Journal of Human Genetics (2018) 63:383–386
https://doi.org/10.1038/s10038-017-0386-7

BRIEF COMMUNICATION

Characteristic dysmorphic features in congenital disorders of glycosylation type IIb

Yoon-Myung Kim[1] · Go Hun Seo[1] · Euiseok Jung[1] · Ja-Hyun Jang[2,3] · Sook Za Kim[4] · Beom Hee Lee[1]

Received: 24 August 2017 / Revised: 24 October 2017 / Accepted: 24 October 2017 / Published online: 13 December 2017

Abstract

Over 100 types of congenital disorders of glycosylation (CDG) have been reported and the number is rapidly increasing. However, each type is very rare and is problematic to diagnose. Mannosyl-oligosaccharide glucosidase (MOGS)-CDG (CDG type IIb) is an extremely rare CDG that has only been reported in three patients from two unrelated families. Using targeted exome sequencing, we identified another patient affected by this condition. This patient had increased serum trisialotransferrin levels. Importantly, a review of the features of all four patients revealed the recognizable clinical hallmarks of MOGS-CDG. The distinct dysmorphic features of this condition include long eyelashes, retrognathia, hirsutism, clenched overlapped fingers, hypoventilation, hepatomegaly, generalized edema, and immunodeficiency.

Introduction

Congenital disorders of glycosylation (CDG) are a group of disorders caused by defects in proteins or lipid glycosylation. Over 100 types of CDG have been reported thus far [1, 2], but the clinical suspicion for each subtype is difficult to determine. Isoelectric focusing of transferrin or apolipoprotein C-III has been used to analyze glycosylation patterns. However, not all types can be detected by these assays.

CDG is usually characterized by severe multisystemic abnormalities in affected patients. Curative treatment is not available in most cases, but definitive diagnosis is still important to determine the need for palliative care for the patient and future reproductive counseling for the parents. Herein, we report a patient who was eventually diagnosed with an extremely rare CDG type, mannosyl-oligosaccharide glucosidase (MOGS)-CDG (CDG type IIb), using targeted exome sequencing. Our patient came from the third family reported with this subtype. Of note, despite its extreme rarity, the affected patients from the three families shared similar dysmorphic features and systemic abnormalities that may facilitate the diagnostic process for this type.

Case description

The patient was the second child born at 37 weeks of gestation from non-consanguineous Korean parents. The first child died at age seven months due to unexplained liver failure.

On prenatal ultrasonography, polyhydramnios, cardiomegaly, hepatomegaly, and hydrocele were found. Soon after birth, he was hypotonic with generalized edema and hepatomegaly. He had dysmorphic facial features with a narrow forehead, hirsutism, light-colored hair, short palpebral fissure, hypertelorism, long eyelashes, a broad nose, retrognathia, and a high-arched palate (Fig. 1a). His fingers overlapped, second over third and fifth over fourth (Fig. 1b). His mother recalled a similar facial appearance of his dead sibling. He showed recurrent apnea and oxygen supplementation via nasal cannula with aminophylline was continuously required. Hepatosplenomegaly with progressive cholestasis and thrombocytopenia was also noted. In addition, thyroid hormone was given due to hypothyroidism with a low thyroxine-binding globulin level. Serum immunoglobulin G was normal, but IgA and IgM were

