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A Rare Case of Movement Disorder with Developmental Delay [Clinical Phenotype of de novo *Gnao1* mutation]: Case Report and Review of Literature

Case Report

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Abstract

Mutations in GNAO1 (guanine nucleotide-binding protein, alpha-activating activity polypeptide O) were recently identified as being causative for early epileptic encephalopathy. Since then approximately 27 patients with severe developmental delay and different neurological phenotypes for epilepsy and involuntary movement disorder have been reported. Here we report a 7 year old female with mutations in GNAO1 harboring the de novo mutation (c.736G > A, p.Glu246Lys) but showing differences in phenotype with pronounced hyperkinetic movements and global developmental delay. The mutation was found using a targeted next generation sequencing gene panel and demonstrates targeted sequencing as a powerful tool for identifying mutations in genes where only a few de novo mutations have been identified.

Keywords: Early infantile epileptic encephalopathy; Othahara syndrome; GNAO1 mutation; Movement disorders; c.736G > A, p.Glu246Lys

Introduction

G-proteins with all their subtypes have long been recognized to be essential for delivery of extracellular information and stimuli via membrane-bound receptors and intracellular second messenger systems. Heterotrimeric G-proteins consist of α-, β-, and γ-subunits.

In mammals, four Gα subtypes are known so far. GNAO1 (MIM 139311) on chromosome 16q13 encodes for Gα0-a subtype which is known to be predominantly expressed in brain tissue [1]. On a cellular level Gα0 works as an inhibitor of voltage-gated Ca2þ channels and activator of inward potassium channels. Knockout of Gα0 in mice leads to a complex and early lethal phenotype with manifestations including tremor, severe epilepsy, and abnormal behavior [2].

Mutations in GNAO1 were first identified to be causative for epileptic encephalopathy in four female individuals with Ohtahara syndrome (OS) by Nakamura et al in 2013 [3]. Since then approximately 23 additional patients have been reported with a variable phenotype which appears to involve severe intellectual disability and motor developmental delay in all patients, a varying degree of either early epileptic syndromes, such as OS in some patients and a variety of involuntary movement disorders in others [4-14]. Until very recently only female patients had been reported to show epileptic phenotypes whereas reported male patients were found to show the same degree of psychomotor retardation but also severe dystonia, which was ameliorated by deepbrain stimulation in some cases [5]. However, severe movement disorders also affect some

of the reported female patients. A single male patient with mutations in GNAO1 was reported only recently [6].

Here we report a 7 yr old patient with mutations in GNAO1 harboring the de novo mutation (c.736G > A, p.Glu246Lys) showing differences in phenotype with pronounced hyperkinetic movements and global developmental delay as compared to already reported cases having similar mutation.

Case Report

The 7 yr old female child born out of third degree of consanguineous marriage with a birth weight of 2.31 kg was born through LSCS at 36 weeks of gestation. At 20 weeks of intrauterine life anomaly scan done was found to be normal. The baby cried immediately after birth. The neonatal period was complicated by poor feeding and jaundice on day 3 of life for which the baby warranted 1 week of NICU admission. In addition to this, there were unspecified stereotypic jerks in bilateral lower limbs. The baby developed social smile at 2 months of age. Head control independent sitting was not achieved and subsequently, other motor functions were delayed. At 3 yrs of age the patient's mother noted involuntary jerky movements involving bilateral upper and lower limbs which were brief without loss of consciousness. The baby also had dystonic posturing of the trunk and extensor spasms along with exaggerated startle and sleep myoclonus since 4 years of age. There were no seizure episodes in the past. At 7 years of age baby had a fever for one week along with worsening of pre existing symptoms along with the first episode of focal tonic seizures with extensor spasm. The patient was developmentally delayed with no eye contact. She was opistotonic and had severe spasticity in bilateral upper and lower limbs. Babinski reflex was bilaterally positive. She had subtle dysmorphic features like dolichocephalic head and high arched palate. Her head circumference was 43 cms at the present admission.

