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THE GNAO1-RELATED DISORDER: A MASQUERADE OF DYSKINETIC CEREBRAL PALSY

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ABSTRACT

GNAO1-related genetic disorder is typically associated with developmental delay and intellectual disability, hyperkinetic movement disorder, and/or epilepsy. It is a rare genetic disease that can mimic extrapyramidal cerebral palsy. Knowledge about this disorder is essential for a proper diagnosis and management.

INTRODUCTION

GNAO1-related disorder is a rare autosomal dominant neurodevelopmental disorder caused by pathogenic variants in the GNAO1 gene. [1] It has a broad phenotypic spectrum, with the core symptoms being a hyperkinetic movement disorder, early-onset epilepsy, and developmental delay. [2] The first case was reported in 2013, with only about 150 cases published in the literature. With an early onset of the movement disorder, it may masquerade as dyskinetic cerebral palsy. Here we present a child with GNAO1-related disorder misdiagnosed as cerebral palsy.

CaseVignette

An eight-year-old girl was admitted with a history of not attaining age-appropriate milestones and involuntary movements of all four limbs and body noticed since one year of age. She was the second-born of third-degree consanguineous parents with a normal antenatal period. She was a term baby with a smooth neonatal transition. She developed neonatal hyperbilirubinemia on day 3 of life and was managed with phototherapy. There was no history of neonatal seizures, encephalopathy, or irritability. She attained social smile at 3 months and did not achieve any further milestones. The mother noticed involuntary movements, arrhythmic, flowing movements of all four limbs, initially intermittent, then continuous, which disappeared during sleep at one year of age. She was diagnosed as extra-pyramidal cerebral palsy and advised physiotherapy at that time. Over the next two years, these movements increased in intensity during episodes of fever; she also developed twisting of both upper limbs and frequent protruding movements of the tongue. There were no visual or hearing concerns. She used to swallow smashed food slowly, with occasional regurgitation.

On examination, she was awake, recognised her parents, made incomprehensible sounds, and followed light in all directions. There was no squint, nystagmus, facial asymmetry, dysmorphism, or neurocutaneous markers. Generalised hypotonia with preserved deep tendon reflexes was noticed. Choreoathetosis with ballistic movements of both upper limbs, dystonic posturing of hands and feet, with occasional opisthotonic posturing was noted. There was no oculogyric crisis. Fundi were normal.

Blood investigations, including complete blood count, renal and liver function tests, thyroid profile, serum lactate, ammonia, creatine phosphokinase, and uric acid, were normal. Peripheral smear for acanthocytes was negative. Ophthalmologist opinion and hearing evaluation were normal. Tandem mass spectrometry and gas chromatography /mass spectrometry were negative. MRI brain along with MRS was normal. (Fig. 1a,b) Whole Exome Sequencing revealed a heterozygous pathogenic missense mutation in exon 7 of the GNAO1 gene (chr16:g. 56351396G> A; depth 50x), which resulted in the amino acid substitution of lysine for glutamic acid at codon 246, confirming a diagnosis of GNAO1-related disorder.

The child was treated with tetrabenazine, baclofen, trihexyphenidyl, and clonazepam. Involuntary movements reduced considerably, and she is on continued physical rehabilitation therapy.

DISCUSSION

Dyskinetic cerebral palsy (DCP) is characterised by abnormal postures or movements associated with impaired muscle tone, movement control, and coordination. It is the second most common type of cerebral palsy after spastic type. [3] However, recently Kamate et al. have stated that in a developing country like ours, dyskinetic cerebral palsy (either predominantly or along with spasticity) is the most common type of cerebral palsy. [4] Several metabolic disorders such as glutaric aciduria, creatine deficiency syndromes, Lesch-Nyhan syndrome, neurotransmitter diseases, and genetic disorders such as ADCY-related disorder and GNAO1-related disorder may present with motor symptoms in early childhood, resulting in a misdiagnosis of cerebral palsy.