✉ Beom Hee Lee
bhlee@amc.seoul.kr

[1] Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

[2] Green Cross Genome, Yongin, Korea

[3] Green Cross Laboratories, Yongin, Korea

[4] Korea Genetic Research Center/ KSZ Children's Hospital, Cheongju, Korea

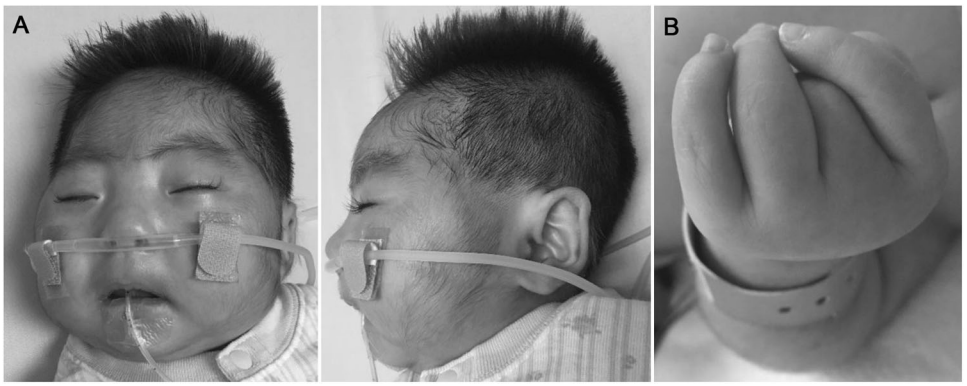

Fig. 1 Pictures of the patient's face (**a**) and hand (**b**) at 3 months of age. Note the dysmorphic features with microcephaly, narrow forehead, hirsutism, long eyelashes, hypertelorism, retrognathia, and clenched overlapped fingers

decreased for the age of the patient. He had no seizure events, but suffered from a recurrent syndrome of inappropriate antidiuretic hormone secretion, which was recovered by volume restriction.

His karyotype was 46, XY and his mitochondrial DNA in peripheral leukocytes had a normal sequence with no large deletions. Array comparative genomic hybridization results were normal.

At four months of age, he expired due to multiple organ failure.

Materials and methods

Written informed consent was obtained for exome sequencing from all parents and the study was approved by the local ethics committee. Exome sequencing was performed at one month of age using genomic DNA extracted from peripheral blood leukocytes. Exomes were captured using the TruSight One Panel (Illumina Inc., San Diego, CA, USA), which enriches a 12-Mb region spanning 4813 genes. Sequencing was performed on the NextSeq platform (Illumina Inc.). Sequence reads were aligned to the reference genome, hg19, using Burrow-Wheeler Aligner (version 0.7.12, MEM algorithm) [3]. Candidate variants were confirmed by Sanger sequencing using custom-designed primers.

Results

The following two variants in the *MOGS* gene, encoding mannosyl-oligosaccharide glucosidase, were considered as candidate variants: c.2405 C > T (p,Thr802Ile) and c.1603C > T (p.Arg535*) of exon 4 (NM_006302.2). Genetic analysis showed that the parents were heterozygous for one of the each mutated alleles.

To confirm CDG, transferrin plasma levels were measured by isoelectric focusing (IEF), as previously described [4]. Trisialotransferrin was elevated, but monosialotransferrin and asialotransferin were not (Fig. 2). Based

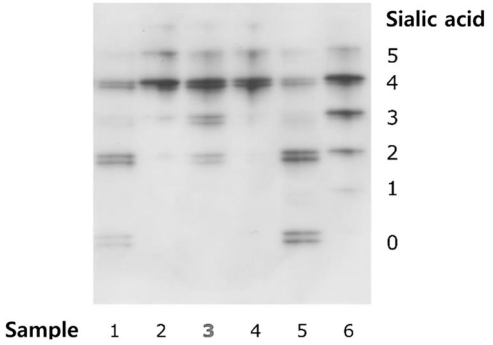

Fig. 2 Isoelectric focusing of transferrin showing an abnormal trisialotransferrin pattern. Patient, sample 3; Normal control, sample 1, 2, 4; PMM2-CDG, sample 5; COG2-CDG, sample 6

on the above results, the patient was diagnosed with MOGS-CDG.

Discussion

Including the case described here, only four patients from three unrelated families have been reported with MOGS-CDG [5, 6]. The first reported patient died at 74 days [5], but two other siblings were reported to be alive at 6 and 11 years [6].

CDG should be included in the differential diagnosis for any congenital condition exhibiting multisystemic manifestations [7, 8]. Despite being an extremely rare CDG type, there are some recognizable clinical features in MOGS-CDG. The two patients, including our case, for whom detailed clinical information was available, showed common dysmorphic features. These include a short palpebral fissure, long eyelashes, a broad nose, retrognathia, hirsutism, and clenched overlapped fingers (Table 1). The presence of other shared manifestations, including generalized edema, apnea, and hypogammaglobulinemia, will help diagnose this subtype.