The younger sibling of this patient had similar complaints of involuntary movements associated with seizures for which the baby wasn't evaluated and died at the age of 6 yrs. No other members in the family had a similar illness or epilepsy.

Electroencephalography was done at the 7 years of age. The interictal EEG in sedated state showed a theta range background activity (5-6 Hz) mixed with high voltage sharps and spikes which is bilateral and asynchronous predominantly frontal (Figure 1). At sleep, there were bilateral high voltage irregular slow waves mixed with epileptiform activity (Figures 2&3).

MRI brain done at 9 months of age was normal. Repeat imaging done at 4 yrs revealed mild frontotemporal atrophy with a generally decreased amount of white matter and size of basal ganglia with some increase in signal intensity in external capsule and periventricular white matter on T2-weighted images.

MRI brain imaging done at the age of 7 revealed bilateral basal ganglia atrophy along with corpus callosal atrophy (Figure 4). T2 weighted images revealed widening of the subarachnoid spaces with prominent sulcus (Figure 5).

During the course of the disease, the patient had multiple extrapyramidal symptoms like myoclonic jerks, extensor spasms and dystonic movements. She had been treated with multiple combinations of drugs including antiepileptics without many benefits. Psychomotor development has been delayed from birth with a gradual progression of symptoms.

During the last admission to our hospital, the baby had one episode of hypoglycemia with metabolic acidosis, arterial pH of 7.14 and Bicarbonate values were 10 mEq/L, which subsequently got corrected with the treatment of underlying fever. CSF analysis done during that time was normal.

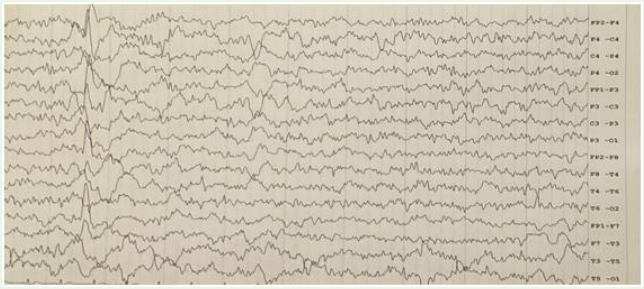

Figure 1: EEG in sedated state: The interictal EEG in sedated state showed a theta range background activity (5-6 Hz) mixed with high voltage sharps of duration (<1 second) which is bilateral and synchronous predominantly frontal.

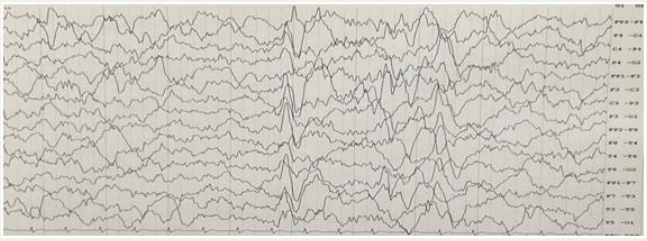

Figure 2: Sleep record (NREM stage 2) Bilateral high voltage irregular slow waves mixed with multifocal spikes and sharp waves.

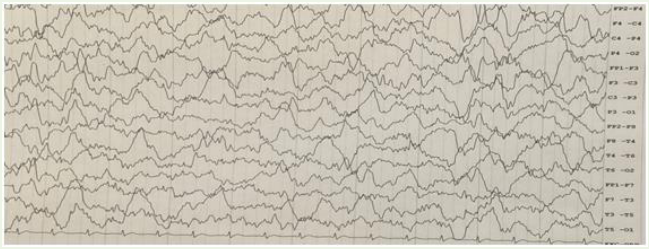

Figure 3: Sleep record (NREM STAGE 3) sleep record showing 200 micro volt delta activity mixed with sharp waves.

