Austin Journal of Clinical Neurology

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Austin Publishing Group

Special Article - Epilepsy and Seizure Disorders

Unusual Case of Glucose-Galactose Malabsorption with Infantile Neuroaxonal Dystrophy

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Received: August 19, 2016; **Accepted:** October 04, 2016; **Published:** October 07, 2016

Abstract

Background: Glucose-Galactose Malabsorption (GGM) is a rare autosomal recessive disorder presenting with diarrhea and failure to thrive during the neonatal period and if left untreated the patient may die due to severe dehydration and metabolic acidosis. This disease results from a mutation in the gene coding for sodium/glucose co-transporter on chromosome 22. Infantile Neuroaxonal Dystrophy (INAD) is another rare autosomal recessive disorder characterized by abnormal nerve ending either in central nervous system or in peripheral nervous system. The patients typically have normal development till2 years of age before onset of progressive regression.

Methods: A retrospective chart review was done.

Results: Molecular Genetic Analysis was done for *SLC5A1* and *PLA2G6* genes. Two different homozygous mutations were found in both the genes confirming the diagnoses.

Conclusion: We report an 8-year-old girl who presented with diarrhea during the neonatal period and was eventually diagnosed with GGM. Later on this patient had developmental regression, not the feature of GGM, for which further investigations were done which confirmed the diagnosis of INAD. To the best of our knowledge it is the first reported case worldwide of having both the conditions in the same patient. Her cousin brother was similarly affected.

Keywords: Glucose-galactose malabsorption; Infantile neuroaxonal dystrophy; Cerebellar atrophy

Introduction

GGM is an autosomal recessive disease with life-threatening diarrhea in newborn period caused by mutation in the Na^+/glucose co-transporter gene *SLC5A1*. Patients with GGM present with the neonatal onset of severe life-threatening watery diarrhea and dehydration [1,2]. *SLC5A1* is a member of a large gene family, the sodium: solute symporter family with *SLC5A1* gene located on chromosome 22q12.3, comprising 15 exons and encoding a 73-kda glycoprotein predicted to possess 14 trans-membrane segments [3]. After expression, the SLC5A1 protein is localized to the brush border membrane of the intestinal epithelium and actively imports luminal glucose or galactose into the enterocyte by coupling sugar transport with Na^+ gradient across the membrane. Mutations in *SLC5A1* have been shown to cause defect in sugar transport [4].

Like in an extended Amish pedigree having a large cohort, watery diarrhea usually starts on day 2 or 3 after birth, soon after the breast feeding or formula is initiated. The diarrhea is often described by parents as 'non stopping', 'keep running', 'in each diaper change no matter how often you change the diaper'. Stool is acidic with pH near 5 or lower, positive for reducing substances. Other laboratory findings may show significant metabolic acidosis, hypernatremic and hyperosmolar dehydration [5]. Use of carbohydrate-free formula, with or without fructose, leads to quick rehydration and, normal growth and developmental pattern afterwards. The infants may be weaned from carbohydrate-free diet to low-carbohydrate diet before 1-year old though patients do have more frequent bowel movements (2-5 times/day) with loose stool compared to normal. The tolerance to carbohydrate-containing diet improves gradually over time in all individuals with reasonable tolerance to regular carbohydrate-containing diets by teenage. Infantile neuroaxonal dystrophy (INAD) is an autosomal recessive disorder caused by mutations in the gene PLA2G6 located on chromosome 22q13.1, which encodes iPLA2-VIa, a calcium independent phospholipase [6]. The iPLA2 enzymes are critical in cell membrane homeostasis as these catalyze the hydrolysis of glycerophospholipids, generating a free fatty acid (usually arachidonic acid) and a lysophospholipid, which may underlie the axonal pathology, observed in *PLA2G6* associated disease [7]. High brain iron is seen in about half of cases of INAD, and it is one of many disorders known as neuro-degeneration with brain iron accumulation (NBIA), a group of progressive extra pyramidal disorders characterized by iron accumulation in the brain. The onset of symptoms usually occurs before 2 years and psychomotor regression is the most frequent presentation. Ataxia or gait instability is also frequent in early disease. Optic atrophy occurs in the majority of affected individuals as are nystagmus and strabismus [8]. There may be early truncal hypotonia, followed by the development of tetra paresis that is usually spastic but can be areflexic [9]. The majority of patients will have evidence of denervation on electromyogram (EMG) and nerve conduction velocity may also be decreased [9]. Fast rhythms on electroencephalogram (EEG) are reported to occur

