CASE REPORT

Early Infantile Epileptic Encephalopathy in asparagine-linked glycosylation thirteen (*ALG13*) gene defect and dramatic response with Ketogenic diet

Prem Chand[1], Asna Sulaiman[12], Meher Angez[3], Salman Kirmani[4]

Abstract

Asparagine-linked glycosylation thirteen (*ALG13*) gene-related congenital disorders of glycosylation (CDGs) include early onset epileptic encephalopathy (EIEE), developmental delays (DD) with intellectual disability (ID), speech and visual abnormalities, and haematologic and endocrine dysfunctions. Worldwide there is a scarcity of available data on this. To add to this scarce data, we report the case of a young girl with this rare genetic mutation who showed remarkable improvement in her seizures by addition of ketogenic diet (KD) to her management regimen.

With an already high rate of consanguineous marriages, metabolic and genetic errors are widely prevalent; hence, to bridge the huge gap in the understanding of such diseases, further research and trials are needed to be carried out to improve identification of the disease along with outcomes.

Keywords: *ALG13* mutation, epileptic encephalopathy and ketogenic diet.

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Introduction

Congenital disorders of glycosylation (CDGs) are an elaborate set of genetic syndromes stemming from impaired synthesis of glycoprotein/lipid resulting in neuro-metabolic diseases. Only a few hundred cases of congenital disorders of glycosylation (CDG) were reported worldwide till 2014,[1] with its numbers still rising.[2,3] *ALG13* is a gene that encodes an X-linked uridine diphosphate (UDP)-N-acetylglucosaminyltransferase protein, involved in the process of N-linked glycosylation in the endoplasmic reticulum.[4-6] Clinical presentation of *AGL13*-CDG includes early onset epileptic encephalopathy (EIEE), developmental delays (DD) with intellectual disability (ID), speech and visual abnormalities, and haematologic and endocrine dysfunctions.[3,4,6] Females, who are heterozygous for a pathogenic variant, can present with a broad phenotypic spectrum, ranging from asymptomatic to severely affected. Very limited studies have been carried out regarding the causes of DD and EIEE in Pakistan. To contribute to the limited existing reported cases, here we describe the case of an 18-month-old female, who presented with distinctive findings of a novel *ALG13* pathological variant.

Case

An 18-month-old female, presented to the Aga Khan University Hospital, Karachi neurology clinic in May 2021 with multiple jerky movements (10 to 15/day) and delayed global milestones. This was first observed by her parents at the age of 10 months, including poor neck holding and weak hand grip, and was nonverbal. Her jerky movements were in the form of flexor and extensor spasm which occurred 10 to 15 times a day on an average, and were more pronounced after she woke from sleep. She is a full-term baby, to a first-generation consanguineous Pakistani couple. The mother had an uncomplicated antenatal period. After birth, the neonatal progress of the baby was normal and the family history was unremarkable. On examination, the patient was awake and alert and had no dysmorphic features or neuro-cutaneous stigmata. Detailed neurologic examination showed decreased tone in all four limbs, poor motor function with intermittent choreiform movements. The fundoscopic examination was completely normal. Baseline laboratory investigations showed complete blood count, thyroid function, and transferrin levels to be in the normal range. Urinary organic and uric acid and plasma amino acid were also normal. Electroencephalogram (EEG) was markedly abnormal with multifocal and generalised spike and wave discharges with electro-decremental response of one to two seconds (Figure 2A). The Electromyography (EMG) nerve conduction was normal with no definite evidence of a myopathy or neuropathy. MRI showed non-specific signals in the periventricular areas (Figure 2B). The initial differential diagnosis was cortical emigrational disorder, metabolic seizures, inborn error of metabolism, and genetic epilepsy.

The patient was started on Levetiracetam (60mg/kg/day) but the seizure frequency remained the same, so ACTH (10

[1,4]Department of Paediatrics and Child Health, Aga Khan University, Karachi, Pakistan; [2]Aga Khan University, Karachi, Pakistan; [3]4th Year MBBS Student, Aga Khan University, Karachi, Pakistan.

