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Case Report / Olgu Sunumu

An overlooked case of a treatable hyperinsulinemic hypoglycemia: congenital glycosylation defect Type Ib

Gözden kaçabilecek ve tedavi edilebilir bir hiperinsülinemik hipoglisemi olgusu: konjenital glikozilasyon defekti Tip Ib

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The known about this topic

Contribution of the study: Hiperinsulinemic hypoglycemia can be the main symptom in patients presenting with CDG Type Ib.

Contribution of the study

Our report emphasizes that, due to the high accessible therapeutic chance, it is highly relevant to consider CDG type Ib in patients with therapy-resistant hypoglycemia with multisystem involvement.

Abstract

Congenital glycosylation defects are autosomal recessive disorders clinically characterized with growth retardation, hypotonia and multisystemic involvement. Congenital glycosylation defect type Ib is due to deficiency in phosphomannose isomerase which converts fructose-6-phosphate into mannose-6-phosphate. Patients usually present with hepatic or gastrointestinal symptoms lacking cranial involvement, making their IQ completely normal. We report a 10-month-old female patient referred to our clinic with persistent hypoglycemia, failure to thrive and hepatosplenomegaly who was diagnosed with congenital glycosylation defect type Ib. Oral D-mannose therapy was initiated shortly after diagnosis and her symptoms resolved in two weeks. Congenital glycosylation defect type Ib is an easily treatable disease and should be kept in mind in differential diagnosis in children and adults who show gastrointestinal symptoms, hyperinsulinemic hypoglycemia, palpable liver and spleen, growth retardation and elevated liver function tests.

Keywords: Congenital defects of glycosylation, D-mannose, hyperinsulinemic hypoglycemia, protein losing enteropathy

Öz

Konjenital glikozilasyon defektleri (CDG) otozomal resesif kalıtım gösteren, gelişme geriliği, hipotoni ve multisistem tutulumla seyreden hastalıklardır. Konjenital Glikozilasyon Defekti Tip 1b fosfomannoz izomeraz enzimindeki eksikliğe bağlı oluşmaktadır. Diğer glikozilasyon defektlerinin aksine, özellikle hepatik ve gastrointestinal bulgularla seyretmektedir. Nörolojik tutulum gözlenmez ve etkilenmiş bireylerin zekâ seviyeleri normaldir. Bu raporda, 10 aylıkken ishal, kusma, büyüme-gelişme geriliği ve hepatosplenomegali nedeniyle önce hiperinsülinemik hipoglisemi tanısı ile diazoksit tedavisi başlanan ve tedaviye yanıt alınamaması nedeniyle merkezimize yönlendirilen bir olgu sunulmaktadır. Klinik ve laboratuvar bulguları konjenital glikozilasyon defekti tip Ib ile uyumlu olan hastaya D-mannoz tedavisi başlandı. Tedaviye dramatik yanıt veren hastanın semptomları iki hafta içerisinde geriledi. Konjenital Glikozilasyon Defekti Tip 1b yeni tanımlanmaya başlamış, D-mannoz tedavisinden belirgin fayda gören bir metabolik hastalıktır. Gastrointestinal semptomlar, hipoglisemi, hepatosplenomegali, karaciğer fonksiyon testlerinde anormallik saptanan ve gelişme geriliği olan olgularda akılda tutulması ve ayrıcı tanıda düşünülmesi önemlidir.

Anahtar sözcükler: D-mannoz, hiperinsülinemik hipoglisemi, konjenital glikozilasyon defektleri, protein kaybettiren enteropati

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Introduction

Congenital disorders of glycosylation (CDG) which previously are referred to as carbohydrate-deficient glycoprotein syndromes are a group of disorders associated with hypoglycosylation of glycoproteins. Congenital glysco-

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sylation defects follow autosomal recessive, autosomal dominant or X-linked recessive inheritance pattern. Malfunction on different organs and systems, mostly affecting the nervous system, gastrointestinal system, the liver and the muscles is expected (1). Since the first description of the disease in 1980, nearly one hundred types of N-glycosylation O-glycosylation disorders have been described to date (2). The most frequent form is caused by phosphomannomutase (PMM) deficiency which is known as CGD type Ia (3). The hypoglycosylation of glycoproteins is determined by transferrin isoelectric focusing test of which affected glycoproteins show altered isoelectric patterns compared to normal controls (4).

In 1998, a new CDG syndrome is described by Niehues, CDG type Ib, which is caused by mutations in the MPI gene (phosphomannose isomerase, OMIM 145550) that converts fructose-6 phosphate into mannose-6 phosphate. Compared to other CDG's, patients with CDG type Ib lack cranial involvement and have normal IQ. In CDG type Ib, gastrointestinal symptoms mimicking protein-losing enteropathy represent the main clinical picture (5). Elevated liver function tests, hepatosplenomegaly, hyperinsulinemic hypoglycemia (HI) may also be frequent presentations of the disease. Unlike most of the other CDG subtypes, an effective therapy is available for CDG type Ib patients.

By oral mannose therapy, clinical manifestations and glycoprotein hypoglycosylation are alleviated (6). In this report,we present a CDG type Ib patient diagnosed in our clinic and demonstrate the successful therapy model.

