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Immune dysfunction in MGAT2-CDG: A clinical report and review of the literature

Sheri A. Poskanzer[1], **Matthew J. Schultz**[2], **Coleman T. Turgeon**[2], **Noemi Vidal-Folch**[2], **Kris Liedtke**[2], **Devin Oglesbee**[2], **Dimitar K. Gavrilov**[2], **Silvia Tortorelli**[2], **Dietrich Matern**[2], **Piero Rinaldo**[2], **James T. Bennett**[1,3], **Jenny M. Thies**[4], **Irene J. Chang**[1,4], **Anita E. Beck**[1,4], **Kimiyo Raymond**[2], **Eric J. Allenspach**[1,5], **Christina Lam**[1,4]

[1]Department of Pediatrics, School of Medicine, University of Washington, Seattle, Washington

[2]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota

[3]Center for Developmental Biology and Regenerative Medicine, Seattle Children's Research Institute, Seattle, Washington

[4]Department of Pediatrics, Division of Genetic Medicine, Seattle Children's Hospital, Seattle, Washington

[5]Department of Pediatrics, Division of Immunology, Seattle Children's Hospital, Seattle, Washington

Abstract

Glycosylation is a critical post/peri-translational modification required for the appropriate development and function of the immune system. As an example, abnormalities in glycosylation can cause antibody deficiency and reduced lymphocyte signaling, although the phenotype can be complex given the diverse roles of glycosylation. Human *MGAT2* encodes N-acetylglucosaminyltransferase II, which is a critical enzyme in the processing of oligomannose to complex N-glycans. Complex N-glycans are essential for immune system functionality, but only one individual with MGAT2-CDG has been described to have an abnormal immunologic evaluation. MGAT2-CDG (CDG-IIa) is a congenital disorder of glycosylation (CDG) associated with profound global developmental disability, hypotonia, early onset epilepsy, and other multisystem manifestations. Here, we report a 4-year old female with MGAT2-CDG due to a

Correspondence Christina Lam, Division of Genetic Medicine, University of Washington and Seattle Children's Hospital, 4800 Sand Point Way NE, M/S MB.8.632, Seattle, WA, USA, ctlam2@uw.edu.
Sheri A. Poskanzer and Matthew J. Schultz should be considered joint first author.

AUTHOR CONTRIBUTIONS

Sheri A. Poskanzer and Christina Lam provided clinical evaluations, performed chart review, drafted the initial manuscript, and revised the manuscript. Matthew J. Schultz, Dietrich Matern, and Kimiyo Raymond interpreted biochemical data, drafted the initial manuscript, and revised the manuscript. Coleman T. Turgeon, Noemi Vidal-Folch, and Kris Liedtke acquired, analyzed, and interpreted biochemical data. Devin Oglesbee, Dimitar K. Garvrilov, Silvia Tortorelli, and Piero Rinaldo critically reviewed and revised the manuscript. James T. Bennett, Irene J. Chang, and Anita E. Beck provided clinical evaluations, critically reviewed the manuscript, and revised the manuscript. Jenny M. Thies interpreted genetic data, critically reviewed the manuscript, and revised the manuscript. Eric J. Allenspach provided expert consultation in immunology, interpreted immunological data, critically reviewed the manuscript, and revised the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

novel homozygous pathogenic variant in *MGAT2*, a 4-base pair deletion, c.1006_1009delGACA. In addition to clinical features previously described in MGAT2-CDG, she experienced episodic asystole, persistent hypogammaglobulinemia, and defective ex vivo mitogen and antigen proliferative responses, but intact specific vaccine antibody titers. Her infection history has been mild despite the testing abnormalities. We compare this patient to the 15 previously reported patients in the literature, thus expanding both the genotypic and phenotypic spectrum for MGAT2-CDG.

Keywords

arrhythmia; CDG; hypogammaglobinemia; immunodeficiency; MGAT2

1 | INTRODUCTION

Congenital disorders of glycosylation (CDG) encompass a rapidly growing and heterogeneous group of individually rare genetic metabolic disorders that involve impairment of proper glycan synthesis, modification, and attachment to specific proteins or lipids. There are currently over 150 CDG described, each of which has a unique phenotypic spectrum with broad multisystem clinical and laboratory manifestations (Brucker et al., 2020; Chang, He, & Lam, 2018; Ferreira et al., 2018; Makhamreh, Cottingham, Ferreira, Berger, & Al-Kouatly, 2020; Pascoal et al., 2020; Verheijen, Tahata, Kozicz, Witters, & Morava, 2020).

