

Case Report: Multi Neurological Dysfunction in an NGLY1 Deficiency Disorder

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Received: November 23, 2020; Published: January 21, 2021

Abstract

NGLY1-enzyme deficiency is a rare congenital disorder of glycosylation (NGLY1-CDG) involving multisystemic neurodevelopmental disorder where affected individuals show developmental delay, epilepsy, intellectual disability, hypo- or alacrimia, abnormal liver function, and poor growth due to feeding difficulties. According to the NGLY1 Foundation, as of March 2018, there are only 63 cases worldwide that have been established. Our case report presents a 3-year-old male child with elevated liver transaminases, developmental delay, epilepsy, and poor growth.

Keywords: NGLY1; Congenital Disorder of Glycosylation (CDG); Neurodevelopmental Disorder

Introduction

NGLY1 deficiency is a rare congenital disorder of glycosylation (CDG).

Rare diseases like NGLY1 deficiency often go undiagnosed, making it difficult to determine the true frequency in the general population. It can affect multiple systems of the body. Affected individuals may have delay in reaching developmental milestones, intellectual disability, movement disorders, seizures, liver disease and alacrima. The specific symptoms and severity of this disorder vary dramatically among affected individuals.

With few patients evaluated so far, it is difficult to give a prognosis especially as the mechanism of harm is not yet fully understood. Most children do not appear to be medically fragile. However, some children have died at a young age primarily due to complications following respiratory infections and/or seizure complications. Our Case report is of a child with focal epilepsy, where the diagnosis was established by clinical and genetic testing [1,4].

Case Report

A 3-year-old male child previously evaluated for developmental delay, bilateral hearing loss and focal epilepsy partially controlled despite two anti-epileptic medication. He had his metabolic panel done which was reported normal.

On physical examination dysmorphic features noted were brachycephaly, frontal bossing, low set ears, micrognathia and clinodactyly. Neurological examination revealed central hypotonia, accompanied with choreo-athetoid movement in the upper and lower limbs which disappears during sleep. Deep tendon reflexes were intact. Further findings of hepatomegaly, bilateral undescended testes, contractures and scoliosis were demonstrated.

Citation: Khurshid Khan Afridi., *et al.* "Case Report: Multi Neurological Dysfunction in an NGLY1 Deficiency Disorder". *EC Emergency Medicine and Critical Care* 5.2 (2021): 21-23.

Mother noticed that her child is not sweating even with exertion.

He had recurrent chest infection that needed hospital admission frequently. He used to have convulsions on daily basis accompanied with deranged liver function at two occasions during hospitalization.

He was born by C-section due to non-reassuring CTG and fetal bradycardia. His birth weight was 2 Kg. He was admitted to NICU for 2 days due to poor sucking and was fed by NG tube.

Parents are first degree relatives with another older sibling with mild developmental and speech delay. Genetic testing was done for his brother and was reported normal.

First MRI was done for seizures at the age of 7 months revealed prominent extra axial CSF spaces in the frontal and temporal region. EEG was performed, recorded severe symptomatic focal epilepsy due to advance neocortical pathology. The EEG was repeated at 2 years demonstrated features of epileptic encephalopathy. ABR test was done which showed moderate bilateral hearing impairment more severe on the left side.

At 25 months, whole-exome sequencing was performed for the patient and his parents. The patient had Homozygous gene of NGLY1 and Both parents were heterozygous for the gene NGLY1. Ophthalmic examination done at 30th month of age displayed optic nerve atrophy.

He is on vigabatrin, clonazepam, Topiramate for his epilepsy with occasional brief seizure.

Discussion

NGLY1 deficiency is a complex neurological syndrome in which there is deficiency of an enzyme known as N-glycanase 1 (NGLY1). This enzyme normally helps the body remove proteins that are not functioning properly. In cytogenetic location: 3p24.2, which is the short (p) arm of chromosome 3 at position 24.2 [2,3].

It is inherited in an autosomal recessive manner. Diagnosis has been confirmed at ages ranging from three months to 10 years, mostly through broad molecular testing, such as exome analysis. While most individuals with NGLY1-CDDG survive until early adulthood, with a relatively stable clinical course [2].

The typical features of NGLY1 deficiency include neurodevelopmental delay, epilepsy, choreoathetosis, hypo- or alacrimia and elevated liver enzymes. Additional features may include developmental delay, hypotonia, peripheral neuropathy, intellectual disability, EEG abnormalities and microcephaly. Birth weight is noted to be below the tenth percentile.

50% of the affected individuals develop myoclonic seizures, documented seizure types also include infantile spasms, atonic, tonic, and absence seizures.

CSF results typically demonstrate three finding that are Low total protein and albumin or low CSF/serum albumin ratios or low CSF 5-hydroxyindolacetic acid, homovanillic acid, and tetrahydrobiopterin levels.

Brain MRI show delay in myelination during early childhood with progressive cerebral and occasional cerebellar atrophy, which correlates with worsening function [3,4].

Nerve conduction studies most often demonstrate an axonal sensorimotor polyneuropathy. Needle electromyogram may show neurogenic findings with acute and chronic changes.

Liver function test shows elevated AST and ALT in the first two years of life which later normalize by four years of age without any specific intervention with normal liver biopsy. Abdominal ultrasound may show splenomegaly, steatosis, and hepatomegaly.

Genetic testing is definite in diagnosing NGLY-1 deficiency.

The treatment of NGLY1 deficiency is directed towards the specific symptoms that are apparent in each individual. There are no standardized treatment protocols or guidelines for affected individuals. Treatment may require the coordinated efforts of a team of specialists. Psychosocial support for the entire family is essential. Genetic counseling may be of benefit for affected individual and their families. As well as a combination of antiseizure medication combined with pain killers, sleeping medications multivitamins and other drugs directed toward the symptoms for each case.

The complexity and rareness of this condition poses a challenge for schools. Most will be taught in special education programs with a focus on life skills. Social skills are a relative strength for NGLY1 patients [3-5].

Conclusion

In our case due to high suspicion based on alacrimia, seizures and hepatic enzymes derangement the diagnosis of NGLY1 deficiency was confirmed by whole exome sequencing, which revealed a deficiency of an enzyme called N-glycanase 1 and further parental carrier testing was done and confirmed the heterozygosity of the mutation. Counseling was done with advice regarding planning for pregnancy and the need for prenatal diagnosis.

Researchers are studying proton pump inhibitors as a potential therapy for NGLY1 deficiency, As PPI's block the activity of endo-beta-N-acetylglucosaminidase (ENGase), and it is possible that this may be beneficial in individuals with NGLY1 deficiency [6].

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Volume 5 Issue 2 February 2021

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