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Case Report

A Toddler Survived a Complex Multi-Systemic Infantile Presentation of COG6-CDG

Hossam Eldeen Hassan[1]*, Ayman Elhomoudi[1], Abdullah Alfalah[2], Abdurahim Abdellahi[3], Maryam Altassan[4] and Ruqaiah Altassan[4,5]

[1]Division of General Paediatrics, Department of Pediatric Oncology, King Faisal Specialist Hospital and Research Center, Medina, Saudi Arabia

[2]Department of Medical Genomics, Centre for Genomic Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

[3]Division of Paediatrics, Department of Infectious diseases, King Fahad Medical City, Riyadh. Saudi Arabia

[4]Department of Paediatrics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

[5]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

***Corresponding Author:** Hossam Eldeen Hassan, Division of General Paediatrics, Department of Pediatric Oncology, King Faisal Specialist Hospital and Research Center, Medina, Saudi Arabia.

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Abstract

Defects in conserved oligomeric Golgi (COG) complex subunits result in Congenital disorders of glycosylation (CDG) type II. These CDG subtypes has multisystem involvement. In this report, we present a 21-month-old female with Conserved Oligomeric Golgi complex subunit 6 - congenital disorders of glycosylation (COG6-CDG) who survived a complicated infantile course. She presented after birth with diarrhea, feeding intolerance, failure to thrive, hepatic failure, and recurrent febrile illnesses associated with neutropenia. A homozygous pathogenic variant in COG6 (c. 1167-24A>G) was detected by next-generation sequencing. In comparison to previous reports with the same deep intronic variant, who manifested a mild form of COG6-CDG or Shaheen syndrome, her initial presentation was severe. Follow-up after a year of recovery from a complex disease course showed significant improvement in her hepatic function and her growth and development. In addition, our patient did not manifest the typical ectodermal features of COG6-CDG.

Keywords: *Conserved Oligomeric Golgi 6 (COG); Congenital Disorder of Glycosylation (CDG); Ectodermal Dysplasia*

Abbreviations

ACTH: Adrenocorticotropic Hormone; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CDG: Congenital Disorder of Glycosylation; CDT%: Carbohydrate Deficit Transferrin; COG: Conserved Oligomeric Golgi; GGT: Gamma-Glutamyl Transferase; INR: International Normalized Ratio; MRI: Magnetic Resonance Imaging; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; TORCH: Toxoplasmosis, Rubella Cytomegalovirus, Herpes Simplex, and HIV; TPN: Total Parental Nutrition; TSH: Thyroid Stimulating Hormone; VSD: Ventricular Septal Defect

Introduction

COG6 (Component of Oligomeric Golgi Complex 6) gene encodes a subunit of the conserved oligomeric Golgi complex which is composed of eight subunits (COG1-8) that are required for maintaining normal Golgi apparatus structure and activity [1].

Deficiency of COG6 leads to a rare autosomal recessive form of congenital disorder of glycosylation (OMIM 614576). Like most CDGs, COG6-CDG has a multisystem involvement with diverse presentation among affected individuals. The main features of the disease include psychomotor developmental delay, failure to thrive, gastrointestinal, liver, hematologic, immunologic, and endocrine abnormalities [2]. Skin involvement is considered a prominent feature in COG6-CDG with mainly hyperhidrosis, hyperkeratosis, and or enamel hypoplasia [3]. To date, 43 individuals with COG6-CDG have been described in the literature with variable clinical presentations ranging between mild to severe phenotypes that can lead to early death [4-17].

Here, we describe a toddler with a confirmed COG6-CDG diagnosis who survived a very complex infantile course. Her initial presentation was severe in comparison to the previously reported patients with the same intronic variant in COG6.

Case Presentation

The patient was a 21-month-old female. She was born at term to consanguineous Saudi parents. Pregnancy was uneventful. Her weight at birth was 3 kg, length 49 cm (both on the 25th percentile), and head circumference was 33 cm (on the 10th percentile).

She presented at the age of 1 week with neonatal jaundice, feeding intolerance, and diarrhea. This was followed by hospitalization at the age of 2 weeks with febrile illness with no clear source. Since then, she required multiple hospitalizations for hypovolemia secondary to feeding intolerance, diarrhea, and sepsis-like pictures. She failed many trials of enteral feeding using different formulas and she was persistently spiking fever with no clear infectious source. At the age of 4 months, she required intensive care for signs of liver dysfunction including refractory hypoglycemia, coagulopathy, and cholestasis.