MGAT2-CDG, previously known as CDG-IIa, is an autosomal recessive CDG with biallelic pathogenic variants in *MGAT2*. *MGAT2* encodes the enzyme N-acetylglucosaminyltransferase II, which catalyzes a step in the N-linked glycan synthetic pathway (Figure S1A). MGAT2-CDG shows a type II carbohydrate-deficient transferrin profile (CDT) and is confirmed with molecular testing (Tan et al., 1996; Chang et al., 2018; Cormier-Daire et al., 2000). Affected individuals with MGAT2-CDG typically have a severe neurologic phenotype that includes profound global developmental delay, psychomotor disability, hypotonia, and early onset epilepsy. Individuals generally have a normal cerebellum and lack peripheral neuropathy. Other multisystem features can include congenital heart disease, scoliosis, osteopenia, endocrine abnormalities, and clotting factor deficiency (primarily factor XI) (Table S1; Alsubhi et al., 2017; de Cock and Jaeken., 2009; Jaeken et al., 1994; Tan, Dunn, Jaeken, & Schachter, 1996; van Geet et al., 2001; Ramaekers, Stibler, Kint, & Jaeken, 1991; Alazami et al., 2012; Alkuraya, 2010; Cormier-Daire et al., 2000).

Major immunological defects have been observed with several CDG (Francisco et al., 2020; Pascoal et al., 2020). The specific immunologic phenotype and the degree of severity can vary between individuals within the same CDG as well as between different CDG. Complex N-linked glycans have a central role in T-cell function and serum proteins; however, patient phenotypes can vary depending upon the specific enzyme defect in each CDG and degree of residual enzyme activity. One published patient with MGAT2-CDG has had a detailed immunologic assessment. This individual was noted to have normal IgM and IgA levels, but

decreased IgG levels until the age of 6 years, when the deficiency resolved spontaneously (Jaeken et al., 1994, personal communication). He did not have a history of frequent infections. Two separately reported individuals from Saudi Arabia have been noted to have scalp psoriasis (Alkuraya, 2010; Alsubhi et al., 2017). Mice carrying a myeloid-specific knockout of the *Mgat2* gene, resulting in myeloid glycosylation defects, have been described to have deficient IgG antibody production in response to infection and vaccination, as well as an induced, autoimmune-mediated depletion of naïve T-cells and decreased T-cell activity (Ryan, Abbott, & Cobb, 2014; Ryan, Leal Jr., Abbott, Pearlman, & Cobb, 2014). Here, we present a patient with MGAT2-CDG with both persistent hypogammaglobulinemia and T-cell proliferation abnormalities.

2 | CLINICAL REPORT

Our patient is a 4-year-old female of Iraqi ancestry, who initially presented with respiratory distress and dysmorphic facial features. She was born via vaginal delivery at 32 weeks and 6 days gestation to a 23-year-old G3P3 mother. Birth weight, birth length, and head circumference were appropriate for gestational age. She spent 2 months in the Neonatal Intensive Care Unit with numerous life-threatening episodes of cyanosis and difficulty breathing requiring respiratory support via positive pressure ventilation and high-flow oxygen. She had hypotonia and a ventricular septal defect. A SNP chromosomal microarray revealed 8.5% runs of homozygosity (ROH), consistent with the level of consanguinity reported by the family. A Prader-Willi/Angelman syndrome methylation study was normal. Her newborn screen indicated an increased risk for cystic fibrosis, but follow-up sweat chloride testing was normal.

Around 6 months of age, she had a gastrostomy tube placed due to persistent feeding difficulties and faltering growth. Postoperation, she was diagnosed with seizures characterized as hypsarrhythmia and infantile spasms by EEG. A biochemical work-up included urine organic acids, plasma amino acids, acylcarnitine profile, and very long chain fatty acids. A carbohydrate-deficient transferrin (CDT) profile was performed due to the presence of inverted nipples, a finding in some patients with CDG (Ferreira et al., 2018).

Of the biochemical testing, only the CDT profile was abnormal, revealing a marked increase of abnormally glycosylated transferrin with incomplete glycan processing and minimal amounts of the fully glycosylated protein. Complete glycosylation of transferrin results in bi-antennary glycans at two asparagine residues (N-linked glycosylation) with glycan structure of NeuAcα2-6Galβ1-4GlcNAcβ1-2Manα1-6 (NeuAcα2-6Galβ1-4GlcNAcβ1-2Manα1-3)Manβ1-4GlcNAcβ1-4 GlcNAcβ1-4-Asn (Figure 1a). The mass spectrometry analysis of the abnormally glycosylated transferrin was consistent with both sites harboring a glycan with incomplete processing of one antenna (Lacey, Bergen, Magera, Naylor, & O'Brien, 2001). This was consistent with a type II carbohydrate deficient transferrin pattern. The predicted glycan structure from the mass observed was Manα1-6(NeuAcα2-6Galβ1-4GlcNAcβ1-2Manα1-3)Manβ1-4GlcNAcβ1-4 GlcNAcβ1-4-Asn, where each glycan has one complete antenna and one antenna lacking an N-acetylglucosamine, galactose, and terminal sialic acid (Figure 1b). Serum N-glycan profiling substantiated this result and demonstrated similarly abnormal N-linked