Correspondence: Prem Chand. e-mail: prem.chand@aku.edu

ORCID ID. 0000-0001-5401-4780

IU/kg/day) was added to the management. There was no promising response and repeat EEG showed similar findings. Levetiracetam was continued and Vigabatrin, Chlonazepam were added, while ACTH was tapered off. Her seizures, however, remained pharmaco-resistant after polytherapy of anti-seizure medicine which hinted towards a more sinister disease. The next generation sequencing (NGS) based gene panel was ordered from the (Invitae 1400 16th Street, San Francisco, CA 94103) for her genetic workup. The result showed that she harboured a heterozygous gene mutation of *ALG13*, Exon 3, c.320A>G (p.Asn107Ser), shown in Figure-1. This sequence change replaces asparagine with serine at codon 3 of the *ALG13* protein (p.Asn3Ser). This variant has also been reported in individuals affected with Lennox-Gastaut syndrome and West syndrome (infantile spams).

After the diagnosis, the antiepileptic drugs (AED) were optimized, and ketogenic diet (KD) was added in a 2:1 ratio to her treatment regimen. After six weeks of treatment, the frequency of clinical seizures were noted to be improving. With subsequent follow-up at four months she had maintained good progress on KD. No seizure episode was noticed for three months after starting KD. There was an incredible change in her alertness, responsiveness, and sleep pattern. She was tapered off AED and physiotherapy was encouraged. After three months on ketogenic diet with ASMs her seizures improved, and she started holding the neck and sitting. Overall prognosis of early infantile epilepsy or genetic epilepsy is not very favourable; however, with early intervention like ketogenic diet, her developmental milestones are getting better and she is seizure free. She is now being tapered off from ASMs. As she was started on KD she showed dramatic response in terms of seizure freedom as well as achieving her growth milestones after three months of KD, after which the doses of ASMs (anti-seizure medicines) were decreased.

Patient name:	[redacted]	**Sample type:**	gDNA	**Report date:**	05/04/2021
DOB:	11/21/2019	**Sample collection date:**	04/16/2021	**Invitae #:**	[redacted]
Sex:	Female	**Sample accession date:**	04/19/2021	**Clinical team:**	[redacted]
MRN:	[redacted]				

Reason for testing
Diagnostic test for a personal history of disease

Test performed
Sequence analysis and deletion/duplication testing of the 306 genes listed in the Genes Analyzed section.
- Invitae Epilepsy Panel
- Add-on FLNA Gene
- Add-on PTEN Gene

RESULT: POSITIVE

One Pathogenic variant identified in ALG13. ALG13 is associated with X-linked ALG13-congenital disorder of glycosylation.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
ALG13	c.320A>G (p.Asn107Ser)	heterozygous	PATHOGENIC
CACNA1A	c.1141C>T (p.Arg381Trp)	heterozygous	Uncertain Significance
COL18A1	c.2510G>C (p.Gly837Ala)	heterozygous	Uncertain Significance
PRDM8	c.649_651dup (p.Gln217dup)	heterozygous	Uncertain Significance

About this test
This diagnostic test evaluates 306 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Figure-1: The genetic test report showing a heterozygous gene mutation of *AGL13*, Exon 3, c.320A>G (p.Asn107Ser).