Case

A 10-month-old (corrected 8-months) girl presented to the emergency department with severe diarrhea and vomiting. Her history was insignificant apart from a preterm birth at 32 weeks and parental consanguinity. On physical exam her height, weight, head circumference was under the 3rd percentile however,her mental and motor developmental steps were found normal. The liver was 2 cm and spleen was 1.5 cm below the mid-costal margin. The serum glucose level was low as 28 mg/dl (>65 mg/dl) and liver function tests (LFT"s) were elevated [alanine-aminotransferase (ALT): 244 IU/L, aspartate-aminotransferase (AST): 274 IU/L]. Further diagnostic analysis due to persistent elevated LFTs and hypoglycemia revealed hyperinsulinemic hypoglycemia with high fasting insulin levels 11.7 mIU/L (≥2). Despite prompt diazoxide treatment hypoglycemia and elevated LFT's persisted. As a further diagnostic step, transferrin isoelectric focusing testing was performed and type I pattern was seen, typical for CDG type Ib. In order to evaluate coagulopathy, protein-C 27% (70%–140%), Protein-S 59.5% (63.5%–149%), Antithrombin-III 40% (83%–128%) were detected low concurrent to our pre-diagnosis. Sanger sequencing revealed a homozygous known mutation (c.413T>C, p.M138T) in the MPI gene, which confirmed the molecular diagnosis of the disease. Oral D-mannose treatment was started with 1.2 mg/kg/day q4 hours. After D-mannose therapy, vomiting, diarrhea, hypoglycemia resolved dramatically, liver and spleen decreased in size, LFTs returned to normal. Shortly,she started to gain weight. Due to regulated blood sugar, diazoxide was stopped. Informed consent was obtained from the family.

Discussion

Congenital glycosylation defects are caused by defects in N-pathway, O-pathway, lipid glycosylation or glycosylphosphatidylinositol synthesis defects and due to their important biological functions, almost all CDG's present during infancy as clinically manifested in various organs or systems. Growth retardation,hypoglycemia, protein-losing enteropathy, hepatic dysfunction are common manifestations of the disease. In most CDG subtypes, neurological abnormalities like neuropathy, cerebellar hypoplasia or developmental delay are also expected (4). However,contrary to the other groups, CGD type Ib shows no neurological abnormalities and IQ levels of the patients are found to be normal. Although our patient had failure to thrive, her developmental steps were found normal for her age. Chronic diarrhea, protein-losing enteropathy, hypoglycemia with hyperinsulinemia, coagulopathy and hepatic dysfunction are the predominant features of CDG type Ib. Hepatic fibrosis is observed in all patients who underwent a liver biopsy (6).

Clinical symptoms for hypoglycemia may not always be overt as seen in CDG Type Ib. Hyperinsulinemic hypoglycemia is not observed frequently among neonates and infants however,can lead to life-threatening conditions if not treated shortly. HI may be caused due to channelopathies, enzyme abnormalities, transcription factor defects or might be a component of a syndrome as spotted in our case (7).

Diagnosis for CGD type Ib can be made by analyzing serum transferrin glycoforms via transferrin isoelectric focusing when suspected. Type I pattern is typical for CDG type Ib as found in our patient. However, type I pattern is also observed for CGD type Ia, the most common type of the CDG's, therefore showing MPI gene enzyme activity or mutations an make the diagnosis certain (8). To date,according to the Human Gene Professional database, 19 mutations in MPI gene have been reported (latest access, March 2018, http://portal.biobase-international.

com). Autosomal recessive inheritance, as well as compound heterozygosity, can cause the disease.

Various studies have shown the efficacy of mannose treatment after the first trial by Niehues et al. (5) on a 6-year-old patient, which successfully normalized the symptoms rapidly. Mannose treatment improves the general clinical status and normalizes the symptoms faster than glycosylation of glycoproteins. Hypoglycemia and protein-losing enteropathy can be resolved in a few weeks as well as decreased liver and spleen sizes later on treatment. 1.2 mg/kg/day q4-hours is recommended as a starting dose and continued q6-hours. After the diagnosis was made, our patient also received oral mannose therapy and her symptoms resolved in two weeks. Oral mannose therapy is usually well tolerated and no severe side effects have been reported in long-term treatment. However, Liem et al. (9) reported a case who was not responsive to oral mannose and developed hypoalbuminemia, edema, diarrhea and pancytopenia on follow-up. The patient received unfractionated heparin intravenous and subcutaneous respectively which reserved her symptoms due to enteropathy. Although our patient's hepatomegaly resolved, some case reports have shown that the liver disease persists in severe cases and evolves into chronic liver disease. Janssen et al. (10) reported a therapy-resistant case who got a liver transplant at the age of 28 successfully.

In conclusion, congenital glycosylation defect type Ib is a multisystem disorder with various clinical manifestations. It is important to keep this disease in mind in differential diagnosis among patients presenting with gastrointestinal symptoms, hyperinsulinemic hypoglycemia, palpable liver and spleen, growth retardation and elevated LFT's. Affected individuals dramatically benefit from D-mannose treatment, which can be easily administered and very effective. Lacking neurological manifestations, treated patients of CDG type Ib can pursue a better quality life shortly.

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