glycosylation on serum proteins compared with an unaffected individual (Figure 1c,d; Li, Raihan, Reynoso, & He, 20i5). This predicted glycan structure would result from deficiency of alpha-1,-6-mannosyl-glycoprotein 2-beta-N-acetylglucosaminyltransferase, sugg esting MGAT2-CDG.

The MGAT2 gene encoding this glycosyltransferase was within a 9.4 Mb run of homozygosity noted on this patient's chromosomal microarray. Targeted sequencing of MGAT2 revealed homozygosity for a 4 bp deletion, c.1006_1009delGACA (p.Asp336LeufsTer17), NM_002408.3. This deletion alters the reading frame of the transcript and is a predicted null variant. This variant has been previously reported once in the heterozygous state in population databases (a single Latino individual in gnomAD [v2.2.1] and no carriers present in the Saudi Genome Project database) and this patient constitutes the only entry in ClinVar at the time of the writing of this manuscript. This variant is also classified as pathogenic by the American College of Medical Genetics and Genomics and Association of Molecular Pathology variant classification criteria (Richards et al., 2015).

Subsequent medical concerns for this patient have included cortical blindness with persistent pupillary membranes, bilateral sensorineural hearing loss (mild to moderate in her right ear, moderate to moderately severe in her left ear), chronic respiratory failure with nocturnal BiPAP dependence, cyanotic episodes possibly secondary to excessive secretions leading to aspiration and bronchospasm, delayed gastric emptying with gastroesophageal reflux disease, gastrojejunostomy tube dependence, global developmental disability, diffuse hypotonia, seizures, scoliosis, kyphosis, and mildly decreased factor XI (Table S1). Around 11 months of age, she was found to have asystolic pauses, initially treated with glycopyrrolate. Electrocardiogram and Holter monitor evaluations did not reveal an intrinsic conduction defect. At 15 months of age, more frequent pauses were recorded on telemetry, the longest being 22 seconds in duration. An implantable epicardial pacemaker was placed just before her second birthday and actively continues to discharge infrequently. Her dysmorphic features include acquired microcephaly, dolichocephaly, down-slanting palpebral fissures, long eyelashes, mild hypertelorism, low-set posteriorly rotated ears with a very prominent antihelix and overfolded earlobe, and a significantly beaked nose with overhanging columella (Figure S2). She has widely set hypoplastic and inverted nipples. Her score on the Nijmegen Pediatric CDG Rating Scale (NPCRS) at age 3 was 52 and at age 4 was 44. The improvement was primarily accounted for in the Systemic Specific Involvement and Current Clinical Assessment categories (Achouitar et al., 2011).

Detailed immunologic evaluation was performed at 2 years of age following several viral respiratory infections, including human meta-pneumovirus, rhinovirus/enterovirus, and parainfluenza type 3. She also had a history of *Clostridium difficile* infection and cellulitis. She previously (at 7 months) had abnormal QuantiFERON Gold testing, suggesting a problem with lymphocyte proliferation control. Absolute T and B cell counts were normal (absolute CD3 2,574/mm^3; CD4: CD8 ratio 1.95; absolute CD19 1,069/mm_3) and had normal naïve to memory ratios (CD4: CD45RA+ 68%;CD45RO+ 14%; CD8: CD45RA+ 92%; CD45RO+ 3%). Despite normal T-cell numbers, proliferative responses to phytohemagglutinin (PHA) was <1% (Table S2). Given the known PHA dependence on

complex N-glycans, other lectins were also tested and she was noted to have extremely low responses to concanavalin A (ConA) and pokeweed mitogen (PWM). Evaluation of her antigen-specific responses revealed reduced tetanus response, but notably enhanced Candida proliferative response. She did not have issues with Candida infections. Given the poor proliferative responses, she was started on trimethoprim-sulfamethoxazole prophylaxis.