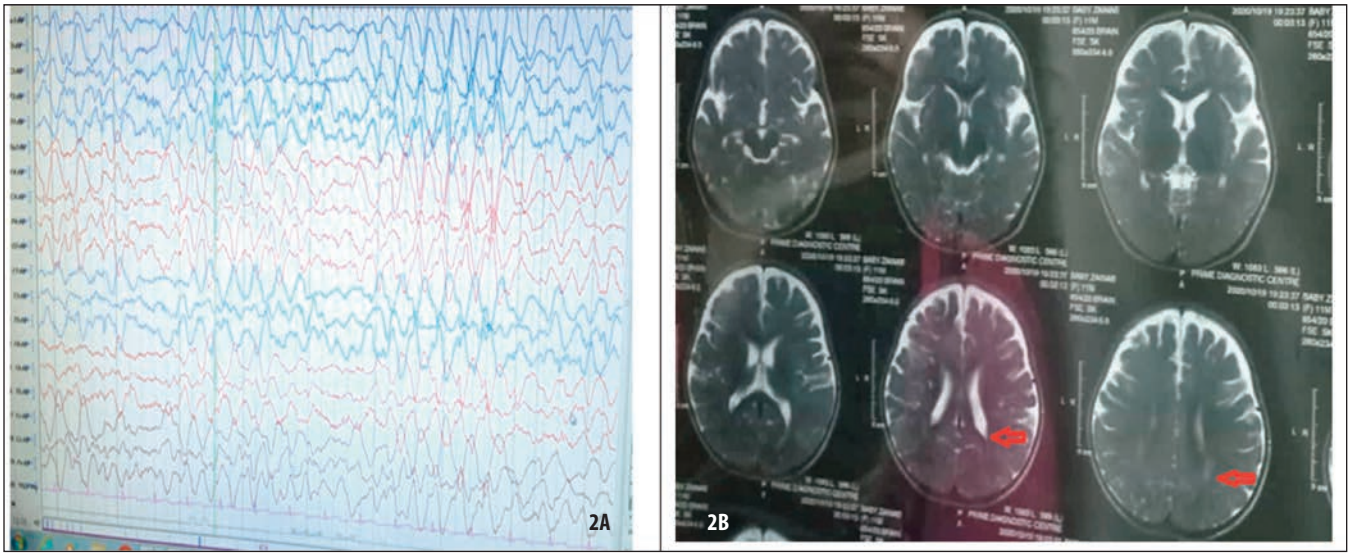

Figure-2: The Electroencephalogram (2A) and MRI scans (2B) of the patient.

Discussion

First identified in 2012, *ALG13*-CDG presents with a variety of symptoms due to its multi-systemic involvement. Patients typically present with early onset epileptic encephalopathy, infantile spasms, hypsarrhythmia, and intellectual disability.[7] Additional features, such as facial dysmorphism, hearing loss, choreoathetoid movements, developmental delay, and bilateral optic nerve atrophy have also been observed in some individuals.[3,7] The familial cases of *ALG13* are mostly asymptomatic; however, the de novo variant carriers develop severe symptoms.[2,8] Up till now *ALG13* mutations have been reported in approximately 21 females and one male.[2,3] Females heterozygous for a pathogenic variant can present with a broad phenotypic spectrum, ranging from asymptomatic to severely affected.[5] A significant number of pathogenic variants identified in *ALG13* have been reported as de novo out of which *ALG13* c.320A > G, p(Asn107Ser) has been reported to be the most common.[5] This mutation classically presents with the aforementioned symptoms—a presentation which was similar to our patient suffering from the same variant; however, facial dysmorphism was not observed in our patient.

Clinical picture of *ALG13*-CDG is dominated by neurological symptoms, characteristic EIEE, which majorly contributes to cognitive and behavioural impairment, leading to developmental delay. Seizures are usually multiform and intractable leading to cognitive, behavioural and neurological deficits and sometimes early death.[9] The typical interictal EEG finding, consists of a disorganised pattern with asynchronous, very high amplitude slowing, and frequent multifocal spike and sharp wave discharges,[9] as seen in our patient. Epilepsy in *ALG13*-related epileptic encephalopathies consists of West syndrome which is often pharmaco-resistant. Seizures are refractory to AEDs, as a result, more aggressive use of AEDs is considered effective in suppressing interictal epileptiform discharges. Immunomodulatory therapies (e.g. corticosteroids, intravenous immunoglobulin [IVIG], and plasmapheresis)[7] and, as in our case, the use of ketogenic diet (KD), which showed remarkable improvement not only in the patient's seizures but in her alertness, responsiveness, and sleep pattern; hence AEDs were even tapered off.

This is a rare genetic epilepsy and we do not have locally available facility to detect genetic epilepsy. The early recognition of *ALG13*-related epileptic encephalopathies and early initiation of ketogenic diet can drastically improve the prognosis.

Conclusion

As was in our case the early recognition of *ALG13*-related epileptic encephalopathies where pharmaco-resistant seizures can be challenging to manage, and early initiation of ketogenic diet can drastically improve the prognosis. In countries like Pakistan, where paediatric neurologists and geneticists are scarce, management of such individuals is tedious and demanding. With an already high rate of consanguineous marriages, metabolic and genetic errors are widely prevalent; hence, to bridge the huge gap in the understanding of such diseases, further research and trials are needed to improve identification of the disease along with outcomes.

Consent: Verbal consent was obtained from the parents of the patient for publishing her case.

Disclaimer: None.

Conflict of Interest: None.

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