Citation: Al-Baradie RS, Chaudhary MW, Burshaid D and Mir A. Unusual Case of Glucose-Galactose Malabsorption with Infantile Neuroaxonal Dystrophy. Austin J Clin Neurol 2016; 3(2): 1093.

frequently. Generalized seizures are reported in a few cases and occur late in the disease. Iron mainly accumulates in the globus pallidus, seen as low signal intensity on T2 weighted images. Early cerebellar atrophy and increased signal intensity in cerebellar cortical T2 weighted sequences is common. Diagnosis is confirmed by the mutation in the gene. Peripheral nerve spheroids on nerve biopsy are highly suggestive of the condition in the patients with compatible clinical setting if the non-invasive molecular analysis for mutation is negative. Unfortunately, it is a life-limiting condition with most of the patients dying in first decade of life as there no specific treatment except symptomatic management with baclofen and botulinum toxin for spasticity. Both the conditions are inherited as autosomal recessive and the possibility of each is higher in highly consanguineous populations. As there is no specific treatment available at present, symptomatic management is all that was offered by multidisciplinary team. The delay in the diagnosis leads to delayed much-needed genetic counseling, prolonged uncertainty about the diagnosis for the caregivers and the physician, and unnecessary investigations even if condition turns out to be untreatable.

Methods

Our index case was born to first-degree consanguineous parents from eastern part of Saudi Arabia (Figure 1) with uneventful pregnancy at full term through emergency caesarian section due to fetal distress with an Apgar score of 8 and 10 at 1 and 5 minutes respectively weighing 2 kg. She was admitted in the NICU shortly after discharge with a history of watery diarrhea and metabolic acidosis while she was on breast milk only. She had positive reducing substances in the urine and stool and she was improved with special fructose based formula. She was diagnosed to have GGM. She was discharged home in a good condition on lactose-containing other carbohydrate-free formula and she was thriving well and doing fine afterwards.

She started to roll over by 6 months and sat independently at the age of 7 months. At the age of 7 months she had focal seizure for which she was admitted and treated in the hospital. Brain MRI was done that showed left middle cerebral artery infarct with moderate cerebellar atrophy (Figure 2). Her extensive metabolic and hypercoagulable workup was unremarkable. She continued to have normal developmental milestones up to the age of 2 years when she started to lose her ability to sit, roll over and head control. By the age of 3.5 years she was unable to sit, crawl, speak, and had difficulties in her vision. She lost her hearing late in the disease. After that she started to have difficulty in feeding with severe GERD and gastrostomy tube was inserted at the age of 4 years along with fundoplication. One year later she was diagnosed to have neuroaxonal dystrophy. Muscle biopsy showed denervation atrophy. She had multiple admissions to the hospital due to aspiration pneumonia and she is following with multidisciplinary team. On physical examination, her weight was 18 kg and her height 110 cm at 8 years. She was hypotonic and had poor head and trunk control with multiple deformities in both feet. She also had contractures in her wrists. She had nystagmus, thoracolumbar scoliosis to right.

Her last admission was late 2015 when she was 8 years old. She was admitted to PICU with a history of severe pneumonia and she passed away due to septic shock. She has a male cousin, currently 8½ years old who has a similar condition. He has epilepsy controlled on Valproate alone since last 2 years, and is non-verbal and non-ambulatory.

Results

The *SLC5A1* gene was analyzed by PCR (Polymerase Chain Reaction) and sequencing of both DNA strands of the entire coding region and the highly conserved exon-intron splice junctions. She had a homozygous c.265G>A (p. G89R) variant in the exon 3 of the *SLC5A1*gene on chromosome 22q12.3. This particular mutation in the *SLC5A1* gene has not been described in the literature earlier. It is at a highly conserved nucleotide and amino acid position. Software analysis by Polyphen, SIFT and AGVGD indicate that the change is probably damaging (CGC Genetics, Lisbon, Portugal). *PLA2G6* gene analysis consisted of PCR amplification and direct sequencing of the entire coding region of the gene, with all corresponding intron-exon boundaries. A homozygous c.2070_2072del (p. Val691del) mutation, previously described in literature, was detected in the *PLA2G6* on chromosome 22q13.1 that does not alter the reading frame of the gene, confirming the diagnosis of INAD.