Hypogammaglobulinemia was another consistent feature. She demonstrated a mildly decreased IgG level (439 mg/dl, reference range 468–1,196 mg/dl at 2 years old), with normal IgM and IgA levels (198 mg/dl, reference range 47–200 mg/dl and 101 mg/dl, reference range 21–117 mg/dl, respectively). She tolerated all age-appropriate vaccinations without complication, including one dose each of MMR and varicella vaccines, and she has had positive antibody titers to rubella, varicella, tetanus, and pneumococcus serotypes 16/22 (including 11 of 12 PCV13 vaccine serotypes tested; Table S2). Secondary to the risk for aspiration from her other medical concerns and the laboratory evidence of a combined immunodeficiency, she was started on intravenous immunoglobulin (IVIG) replacement therapy at 2 years 8 months old. Measurements of IgG levels were repeated over time and continued to decline to 188 mg/dl, demonstrating ongoing loss of IgG, so she was provided with an additional IVIG infusion. She has received eight IVIG infusions with normalization of IgG levels immediately following infusions. Infusions have been paused and her IgG levels have trended downwards over 6 months to 234 mg/dl (reference range 574–1,309 mg/dl; Figure 2).

There are no other affected relatives in this patient's family with MGAT2-CDG or with evidence of an immunodeficiency. Family history is notable for intellectual disability and small for gestational age (SGA) in her mother, and global developmental delay, dysmorphic features, a history of febrile seizures, and multiple episodes of syncope of uncertain etiology in her full brother. Her brother's cardiac workup, including echocardiogram and long-term home telemetry, did not reveal a cardiac cause for syncope. Both relatives had targeted variant testing and both are heterozygous for the c.1006_1009delGACA variant in *MGAT2*. The patient's father and an additional full brother are healthy.

3 | DISCUSSION

This clinical report of MGAT2-CDG highlights a novel pathogenic variant in *MGAT2*, c.1006_1009delGACA, and expands the phenotype to include cardiac arrhythmia, specifically episodic asystole requiring epicardial pacemaker placement, and combined immunodeficiency. We present the first comprehensive immunologic evaluation of a patient with MGAT2-CDG and demonstrate the presence of both persistent hypogammaglobulinemia and T-cell proliferation abnormalities.

Interestingly, and fortunately, this individual has lacked any serious illnesses or infections, although this may be confounded by the fact that she lives in a residential medical facility, where there are minimal infectious exposures. Of note, the individual described by de Cock and Jaeken (2009) also had MGAT2-CDG and low IgG without significant infections. A similar paradox of hypogammaglobulinemia and lack of frequent or severe infections was noted in the two children with MOGS-CDG described by Sadat et al. (2014), who explored

multiple mechanisms to determine the etiology of their individuals' hypogammaglobulinemia. They determined that the individuals had normal IgG synthesis, secretion, and stability in vitro, but reduced IgG half-life in vivo when infused into $Rag^{1-/-}$ mice when compared to unaffected controls. The authors acknowledged that they were not able to provide a precise etiology for why the children did not have significant bacterial infections despite the low IgG. Further investigation is needed to determine if the mechanism is the same in MGAT2-CDG.

A prominent difference between the individuals with MOGS-CDG and our patient is that our patient demonstrated a protective antibody response to live vaccines for rubella and varicella (enveloped viruses), while the two individuals with MOGS-CDG did not respond adequately to any live virus vaccines. Since these viruses rely on host protein glycosylation for entry and active viral replication, the intrinsic defect in N-glycosylation in MOGS-CDG was proposed as the etiology for reduced susceptibility to viral infection. Francisco et al. (2020) also reported three patients with MOGS-CDG who did not identify viral infection as the most common infectious agent. However, MGAT2-CDG is also a disorder of N-glycosylation, potentially providing evidence against this theory. Alternatively, this difference in vaccine response could be related to the individual locations of these two enzymes in the N-glycosylation pathway. Mannosyl-oligosaccharide glucosidase, encoded by *MOGS*, acts on the glycan precursor upstream of MGAT2 activity and glycan processing to a complex N-glycan. Therefore, all complex N-glycans would be expected to be reduced in MOGS-CDG, whereas complex glycans distal to MOGS, but proximal to the MGAT2, would be predicted to be spared in MGAT2-CDG.

