Attenuated Form of Glycine Encephalopathy: An Unusual Cause of Episodic Ataxia and Hyperactivity

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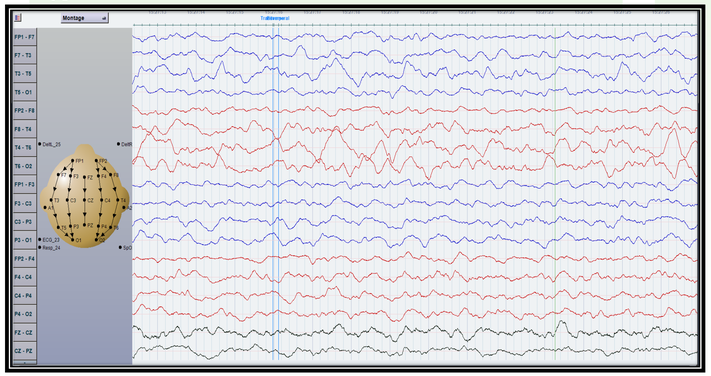
BACKGROUND

- Nonketotic hyperglycinemia (OMIM ID#605899), is a rare inborn error of glycine metabolism characterized by the accumulation of glycine in all tissues, including CNS.
- This rare neurometabolic disorder is inherited in autosomal recessive manner by mutations in the *GLDC , AMT or GCSH* genes and has three subtypes based on clinical outcomes.[2] Attenuated form of glycine encephalopathy which contributes to 15 % in aggregate of NKH has variable presentation with neurodevelopment delay and well controlled seizures.
- Glycine stimulates glycinergic receptors of the brainstem and spinal cord resulting in an inhibitory effect (neonatal hypotonia) while it acts at the glycinergic modulatory site of the N-methyl-D-aspartate (NMDA) receptor in the cerebral cortex resulting in neuroexcitatory effect(refractory seizures)Here we report case of four year old boy of Pakistani ethnicity having expressive speech deficits and infrequent seizure background presented with infective illness provoked episodic ataxias.

OBJECTIVES

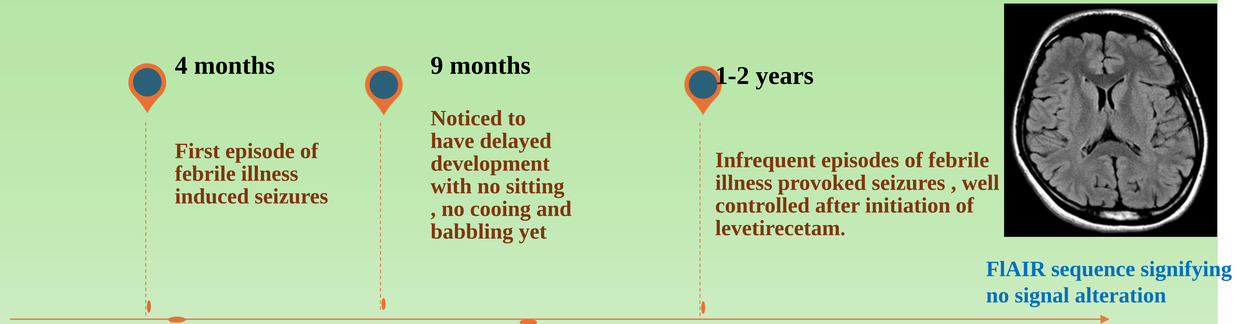
To describe the unusual phenotype and delayed presentation of a rare metabolic disorder which is typically fatal in neonatal period due to progressive encephalopathy, refractory seizures and hypotonia.



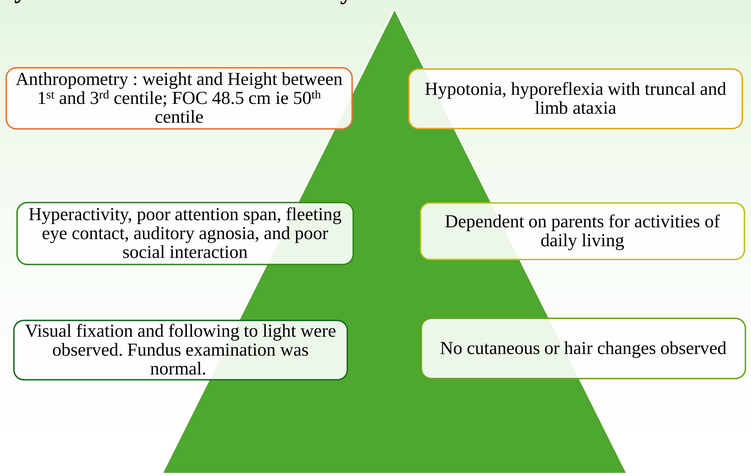
EEG suggested bihemispheric slow waves & absent sleep markers

CASE REPORT

A 4-year-old boy of Pakistani ethnicity, first born child to consanguineous parents, with no significant family history of note and normal perinatal events with clinical details as per timeline below:



FlAIR sequence signifying no signal alteration



INVESTIGATIONS & MANAGEMENT

- Based on significant expressive and receptive speech delay, past H/O febrile illness provoked seizures and periodic ataxias with worsening of hyperactivity and inattention, we extended the diagnostic work up.
- No hypoglycemia, ketosis or acidosis found. Normal lactate and ammonia levels.Normal Neuroimaging and EEG showed slowing of background activity with absent sleep markers
- Plasma amino acids and urinary organic acid quantification by chromatography requested in attempt to delineate underlying metabolic basis of episodic symptoms provoked by febrile illness. Plasma amino acid quantification suggested markedly raised plasma glycine levels against normal range of 113-261 umol/L

At Diagnosis	6 months	9 months	12 months
903 umol/L	812 umol/L	739 umol/L	354 umol/L

Whole Exom Sequencing

GENE	VARIANT COORDINATES	ZYGOSITY	TYPE & CLASSIFICATION
GLDC (OMIM# 238300)	chr9:6588629T > C	Homozygous	Splicing Pathogenic class 1

- After genetic and spectrometric confirmation of attenuated NKH, glycine lowering therapies were initiated including sodium benzoate, low dose dextromethorphan, concomitant carnitine supplementation, behavioral and speech therapy.
- Patient had marked improvement resulting in withdrawal of levetirecetam, no further need of behavioral therapy, attaining full sentences speech at 5.5 years and started attending nursery.

DISCUSSION

- Episodic ataxia (EA) is a clinically heterogeneous group of disorders with widespread etiology ranging from benign paroxysmal vertigo, migraine variants, channelopathies like CACNA1A/KCN1A and inherited metabolic defects like mitochondrial disorders, organic acidemias & glucose transporter defects
- Through this case we wished to highlight unusual presentation with periodic ataxias and hyperactivity issues attributable to attenuated form of glycine encephalopathy, posing a favorable outcome with early intervention

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2. Nowak, M.; Chuchra, P.; Paprocka, J. Nonketotic Hyperglycinemia: Insight into Current Therapies. J. Clin. Med. 2022, 11, 3027