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Case Report

Effective Treatment of Refractory Chorea in GNAO1 Variants by Folinic Acid

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Abstract Folinic acid is known to affect synthesis and catabolism of neurotransmitter, but its role in movement disorder is unknown. In our case study, we found significant clinical improvement of refractory chorea in a girl with GNAO1 variant after therapeutic trial of folinic acid. This novel therapy not only provides safe pharmacological means for potentially lethal and debilitating condition, but spares the need of surgery for control of involuntary movement. The benefit of folinic acid was found not secondary to the cerebral folate deficiency. Future study will be required to delineate the mechanism of folinic acid in controlling movement disorders.

Key words *Chorea; GNAO1 mutation; Folinic acid*

Case Report

A thirteen month old girl presented with global delay with dystonia. Her birth history was normal and her parents were nonconsanguineous. She had poor truncal tone and persistent fisting at five months. At age one she could vocalise but not yet babble. There were brief episodic lower limb spasms associated with fisting. Extraocular movements were normal. Vision and hearing were normal, and she had no history of seizure. Her elder sister, age eleven at the time, was healthy. Examination showed normal head circumference and growth parameters. There were no dysmorphic features or neurocutaneous stigmata. There was axial hypotonia with extremity hypertonia and brisk jerks. Systemic examinations were otherwise normal.

Complete blood counts, renal and liver function tests, muscle enzymes, thyroid functions, lipid profiles, prolactin, glucose, venous blood gas, lactate, ammonia, plasma and urine creatine, plasma amino acid pattern, carnitine profiles, very long chain fatty acid assays, transferrin isoform, anti-acetylcholine antibody assays and urine organic acids were normal. Cerebral spinal fluid (CSF) assays were normal for protein, glucose, lactate, amino acids, neurotransmitters and 5-methyltetrahydrofolate (5-MTHF). Cranial magnetic resonance imaging was unremarkable. Nerve conduction study, electromyography, repetitive stimulation, brainstem and visual evoked potentials were normal. Her karyotype was 46XX.

Throughout the years, she remained non ambulatory. She had good head control and some voluntary arm movement. She only vocalised with no expressive speech. Oral feeding was satisfactory. There was no developmental regression. She remained stable until age eight when there was a sudden onset of intractable generalised chorea and ballismus movement, precipitated by an apparently trivial viral febrile illness. Creatine kinase rose to 47343 iu/L with myoglobinuria. Renewed investigations, including cranial computer tomography and magnetic resonance imaging (MRI),

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electrovideo oencephalography, sepsis workup, virology study, ceruloplasmin, peripheral smear, anti-streptolysin-O titre, anti-NMDAR study, CSF protein, glucose, lactate and culture, and urine organic acid assay again did not reveal any abnormality.

Neurodevelopmental disorder with involuntary movements (NEDIM; OMIM # 617493) was suspected and sequencing of the *GNAO1* gene showed that the patient is heterozygous for a mutation in the *GNAO1* gene, NM_020988.2:c.736G>A(p.Glu246Lys). This was not identified in the parents and elder sister, suggestive of de novo mutation.

The movement disorder (MD) remained intractable four weeks after onset. It persisted throughout the day, and only temporarily ceased during sleep. She did not respond to empirical treatment with antibiotics, antiviral agents, immunoglobulin infusion, and pulse methylprednisolone. There was no response to levodopa and carbamazepine. Despite combination treatment with risperidone, nitrazepam, tetrabenazine and clonazepam, she required deep sedation with midazolam infusion. Neurosurgeon was consulted for consideration of deep brain stimulation (DBS) to abort the MD. Folinic acid was administered as a therapeutic trial for secondary cerebral folate deficiency. Within two days there was marked reduction in MD, improvement in awareness and oromotor functions, and voluntary upper limb movements. Interestingly, pretreatment CSF 5-MTHF level was normal. The MD remained well controlled with folinic acid (75 mg per day), low dose nitrazepam, carbamazepine and risperidone. Two mild relapses were precipitated during febrile illnesses two months after discharge, which were easily aborted by short-term sedation and transient escalation of folinic acid. In the ensuing ten months, no further relapse was observed despite intercurrent febrile illnesses, obviating the need for DBS.