Our patient demonstrates diagnostic evidence for impaired cellular immunity despite normal specific antibody responses. Very low proliferative responses were observed to multiple lectins, including PHA, ConA, and PWM. These lectins are plant mitogens that stimulate cell proliferation and function by binding to glycosylated surface proteins (Miller, 1983). Since one of PHA's lectin binding sites incorporates a mature glycan that is dependent on MGAT2 for formation (Carlson et al., 2017; Bonnardel et al., 2019; Figure S1B), our patient's absent PHA response was expected. However, her extremely low responses to ConA and PWM were unexpected. One of the lectin binding sites for ConA is GlcNAc(β1-2)Man(α1-3)[GlcNAc(β1-2)Man (α1-6)]Man (Figure S1C), whose formation is also dependent on MGAT2, which could be the reason for the low response to ConA. However, ConA appears to have a higher affinity for the (Man(α1-3) [Man(α1-6)]Man) component of the glycan (Bonnardel et al., 2019; Moothoo& Naismith, 1998; Naismith & Field, 1996, Figure S1D), and high mannose moieties upstream of MGAT2 would still be present with MGAT2 deficiency, providing a limitation to this theory. Another possible mechanism of extremely low response to ConA and PWM could be generalized hyper-reactivity to mitogens similar to what is seen in PGM3-CDG (Carlson et al., 2017). As standard diagnostic proliferative assays are based upon thymidine incorporation, the assay does not distinguish between reduced proliferation and activation-induced cell death. In support of a hyperactive response, the measured proliferation to Candida, a known poor stimulatory antigen, was consistently 5–6 fold higher in our patient's cells compared to controls. Finally, there is the possibility that the low lectin responses are a consequence of

the assay itself as opposed to a true in vivo deficiency. Future studies will be needed to distinguish these possibilities.

The information provided in our clinical report is limited by the current lack of a unifying diagnosis for our patient's full brother, who has a history of global developmental delay, dysmorphic features, and episodes of syncope. With the presence of significant ROH in the setting of known consanguinity and the presence of only heterozygosity for the familial *MGAT2* variant in her brother, there is possibly an additional autosomal recessive disorder in the family that could be confounding our patient's phenotype. Untargeted genetic testing, such as exome sequencing in this family, could be helpful in providing additional genotypic information, though this has not been possible at the time of this report. However, neither her mother nor her brother are known to have clinical features that would indicate concern for an underlying immunodeficiency and her brother has had a negative cardiac evaluation for his episodes of syncope, which supports the association of these abnormal immunologic and cardiac phenotypes with MGAT2-CDG.

In conclusion, this clinical report expands the phenotype of MGAT2-CDG and highlights a novel pathogenic variant causative of the disorder. As the number of individuals with different CDG continues to rise due to improved awareness, leading to increased biochemical screening and expanded use of large scale molecular testing such as exome sequencing, further natural history and novel variants will be revealed, including in additional individuals with MGAT2-CDG.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The novel variant reported in the manuscript has been previously reported once in the heterozygous state in population databases (a single Latino individual in gnomAD [v2.2.1] and no carriers in the Saudi Genome Project database). This patient constitutes the only entry in ClinVar at the time of the writing of this manuscript.

REFERENCES

Achouitar S, Mohamed M, Gardeitchik T, Wortmann SB, Sykut-Cegielska J, Ensenauer R, … Morava E (2011). Nijmegen paediatric CDG rating scale: A novel tool to assess disease progression. Journal of Inherited Metabolic Disease, 34(4), 923–927. 10.1007/s10545-011-9325-5 [PubMed: 21541726]

Alazami AM, Monies D, Meyer BF, Alzahrani F, Hashem M, Salih MA, & Alkuraya FS (2012). Congenital disorder of glycosylation IIa: The trouble with diagnosing a dysmorphic inborn error of metabolism. American Journal of Medical Genetics. Part A, 158A(1), 245–246. 10.1002/ajmg.a.34347 [PubMed: 22105986]

Alkuraya FS (2010). Mental retardation, growth retardation, unusual nose, and open mouth: An autosomal recessive entity. American Journal of Medical Genetics. Part A, 152A(9), 2160–2163. 10.1002/ajmg.a.33575 [PubMed: 20684000]

Alsubhi S, Alhashem A, Faqeih E, Alfadhel M, Alfaifi A, Altuwaijri W, … Tabarki B (2017). Congenital disorders of glycosylation: The Saudi experience. American Journal of Medical Genetics. Part A, 173(10), 2614–2621. 10.1002/ajmg.a.38358 [PubMed: 28742265]

Bonnardel F, Mariethoz J, Salentin S, Robin X, Schroeder M, Perez S, … Imberty A (2019). UniLectin3D, a database of carbohydrate binding proteins with curated information on 3D structures and interacting ligands. Nucleic Acids Research, 47(D1), D1236–D1244. 10.1093/nar/gky832 [PubMed: 30239928]

Brucker WJ, Croteau SE, Prensner JR, Cullion K, Heeney MM, Lo J, … Bodamer O (2020). An emerging role for endothelial barrier support therapy for congenital disorders of glycosylation. Journal of Inherited Metabolic Disease, 43, 880–890. 10.1002/jimd.12225 [PubMed: 32064623]