GNAO1-related disorder is an autosomal dominant disorder characterised by hyperkinetic movement disorders, epilepsy, developmental delay and intellectual disability. It can present as an infantile-onset developmental and epileptic encephalopathy with or without prominent movement disorder; infantile- or early childhood-onset prominent movement disorder and neurodevelopmental disorder with or without epilepsy; childhood- or adult-onset movement disorder. [5] Our child fits in with the second phenotype of developmental delay with hyperkinetic movement disorder without epilepsy.

Though the hyperkinetic movement disorder was non-progressive, associated with a developmental delay, and neonatal hyperbilirubinemia, normal neuroimaging and worsening of involuntary movements during periods of fever

and intercurrent infection made us think beyond cerebral palsy. Developmental delay, hypotonia, and normal imaging can occur in neurotransmitter-related disorders, despite the oculogyric crisis, a characteristic feature in some of these disorders, being lacking in our patient. Other genetic causes of chorea, such as ADCY5- and GNAO1-related disorders, were considered in our child.

The persistence of dyskinesia during sleep and exacerbations during sleep-wake transitions, a characteristic feature of ADCY5-related disorder, was not present in our case. The absence of respiratory distress in the neonatal period and a normal thyroid profile negated NKX2-1-related disorder.

The common movement disorders in GNAO1-related disorder are choreoathetosis and dystonia which can be severely disabling and painful. Stereotypies, ballismus, and facial dyskinesias have also been reported.[6] Exacerbations can occur spontaneously or can be triggered by intercurrent illnesses as well as by emotional stress, excitement, voluntary movements, or change in position, which was noticed in our patient.[7] Significant axial hypotonia is often found in GNA01-related disorder, contributing to delays in motor development. [6] Severely affected individuals often do not develop head and/or trunk control. Developmental and epileptic encephalopathy is the most common epilepsy phenotype and typically drug-resistant. In children with non-DEE epilepsy, seizure onset is mostly between three and ten years and well-controlled with anti-seizure medications.

The GNAO1 gene encodes the alpha o1 (o) subunit of guanosine nucleotide-binding proteins, also known as G-proteins. These proteins play a fundamental role in controlling signaling through G-protein-coupled receptors (GPCRs) and the cyclic adenosine monophosphate (cAMP) cascade, a critical pathway involved in postsynaptic brain connectivity modulation, with a crucial role at the level of the basal ganglia, especially the striatal medium spiny neuron circuitry of both the direct and indirect pathways. [8] Pathogenic mechanisms underlying GNAO1 mutations remain largely unexplained. The epileptic encephalopathy phenotype is thought to be more closely linked to GNAO1 loss-of-function variants, while movement disorders, with or without epilepsy, are predominantly linked to gain-of-function variants; recent literature suggests that all GNAO1 variants can disrupt GPCR signaling through loss-of-function mechanisms and dominant-negative interference, which are not mutually exclusive.[9]

Management mainly rests on the treatment of movement disorders with benzodiazepines and anticholinergic and dopaminergic drugs, physiotherapy, occupational therapy, speech-language therapy, and nutritional care. Recently, deep brain stimulation has shown good benefits, including clinically meaningful improvements in dystonia severity and disability, and an acceptable safety profile. In addition to its value in an elective setting, it can be used in a life-saving setting, as in status dystonicus.[10]

CONCLUSION

Infantile-onset hyperkinetic movement disorder and developmental delay with or without seizures would point towards a genetic cause such as GNAO1-related disorder, which might be dismissed as dyskinetic cerebral palsy. A precise diagnosis of a genetic disorder has important implications for management and for advising the family regarding prognosis and genetic counselling.

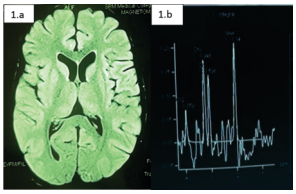


Figure 1. a) MRI Brain T2 Axial – Normal. b) MRS - Normal

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