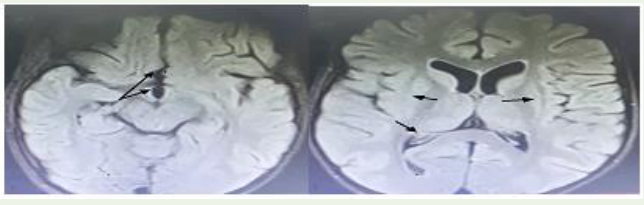

Figure 4: T2 FLAIR images at age 7 (AXIAL VEIW) Corpus callosal thinning and atrophy of the basal ganglia with prominent occipital horn of right lateral ventricles which denotes focal atrophy (marked by arrows).

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Over the years extensive metabolic work up was performed which were all under normal limits. Work up for Inborn Errors of Metabolism (TMS) was also found to be normal. Serum Lactate was under normal limits (53mg/dl). Previous CSF analysis for the done autoimmune panel was negative. At the age of 7 yrs whole exon sequencing was done after obtaining consent from the parents. The genetic exon sequencing revealed GNAO1(+) transcript at exon 7 (variant 736 G>A) (Figure 6).

Methods

Molecular Analyses

We collected the DNA samples from the girl and her parents. Genomic DNA from the family was extracted from EDTA anticoagulated blood samples using standard methods. To identify the disease-causing gene, targeted next generation sequencing of 40 different genes associated with childhood epilepsy was performed. Whole exon sequencing (WES) was performed in our patient. Identified GNAO1 mutations were validated and segregation tested in our patient by Sanger sequencing.

Results

WES was initiated and showed heterozygous de novo c.736G > A, p.Glu246Lys mutation in exon 7 of GNAO1 in our patient but not in the parents. The mutation was predicted to be "probably damaging" (PolyPhen2) and "disease causing" (MutationTaster). This mutation affects specifically exon 7 of transcript variant 1 (NM_020988.2) and affects a highly conserved glutamic acid at position 246. Up to the time of this report the de novo c.736G > A, p.Glu246Lys variant has been reported in five other patients (four females, one male).

Discussion

GNAO1 encephalopathy is a rare neurodevelopmental disorder characterized by distinct movement presentations and early onset epileptic encephalopathy. De novo *GNAO1* mutations were originally first reported in Ohtahara syndrome and EOEE in 4 children, associated with abnormal movements in 2 children.

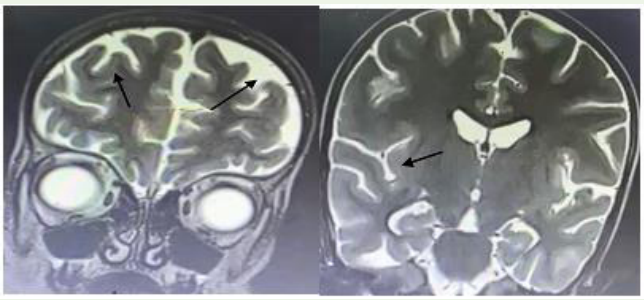

Figure 5: T2 FLAIR images at age 7 (AXIAL VEIW) Corpus callosal thinning and atrophy of the basal ganglia with prominent occipital horn of right lateral ventricles which denotes focal atrophy (marked by arrows).

Gene (Transcript)#	Location	Variant	Zygosity	Disease (OMIM)
***GNAO1* (+)** (ENST00000638705.1)	Exon 7	c.736G>A **(p.Glu246Lys)**	Heterozygous	Developmental and epileptic encephalopathy-17; Neurodevelopmental disorder with involuntary movements

Figure 6: Exome Sequencing: Mutation in exon 7 (p.Glu246Lys variant).

Since this initial description, 30 additional patients have been reported with an emerging phenotype characterized by the neurodevelopmental delay with an early onset of a hyperkinetic movement disorder, inconsistently associated with epilepsy. The occurrence of stereotypes (previously reported in 2 patients with EOEE) and characteristic paroxysmal exacerbations, associated often with clear triggers, may both be considered as 2 further important discerning clinical features of *GNAO1*encephalopathy.