Carlson RJ, Bond MR, Hutchins S, Brown Y, Wolfe LA, Lam C, … Lyons JJ (2017). Detection of phosphoglucomutase-3 deficiency by lectin-based flow cytometry. The Journal of Allergy and Clinical Immunology, 140(1), 291–294 e294. 10.1016/j.jaci.2016.12.951 [PubMed: 28063873]

Chang IJ, He M, & Lam CT (2018). Congenital disorders of glycosylation. Annals of Translational Medicine, 6(24), 477. 10.21037/atm.2018.10.45 [PubMed: 30740408]

Cormier-Daire V, Amiel J, Vuillaumier-Barrot S, Tan J, Durand G, Munnich A, … Seta N (2000). Congenital disorders of glycosylation IIa cause growth retardation, mental retardation, and facial dysmorphism. Journal of Medical Genetics, 37(11), 875–877. 10.1136/jmg.37.11.875 [PubMed: 11228641]

de Cock P, & Jaeken J (2009). MGAT2 deficiency (CDG-IIa): The life of J. Biochimica et Biophysica Acta, 1792(9), 844–846. 10.1016/j.bbadis.2009.02.001 [PubMed: 19419693]

Ferreira CR, Altassan R, Marques-Da-Silva D, Francisco R, Jaeken J, & Morava E (2018). Recognizable phenotypes in CDG. Journal of Inherited Metabolic Disease, 41(3), 541–553. 10.1007/s10545-018-0156-5 [PubMed: 29654385]

Francisco R, Pascoal C, Marques-da-Silva D, Brasil S, Pimentel-Santos FM, Altassan R, … Videira PA (2020). New insights into immunological involvement in congenital disorders of glycosylation (CDG) from a people-centric approach. Journal of Clinical Medicine, 9 (7), 1–30. 10.3390/jcm9072092

Jaeken J, Schachter H, Carchon H, de Cock P, Coddeville B, & Spik G (1994). Carbohydrate deficient glycoprotein syndrome type II: A deficiency in Golgi localised N-acetyl-glucosaminyltransferase II. Archives of Disease in Childhood, 71(2), 123–127. 10.1136/adc.71.2.123 [PubMed: 7944531]

Lacey JM, Bergen HR, Magera MJ, Naylor S, & O'Brien JF (2001). Rapid determination of transferrin isoforms by immunoaffinity liquid chromatography and electrospray mass spectrometry. Clinical Chemistry, 47(3), 513–518. [PubMed: 11238305]

Li X, Raihan MA, Reynoso FJ, & He M (2015). Glycosylation analysis for congenital disorders of glycosylation. Current Protocols in Human Genetics, 86, 17.18.11–17.18.22. 10.1002/0471142905.hg1718s86

Makhamreh MM, Cottingham N, Ferreira CR, Berger S, & Al-Kouatly HB (2020). Nonimmune hydrops fetalis and congenital disorders of glycosylation: A systematic literature review. Journal of Inherited Metabolic Disease, 43(2), 223–233. 10.1002/jimd.12162 [PubMed: 31420886]

Miller K (1983). The stimulation of human B and T lymphocytes by various lectins. Immunobiology, 165(2), 132–146. 10.1016/S0171-2985(83)80055-2 [PubMed: 6354918]

Moothoo DN, & Naismith JH (1998). Concanavalin a distorts the beta-GlcNAc-(1→2)-man linkage of beta-GlcNAc-(1→2)-alpha-man-(1→3)-[beta-GlcNAc-(1→2)-alpha-man-(1→6)]-man upon binding. Glycobiology, 8(2), 173–181. 10.1093/glycob/8.2.173 [PubMed: 9451027]

Naismith JH, & Field RA (1996). Structural basis of trimannoside recognition by concanavalin A. The Journal of Biological Chemistry, 271(2), 972–976. 10.1074/jbc.271.2.972 [PubMed: 8557713]

Pascoal C, Francisco R, Ferro T, Dos Reis Ferreira V, Jaeken J, & Videira PA (2020). CDG and immune response: From bedside to bench and back. Journal of Inherited Metabolic Disease, 43(1), 90–124. 10.1002/jimd.12126 [PubMed: 31095764]

Ramaekers VT, Stibler H, Kint J, & Jaeken J (1991). A new variant of the carbohydrate deficient glycoproteins syndrome. Journal of Inherited Metabolic Disease, 14(3), 385–388. 10.1007/bf01811710 [PubMed: 1770799]

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, … Committee, A. L. Q. A. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine, 17(5), 405–424. 10.1038/gim.2015.30 [PubMed: 25741868]