Her enteral feeding was held and she was kept on total parenteral nutrition (TPN) to overcome the persistent vomiting and diarrhea. Her growth was significantly affected and her weight dropped to 2.44 kg (below the 3rd ile). Her physical examination was remarkable for facial dysmorphism in the form of triangular face, dysplastic and low-set ears, long eyelashes, and smooth philtrum.

Cardiac examination was positive for pan-systolic murmur related to the ventricular septal defect (VSD). Biochemical investigation revealed persistent leukopenia with mainly neutropenia, normocytic anemia, high liver transaminases (alanine aminotransferase (ALT 368 U/L (RR 10 - 45 U/L)), aspartate aminotransferase (AST 808 U/L (RR 10 - 45 U/L)), and gamma-glutamyltransferase (GGT 323 (RR 7 - 32)), prolonged coagulation profiles (PT, PTT and INR), abnormal complements (C3 0.27 g/l, C4 0.04 (RR 0.9 -1.8), and CH50 22.8 U/ml (RR 40 - 90)). Thyroid stimulating hormone (TSH 4.8 Mu/l (RR 0.2 - 4.2)), and free T4 6.4 pmol (RR 12 - 27). TORCH screening was negative, and blood and urine cultures were repeatedly negative. Normal inflammatory indices (normal C-reactive protein). Serum immunoglobulins levels were normal. Her Carbohydrate deficient transferrin (CDT%) revealed normal pattern. Brain magnetic resonance imaging (MRI) showed hypoplastic corpus callosum. Echocardiogram showed muscular ventricular septal defect with a restrictive left to right shunt. Liver ultrasound revealed an increase in parenchymal echogenicity. Clinical exome sequencing identified a previously reported homozygous pathogenic variant in COG6 (NM _020751.3: c. 1167-24A>G) [6]. Parental carrier testing confirmed the in-trans inheritance of the variant.

She was discharged home at the age of 6-month after ensuring adequate oral tolerance of hypoallergic amino acid-based formula and stabilization of her liver function. Follow-up over a year post-hospitalization showed significant improvement in her growth parameters (weight increased to 10.6 (25th ile), and length reached 74.6 cm (25th ile), and her liver transaminases, coagulation factor, complements levels, and thyroid function normalized.

Discussion and Conclusion

COG6 deficiency was first linked to an autosomal recessive form of CDG by Lübbehusen., *et al*. in 2010 [4]. The first described patient presented with a severe neurologic disease that led to neonatal death. This was followed by a report of a patient with more systems

involvement including hepatopathy, inflammatory bowel disease, psychomotor retardation, and immunopathy [5]. Developmental delay, hepatopathy, recurrent infections, hyperhidrosis, and ectodermal dysplasia are commonly reported features in COG6-CDG [7,17].

Transferrin analysis can be a useful biomarker for COG-CDGs in general. Transferrin glycosylation analysis in reported patients with COG6-CDG displayed an abnormal (type II) pattern except in patients reported by Shaheen., *et al*. who harboured the deep intronic variant (1167-24A>G). These patients presumed to have a milder phenotype [6].

Chronic diarrhea, vomiting, and feeding intolerance leading to failure to thrive can be a presenting symptom of COG6-CDG [16,17]. The diarrhea was the first symptomatic presentation in our patient.

Skin abnormalities are prominent manifestations of some CDG subtypes. In COG6-CDG, hypohidrosis, hyperthermia, enamel hypoplasia, and palmoplantar hyperkeratosis are frequently reported in affected patients. The pathomechanism of skin involvement in COG6-CDG is not well understood but central cause has been hypothesized [3]. Our patient did not manifest any skin abnormalities in contrast to the patients reported by Shaheen., *et al*. [6].

In comparison to previous reports, specifically those with the same deep intronic variant (c. 1167-24A>G), our patient had a severe phenotype with multisystem involvement typical to CDG. However, her 1-year follow-up post-hospitalization showed a favourable survival course with resolved hepatopathy and failure to thrive.

In conclusion, our patient adds to the broad phenotypic spectrum of COG6-CDG and underlines the value of exome/genome sequencing in patients with severe disease course.

Informed Consent Statement

Informed consent was obtained from the patient's legal guardians for the publication of this case report.

Conflicts of Interest

The authors declare that they have no competing interests.

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