Research Article

Deficiency of Ubiquitin Ligase RBCK1 Causes Polyglucosan Myopathy and Severe Childhood Cardiomyopathy

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Abstract

Objectives: The abnormal accumulation of alpha-amylase-resistant glycogen, or polyglucosan, can affect multiple tissues in the body. This form of glycogen storage disease is generally due to glycogen branching enzyme (GBE) deficiency or to defective ubiquitin ligases. Here, we present a six-year-old girl, born to consanguineous parents, who suffered from polyglucosan-associated cardiomyopathy, myopathy, hepatopathy, and pulmonary hypertension.

Study design: The patient presented at age four to a hospital in Saudi Arabia with weakness and congestive heart failure requiring inotropic support and mechanical ventilation. She was referred to our center for heart transplant evaluation. Heart, skeletal muscle, and liver biopsies were performed. We measured the glycogen concentration in muscle tissue and GBE activity in peripheral blood lymphocytes. We also carried out DNA sequencing of GBE1, PRKAG2, and RBCK1.

Results: Heart, skeletal muscle, and liver biopsies variably showed periodic acid-Schiff-positive, partially amylase-digested polyglucosan accumulation, significantly increased glycogen concentration, but marginally increased GBE activity. Ultimately, genetic analysis revealed a novel homozygous mutation (p.Cys371Phe) in the gene RBCK1, which encodes an E3 ubiquitin ligase.

Conclusion: This case expands the clinical spectrum of RBCK1 mutations, and highlights that this gene should be considered in the differential diagnosis of polyglucosan storage diseases, especially when GBE activity is not decreased.

ABBREVIATIONS

GSD: Glycogen Storage Disease; GBE: Glycogen Branching Enzyme; H&E: Hematoxylin-Eosin; PAS: Periodic Acid-Schiff

INTRODUCTION

Glycogen storage diseases (GSDs) are caused by defects in the various enzymes needed for glycogen biosynthesis, glycogen breakdown, or glycogenesis. In most cases of glycogenoses, normal spherical glycogen (characterized by numerous branched peripheral chains) accumulates. However, there are two main exceptions. Accumulation of glycogen with abnormally short peripheral chains is seen in debrancher enzyme deficiency (i.e. GSD type III) [1]. And the deposition of a distinctly abnormal amylopectin-like polysaccharide called polyglucosan (characterized by fewer and poorly branched peripheral chains) accumulates in glycogen branching enzyme (GBE) deficiency (i.e. GSD type IV) [2].

The wide clinical spectrum of disease we have seen in GBE deficiency can be explained by the amount of residual enzyme activity. Those with very little enzyme activity (0 to 7%) present with a fatal infantile form of disease, which consists of hepatopathy, liver cirrhosis, and severe cardiomyopathy. Those with 8 to 25% residual enzymatic activity generally present with neuromuscular disease, cardiomyopathy, or central nervous system disease [3].

A neuromuscular form of GBE deficiency has also been described in the literature, and is classified into three groups based on age at presentation. The first is notable for antenatal onset, polyhydramnios, decreased fetal movements, fetal akinesia, arthrogryposis multiplex congenita, and ultimately hydrops fetalis and death during fetal life. A second lethal form presents similarly to spinal muscular atrophy type 1. Lastly, there is a third and more benign myopathic form that can present with proximal muscle weakness anytime from childhood to adulthood [4].