Ryan SO, Abbott DW, & Cobb BA (2014). Myeloid glycosylation defects lead to a spontaneous common variable immunodeficiency-like condition with associated hemolytic anemia and antilymphocyte autoimmunity. Journal of Immunology, 192(12), 5561–5570. 10.4049/jimmunol.1400385

Ryan SO, Leal SM Jr., Abbott DW, Pearlman E, & Cobb BA (2014). Mgat2 ablation in the myeloid lineage leads to defective glycoantigen T-cell responses. Glycobiology, 24(3), 262–271. 10.1093/glycob/cwt107 [PubMed: 24310166]

Sadat MA, Moir S, Chun TW, Lusso P, Kaplan G, Wolfe L, … Rosenzweig SD (2014). Glycosylation, hypogammaglobulinemia, and resistance to viral infections. The New England Journal of Medicine, 370 (17), 1615–1625. 10.1056/NEJMoa1302846 [PubMed: 24716661]

Tan J, Dunn J, Jaeken J, & Schachter H (1996). Mutations in the MGAT2 gene controlling complex N-glycan synthesis cause carbohydrate-deficient glycoprotein syndrome type II, an autosomal recessive disease with defective brain development. American Journal of Human Genetics, 59(4), 810–817. [PubMed: 8808595]

van Geet C, Jaeken J, Freson K, Lenaerts T, Arnout J, Vermylen J, & Hoylaerts MF (2001). Congenital disorders of glycosylation type Ia and IIa are associated with different primary haemostatic complications. Journal of Inherited Metabolic Disease, 24(4), 477–492. 10.1023/a:1010581613821 [PubMed: 11596651]

Verheijen J, Tahata S, Kozicz T, Witters P, & Morava E (2020). Therapeutic approaches in congenital disorders of glycosylation (CDG) involving N-linked glycosylation: An update. Genetics in Medicine, 22 (2), 268–279. 10.1038/s41436-019-0647-2 [PubMed: 31534212]