Discussion

We report an index case of GGM with INAD, with similar condition in her cousin. The mutation in the *SLC5A1*gene was novel and patient responded to the special fructose based formula developing normally until 2 years of age. Several different mutations in *SLC5A1*causing GGM include missense, nonsense, frame shift, splice site, and promoter mutations. The nonsense, frame shift, and splice site mutations all produce nonfunctional truncated proteins. In majority of missense mutations, the proteins are translated and are stable in the cell, but do not reach the plasma membrane [10]. The intestinal sodium/glucose co transporter is responsible for 'active' glucose absorption across the brush border membrane of the cells that line the gastrointestinal tract. This is an energy-requiring action that is driven by the sodium/potassium ATPase located at the basolateral cell membrane. The trans-epithelial absorption of glucose and galactose is then completed at the basal lateral membrane through the facilitated glucose transporter.

The intriguing symptoms of psychomotor regression, which are not part of GGM, led to search for other coexisting condition. After a delay of 3 years she was confirmed to have INAD on the basis of her above described mutation in the PLA2G6 gene. This particular mutation has been described in literature [11]. The interesting thing to note is the close proximity of these two genes at 22q12.3 and 22q13.1 respectively, though both are point mutations and not a case of contiguous gene deletion.

Hypercoagulable state and/or strokes are not previously described as features of either of two conditions. Presence of the left middle cerebral artery infarct detected at 7 months of age after she presented with focal seizures led to detailed evaluation. She was compliant to diet and had no episodes of diarrhea or dehydration around the time of seizure-onset, and was extensively investigated for any known hypercoagulable state without any clue to the cause of her stroke. It is difficult to comment with any degree of accuracy about the timing of the stroke as the first MRI brain showed old infarct and hence she was labeled as prenatal stroke though dehydration in remote past with

infarction is a possibility.

Seizures in patients with NAD are late and easy to control but our patient had early onset seizure probably as a result of stroke. Her cousin had typically late onset seizures at 6 years of age and both had marked cerebellar atrophy described in previous case reports.

References

1. Wright EM, Martín MG, Turk. Familial glucose-galactose malabsorption and hereditary renal glycosuria. In: ScriverCR, BeaudetAL, SlyWS, ValleD, eds. Metabolic and molecular bases of inherited disease, Vol. 3. New York: McGraw-Hill, 2001: 4891-4908.
2. Wright EM. I. Glucose galactose malabsorption. Am J Physiol. 1998; 275: G879-G882.
3. Turk E, Wright EM. Membrane topology motifs in the SGLT cotransporter family. J Membr Biol. 1997; 159: 1-20.
4. Wright EM, Turk E, Martin MG. Molecular basis for glucose-galactose malabsorption. Cell Biochem Biophys. 2002; 36: 115-121.
5. Xin B, Wang H. Multiple sequence variations in SLC5A1 gene are associated with glucose-galactose malabsorption in a large cohort of Old Order Amish. Clin Genet. 2011; 79: 86-91.
6. Morgan NV, Westaway SK, Morton JE, Gregory A, Gissen P, Sonek S. PLA2G6, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. Nat Genet. 2006; 38: 752-754.
7. Baburina I, Jackowski S. Cellular responses to excess phospholipid. J Biol Chem. 1999; 274: 9400-9408.
8. Kurian MA, Morgan NV, MacPherson L, Foster K, Peake D, Gupta R. Phenotypic spectrum of neuro-degeneration associated with mutations in the PLA2G6 gene (PLAN). Neurology. 2008; 70:1623-1629.
9. Nardocci N, Zorzi G, Farina L, Binelli S, Scaioli W, Ciano C, et al. Infantile neuroaxonal dystrophy: clinical spectrum and diagnostic criteria. Neurology. 1999; 52: 1472-1478.
10. Abdullah AM, el-Mouzan MI, el Shiekh OK, al Mazyad A. Congenital glucose-galactose malabsorption in Arab children. J Pediatr Gastroenterol Nutr. 1996; 23: 561-564.
11. Khateeb S, Flusser H, Ofir R, Shelef I, Narkis G, Vardi G, et al. PLA2G6 mutation underlies infantile neuroaxonal dystrophy. Am J Hum Genet. 2006; 79: 942-948.

Austin J Clin Neurol - Volume 3 Issue 2 - 2016
ISSN : 2381-9154 | www.austinpublishinggroup.com

Citation: Al-Baradie RS, Chaudhary MW, Burshaid D and Mir A. Unusual Case of Glucose-Galactose Malabsorption with Infantile Neuroaxonal Dystrophy. Austin J Clin Neurol 2016; 3(2): 1093.