading to epileptic encephalopathy. The p.Asp174Asn variant of first case likely represents a pathogenic mutation with a loss-of-function effect, contributing to the observed epileptic encephalopathy phenotype

The second case presented with a c.626G>A (p.Arg209His) variant, which has been previously reported to be associated with hyperkinetic movement disorders without epilepsy.[16]

Conclusion:

This case report sheds light on the variable clinical characteristics of children with GNOA1 gene mutations

in a tertiary care hospital in Bangladesh. It is recommended that clinicians should consider this entity when evaluating patients with global developmental delay and early onset movement disorder and or epilepsy. The findings suggest that further research and collaborations are necessary to expand knowledge on GNOA1 gene mutations.

Conflict of interest: None

Referrence:

1. Briere L, Thiel M, Sweetser DA, et al. GNAO1-Related Disorder. 2023.
2. Nakamura K, Kodera H, Akita T, Shiina M, Kato M, Hoshino H, et al. De Novo mutations in GNAO1, encoding a Galphao subunit of heterotrimeric G proteins, cause epileptic encephalopathy. Am J Hum Genet. 2013;93(3):496–505.
3. Schorling DC, Dietel T, Evers C, Hinderhofer K, Korinthenberg R, Ezzo D, et al. Expanding phenotype of de novo mutations in GNAO1: four new cases and review of literature. Neuropediatrics. 2017;48(5):371–7
4. 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
5. 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(1):129–34
6. Menke LA, Engelen M, Alders M, Odekerken VJ, Baas F, Cobben JM. Recurrent GNAO1 mutations associated with developmental delay and a movement disorder. J Child Neurol. 2016;31(14):1598–601
7. Schirinzi T, Garone G, Travaglini L et al., "Phenomenology and clinical course of movement disorder in GNAO1 variants: results from an analytical review," Parkinsonism & Related Disorders, 2019;61: 19–25.
8. Axeen E, Bell E, Robichaux Viehoever A, Schreiber JM, Sidiropoulos C, Goodkin HP. Results of the first GNAO1-related neurodevelopmental disorders caregiver survey. Pediatr Neurol. 2021;121:28-32
9. Briere L, Thiel M, Sweetser DA, et al. GNAO1-Related Disorder. Gene review.2023 Nov 9.