GNAO1-related Neurodevelopmental Disorder Presenting as Acute Encephalitis Syndrome: A Phenotypic Expansion

Dear Sir,

Acute encephalitis syndrome (AES) is characterized by an acute onset of fever and change in sensorium, with or without seizures, focal deficits, or movement disorders.[1] The most common etiologies of AES in India include viral infections such as Japanese encephalitis, dengue, and herpes simplex viruses. Central nervous system (CNS) demyelination, particularly acute disseminated encephalomyelitis (ADEM) and neurometabolic disorders like organic acidemia, urea cycle, and mitochondrial and fatty acid oxidation disorders can sometimes present with clinical features resembling AES.[2]

A previously healthy, developmentally normal, 6-month-old male infant presented with a sudden onset of high-grade fever, irritability, poor feeding, and altered consciousness for 2 days. The baby was first born to a non-consanguineous parent, with normal antenatal and perinatal period, and was immunized appropriately for age. The fever had started abruptly 48 hours prior, was high-grade, continuous, and without any associated respiratory or gastrointestinal symptoms. On examination, the infant was lethargic, had a poor eye-opening and verbal response, paucity of spontaneous limb movements, central hypotonia, and no neck stiffness or bulging fontanelle. There

was also a history of two episodes of right focal-to-bilateral tonic-clonic seizures lasting about 1-minute each on the day of admission. With an initial clinical possibility of acute febrile encephalopathy, the child was started on intravenous ceftriaxone and acyclovir, along with levetiracetam.

Laboratory investigations revealed lymphocytic leukocytosis, elevated inflammatory markers (CRP-31 mg/dl), normal serum electrolytes, hepatic and renal function tests. Magnetic resonance imaging (MRI) of the brain was normal. Cerebrospinal fluid (CSF) analysis was unremarkable and multiplex polymerase chain reaction (PCR) for neurotropic viruses was negative. Blood and urine cultures, as well as a workup for tropical illnesses like cerebral malaria, dengue, scrub typhus, and enteric fever, were negative. Electroencephalography (EEG) showed diffuse slowing with multifocal epileptiform discharges. After admission, although the fever spikes subsided and sensorium improved, the infant continued to have focal tonic, focal clonic, and focal-to-bilateral tonic-clonic seizures and required multiple antiseizure medications (ASMs) like phenytoin, phenobarbitone, clobazam, and oxcarbazepine. Oral pyridoxine, pyridoxal 5-phosphate, folic acid, and biotin were also added in suspicion of vitamin-responsive epilepsies, but without any favorable clinical response. CSF panel for autoantibodies associated with autoimmune encephalitis was negative. Arterial lactate, blood ammonia, tandem mass spectrometry (TMS), and urine gas chromatography-mass spectrometry (GCMS) were also unremarkable. Finally, whole exome sequencing was sent, which detected a likely pathogenic de novo heterozygous gain of a function missense variant in exon 8 of the GNAO1 gene (c. 1033G > A, p.Ala345Thr) that resulted in the amino acid substitution of Threonine for Alanine at codon 345 and parents were counseled accordingly. On the last follow-up, at 9 months of age, the seizure frequency has reduced to occasional brief seizures after starting the ketogenic diet (3:1), but the child developed hyperkinetic extrapyramidal choreoathetoid movements for the last 2 months and started on oral tetrabenazine.

De novo mutations in the GNAO1 gene were initially reported in infants with early infantile epileptic encephalopathies with drug-resistant epilepsy such as Ohtahara syndrome. However, as more and more cases were reported, two clinically different phenotypes were recognized with mutations caused by the GNAO1 gene. The first one is the neurodevelopmental disorder with involuntary movements (NEDIM) phenotype, in which the affected infants or children have global developmental delay and later on intellectual disability. But the most prominent feature of this phenotype is early onset hyperkinetic movement disorders like chorea and athetosis.[3] Even in this phenotype, seizures have been seen in a substantial proportion of cases. The sequence of onset of movement disorder and seizure varied in reported cases, with one following another, but in most cases the movement disorder was early onset and was severe enough to incapacitate the child to prevent independent sitting, standing, walking, or eating.[4] Another peculiar characteristic feature of movement disorder in GNAO1 mutation-affected children was out-of-proportion exacerbation by intercurrent illnesses, fever, and stress. While most affected patients had normal neuroimaging, single reports of cerebral atrophy and corpus callosal thinning are also present in the literature.[5] The occurrence of stereotypies and characteristic paroxysmal exacerbations associated often with clear triggers are sometimes considered as important discerning clinical features of GNAO1 encephalopathy. Facial/orolingual dyskinesia is a clue for GNAO1 and ADCY5, in the cAMP axis postsynaptic movement disorders. Similarly, paroxysmal aggravation with severe chorea-ballismus (status hyperkineticus) can be a clue for GNAO1.[6] On the other hand, children with developmental and epileptic encephalopathy 17 phenotype often show early onset intractable seizures resembling Ottahara syndrome and burst suppression in EEG. A general theme observed by previous authors regarding GNAO1 pathogenic variants was that the "gain of function" (GOF) mutation usually presents with hyperkinetic movement disorders and the "loss of function" (LOF) mutation presents with epileptic encephalopathy.

GNAO1 encodes a specific type of Gα subunit, known as Gαo, which is a component of heterotrimeric proteins, that binds to guanine nucleotides. This gene is preferentially expressed in the brain and plays a pivotal role in regulating the excitability of neurons, as well as neurotransmission. Not only GNAO1, but also mutations in genes coding for other G-protein subunits like GNAL, cyclic nucleotide phosphodiesterases like PDE10A, adenylyl cyclases like ADCY5, and G-protein-coupled receptors like GPR88, have been implicated in the etiopathogenesis of early onset movement disorders.[7] These findings provide support for the hypothesis that disruptions in the G-protein-cAMP pathway axis contribute significantly to the underlying mechanisms of dystonia and chorea. Although the precise pathophysiological mechanisms of these genetic movement disorders are not fully understood, potential disease mechanisms include hindrance with transduction or modulation of transmembrane signaling, impairment of neuronal excitability, and presynaptic autoinhibitory effects.[8] These mechanisms may help explain the simultaneous occurrence of various neurological manifestations, such as epilepsy and hyperkinesia. The clinical presentation of our case was atypical in the sense, none of the previous cases reported had onset of symptoms after a febrile illness, resembling acute febrile encephalopathy. However, later the index case developed drug-resistant epilepsy and also movement disorder, which are characteristics of this disorder.

The management of GNAO1-related disease primarily focuses on providing symptomatic management and addressing the primary concerns of the child, as the manifestations can be heterogeneous.[9,10]

This case highlights the importance of considering GNAO1 mutations as a potential cause of acute febrile encephalopathy, especially when the etiology remains unknown. Early recognition of GNAO1-related disease enables proper

management, genetic counseling, and ongoing support for affected individuals and their families.

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Conflicts of interest

There are no conflicts of interest.

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