In this case report, it is evident that our patient predominately presented with severe hyperkinetic movements with first episode of clinical seizure activity at the age of 7 .The identified c.736G > A/p. Glu246Lys variant has been reported in five other patients, so far none of whom showed any epileptic seizures. Of note is that no differences in phenotype were reported in affected twins of different sex carrying this mutation, both showing chorea, but not seizures. Very recently it was suggested that mutations affecting codons 209 or 246 of GNAO1 specifically lead to a phenotype that involves involuntary movement disorder and developmental delay but are characterized by the absence of epilepsy. As the c.736G > A/p. Glu246Lys variant would only affect transcript variant 1 of GNAO1 it appears possible that a milder phenotype in regards to epilepsy results from a selective relevance of transcript variants other than one that could result in some functional GNAO1 in certain neuronal cell types.

There are some similarities as well as differences in the clinical features of the present patient as well as previously reported cases. Most of the previously reported patients had predominantly hyperkinetic movements and only one had a focal seizures. The commonly noted movement disorders were dystonia and chorea. Athetoid movements were noted only in one patient. Our patient in addition to dystonia had myoclonic jerks along with extensor spasms which wasn't reported in any of the previous patients with c.736G > A/p.Glu246Lys variant. Though clinical seizures activity wasn't the predominant feature of previously reported cases with c.736G > A/p. Glu246Lys variant our patient had one episode of focal tonic seizures which is only the second case reported till date. (Table 1 summaries all reported patients with mutations in GNAO1 with c.736G > A/p. Glu246Lys variant).

With respect to the latest reports of patients showing a phenotype with a predominant involuntary movement disorder, it appears that the spectrum of symptoms is broader than initially suggested so that mutations in GNAO1 should be considered in all patients showing severe mental and motor retardation and either early or severe epilepsy and/or some involuntary movement disorder. Unfortunately, this is not always possible due to high costs of these investigations, but on the other hand, the early etiological diagnosis might reduce unnecessary investigations and might lead to a targeted treatment reducing side effects from the trial-and-error treatment approach. Taking into account the changing of the symptoms during course of the disease, the long-term follow-up will eventually benefit from knowing the basis of disease and its prognosis. Furthermore,

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Table 1: Summary of all reported patients with mutations in GNAO1 (c.736G > A/p.Glu246Lys variant).

Patient no.	Reference	Sex		Age at Report	Nucleotide change	Amino acid change	Inheri-tance	Epileptic syndrome/ seizures (age on at set)	EEG	Seizure Control	Movement Disorder Onset			Presen-tation	MRI (age)
												Epilepsy	Movement Disorder		
1	Saitsu et al (2016)	F		13 y	c.736G>A	p.Glu246Lys	De nova	-	No Seizure	-	Athetosis (4 y)	-	NA	ID, MDD	Normal (12 y)
2	Ananth et al(2016)	M	Twins	5y	c.736G>A	p.Glu246Lys	De nova		NA	-	Chorea (4 y)	-	NA	ID, MDD	Normal (12 mo)
3		F		5y	c.736G>A	p.Glu246Lys	De nova	-	NA	-	Chorea (4 y)	-	TBZ	ID, MDD	Atrophy (5.5 y)
4		F		10y	c.736G>A	p.Glu246Lys	De nova	-	NA	-	Chorea (6 mo)	-	BCL,CLB, TBZ, Haloperiodol, DZP	ID, MDD	Global Atrophy (9 y)
5		M		15y	c.736G>A	p.Glu246Lys	De nova	-	NA	-	Dyskinesia (5 mo) Chorea (14 y)	-	TBZ,DZP	ID, MDD	T2 hypo-intensity globus-pallidi (14 y)
6 (patient A)	Present Report	M	Sibling	8y	c.736G>A	p.Glu246Lys	De nova	-	Normal	-	Dystonia		L-DOPA	ID, MDD	Normal (25 mo)

it plays an important role in the process of informing the parents about the cause of the disease and is of utmost importance in genetic Counseling.

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