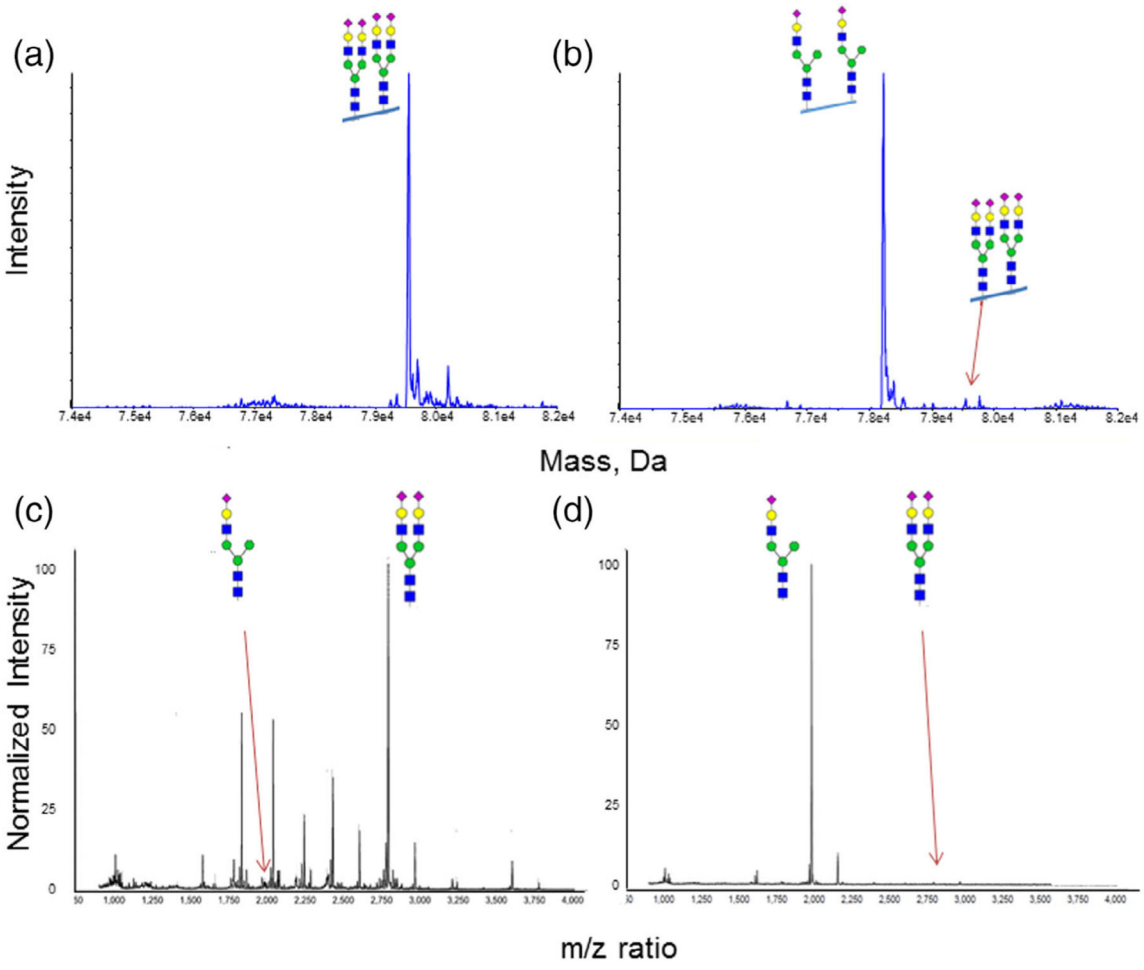

FIGURE 1.

Biochemical testing. (a) Transferrin profile of an individual without a CDG. Illustration represents protein with bi-antennary glycans at both N-linked sites. (b) Our patient's transferrin profiling showing near absence of normally glycosylated transferrin and accumulation of an abnormally processed glycan. (c) Serum N-glycan profile of an individual without a CDG. (d) Our patient's serum N-glycan profile demonstrates accumulation of the abnormal glycan on serum proteins. Blue square, N-acetylglucosamine; green circle, mannose; yellow circle, galactose; pink diamond, sialic acid; m/z ratio, mass to charge ratio; Da, dalton

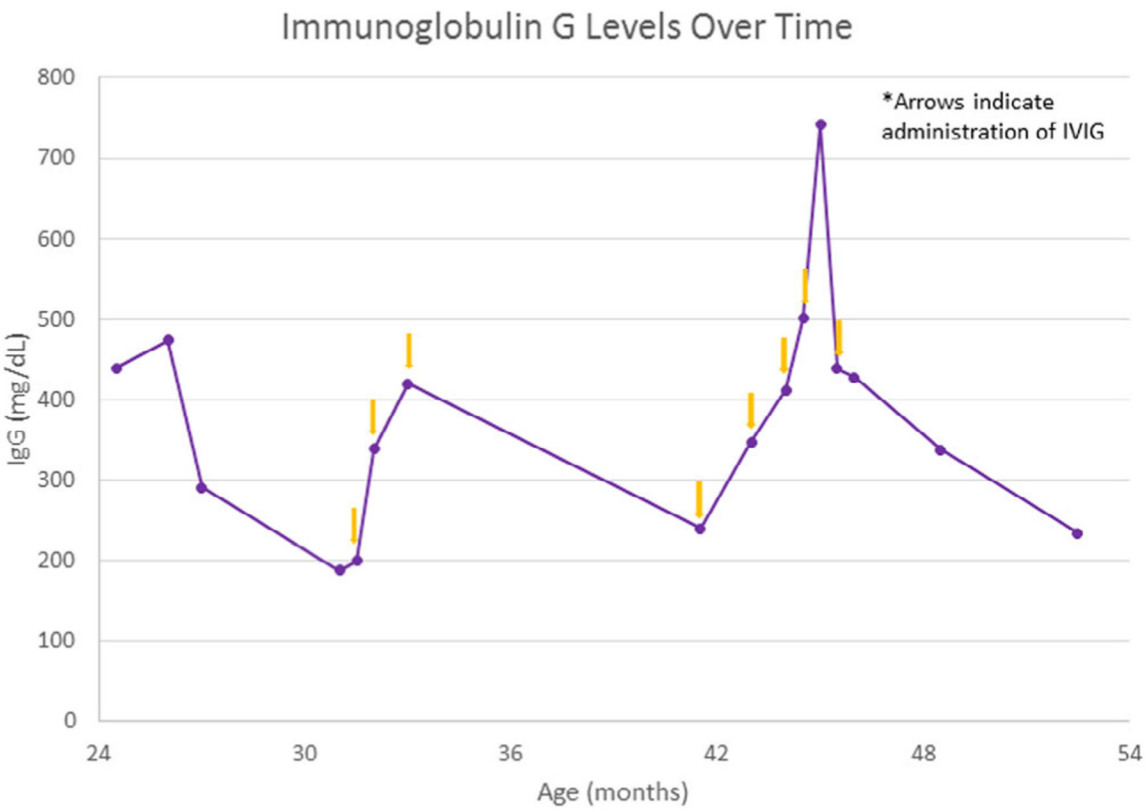

FIGURE 2.

Immunoglobulin G levels over time. Arrows indicate administration of IVIG. Mg/dl, milligrams per deciliter; IVIG, intravenous immunoglobulin