Discussion

GNAO1 encodes the alpha subunit of the heterotrimeric guanidine nucleotide binding proteins (G-proteins). G0 is expressed in neurons and implicated in the modulation of synaptic transmission. Gα0 subunit encoded by GNAO1 is widely expressed in brain tissue. GNAO1 mutations were first reported to be associated with early onset epileptic encephalopathies, in particular Ohtahara syndrome. Subsequent reports expanded the GNAO1 variants to be associated involuntary chorea, ballismus, or athetoid movements in children with hypotonia and global developmental delay. Literature review identified 13 GNAO1 cases presented predominantly with MD. All presented with hypotonia and severe global developmental delay, and only one achieved ambulation with walker.[1,2] Twelve cases had chorea onset between 6 months to 4 years; one developed MD at age 14. Eleven cases never had seizures. Initial cranial MRI were normal in 12 cases; follow-up studies revealed global atrophies in 4. Choreoathetosis and ballismus were often precipitated by febrile illnesses and infections, and the ensuing MD were typically intractable requiring repeated Intensive Care Unit admissions. Most were refractory to pharmacological treatment with anticonvulsants, antidystonic agents including benzodiazepines and neuroleptics. Only two patients showed reduction in chorea after addition of tetrabenazine. Two cases succumbed to MD related complications during hospitalisation. Three patients required DBS implantation to control the intractable MD, with subsequent reduction in medication dosages, hospital stay and severity of MD during exacerbations.[3,4] The mutations causing MD are recurrent de novo missense substitutions affecting residues Arg209 or Glu246.

To our knowledge, this is the first reported case of successful pharmacological control to achieve long-term sustained remission of intractable MD in GNAO1 variants p.Glu246Lys without concomitant cerebral folate deficiency. In the present case, baseline CSF 5-MTHF levels was normal at age 2, and repeated assay at peak of chorea before folinic acid trial was again normal (performed by MNG Laboratories in Atlanta). Nevertheless, the movement disorder is not secondary to cerebral folinic acid deficiency as evidenced by the normal CSF 5-MTHF levels in our case. A case was reported in 2017 on a patient with the same GNAO1 variant with co-existing cerebral folate deficiency who responded to folinic acid treatment.[5] However, there are conflicting results from another study of 7 patients with GNAO1 mutation,[6] in which 2 patients with low 5-MTHF level did not show clinical significant improvement with folinic acid. It seems that the mechanism of folinic acid does not solely depend on CSF 5-MTHF status.

Though folinic acid can affect synthesis and catabolism of neurotransmitters,[7] further studies will be required to delineate the mechanism of folinic acid in controlling MD. The mutation, p.Glu246Lys is a recurrent activating GNAO1 mutation[8] and it is likely that folinic acid can

suppress, directly or indirectly, the hyperactivity of the G-proteins. In fact, folate is known to interact with cerebral G-proteins.[9] G0 is the most abundant membrane protein in CNS and is important in synaptic transmission. Further studies will be needed for the elucidation of mechanism for the interaction of GNAO1 with folate.[10]

Conclusion

Patients with neurodevelopmental disorder with involuntary movements should be treated initially with folinic acid before DBS for MD control.

Conflict of Interest

There are no conflicts of interest to declare.

References

1. Saitsu H, Fukai R, Ben-Zeev B, et al. Phenotypic spectrum of GNAO1 variants: epileptic encephalopathy to involuntary movement with severe developmental delay. Eur J Hum Genet 2016;24:129-34.
2. Ananth AL, Robichaux-Viehoever A, Kim YM, et al. Clinical course of six children with GNAO1 mutations causing a severe and distinctive movement disorder. Paediatr Neurol 2016;59:81-4.
3. Kulkarni N, Tang S, Bhardwaj R, Bernes S, Grebe TA. Progressive movement disorder in brothers carrying GNAO1 mutation responsive to deep brain stimulation. J Child Neurol 2016;31: 211-4.
4. Sanem Y, Tuncer T, Serdar C, Gökben S, Tekgul F, Serdaroglu G. Excellent response to deep brain stimulation in a young girl with GNAO1-related progressive choreoathetosis. Childs Nerv Syst 2016;32:1567-8.
5. Yeung WL. Treatment of a case with GNAO1 associated movement disorder and cerebral folate deficiency: role of folinic acid? Presented at 14th Asian-Oceanian Child Neurology Congress at Fukuoka 2017.
6. Danti FR, Galosi S, Romani M, et al. GNAO1 encephalopathy: Broadening the phenotype and evaluating treatment and outcome Neurol Genet 2017;3:e143.
7. Ramaekers VT, Sequeira JM, Quadros EV. The basis for folinic acid treatment in neuro-psychiatric disorders. Biochimie 2016; 126:79-90.
8. Feng H, Sjögren B, Karaj B, Shaw Vincent, Gezer A, Neubig RR. Movement disorder in GNAO1 encephalopathy associated with gain-of-function mutations. Neurolog. 2017;89:762-70.
9. Hartley DM, Snodgrass SR. Folate interactions with cerebral G proteins. Neurochem Res 1990;15:681-6.
10. Feng H, Khalil S, Neubig RR, Sidiropoulos C. A mechanistic review on GNAO1-associated movement disorder. Neurobiol Dis 2018; 116:131-41.