Currently, IEF is the first step in screening for CDG [4]. However, transferrin polymorphisms can confuse the interpretation of results [9] and a normal IEF pattern may

Table 1 Clinical characteristics of patients reported to have MOGS-CDG

Patient	1	2	3	4
Study	De Praeter et al. (2000) [5]	Sadat et al. (2014) [6]	Sadat et al. (2014) [6]	Present study
Prenatal problem	None	None	None	Polyhydramnios, cardiomegaly, hepatomegaly
Perinatal problem	Respiratory difficulty	None	None	Respiratory difficulty
Birth profile	GA 36 weeks	ND	ND	GA 37 weeks
	Weight 2540 g			Weight 2660 g
	Length 48 cm			Length 46 cm
	HC 33 cm			HC 30.8 cm
Dysmorphic features	Prominent occiput, short palpebral fissure, long eyelashes, broad nose, retrognathia, high-arched palate, clenched overlapped fingers, hirsutism, focal alopecia	Dysmorphic facial features (not described)	Dysmorphic facial features (not described)	Short palpebral fissure, long eyelashes, broad nose, retrognathia, clenched overlapped fingers, hirsutism
CNS	Seizure, hypotoniaNormal brain MRI	Seizure, hypotonia, small corpus callosum	Seizure, hypotonia, small corpus callosum	HypotoniaNormal brain MRI
Ophthalmological	Abnormal visual evoked responses	Optic nerve atrophy	Optic nerve atrophy	Mild anterior subcapsular opacity
Hearing	Abnormal brain stem response audiometry	Sensory neural hearing loss	Sensory neural hearing loss	Abnormal brain stem response audiometry
Respiratory	Hypoventilation and apnea, lung edema	None	None	Hypoventilation and apnea, lung edema
Heart	None	None	None	Moderate ASD, LVH
Gastrointestinal	Hepatomegaly, gastric tube feeding	Chronic constipation	Chronic constipation	Hepatomegaly, gastric tube feeding
Genitalia	Hypoplasia	Hypoplasia	Hypoplasia	None
Immunology	IgA deficiency	IgG, IgA, IgM deficiency	IgG, IgA, IgM deficiency	IgA, IgM deficiency
Others	Thoracic scoliosis, fluid retention	Recurrent bone fractures	Recurrent bone fractures	SIADH
IEF	Normal pattern	Not done	Not done	Trisialtransferrin ↑
MOGS mutation	p.[Arg486Thr]; [Phe652Leu]	p.[Gln124*]; [Ala22Glu; Arg100His]	p.[Gln124*]; [Ala22Glu; Arg100His]	P[Thr802Ile]; [Arg535*]
Outcome	Died (74 days)	Alive (11 years)	Alive (6 years)	Died (4 months)

ND no data available, *HC* head circumference, *MRI* magnetic resonance imaging, *ASD* atrial septal defect, *LVH* left ventricular hypertrophy, *SIADH* syndrome of inappropriate antidiuretic hormone secretio

also be observed in some patients [5, 8]. In our case, elevated trisialotransferrin was consistent with type 2 CDG [10]. In a previous case (patient 1, Table 1), IEF was normal and the diagnosis of MOGS-CDG was made by urinary oligosaccharide identification using thin layer chromatography and glucosidase I activity measurement in cultured skin fibroblasts and genetic testing [5]. The two siblings of the other case were diagnosed by urine chromatography analysis, mass spectrometry, and genetic testing [6].

Thyroid-binding globulin is decreased and hypogammaglobulinemia is observed in all MOG-CDG cases [11, 12]. Hypogammaglobulinemia results from the shortened half-life of immunoglobulins due to a glycosylation defect. However, two patients (case 2 and 3) who survived for several years, paradoxically did not have a serious infection to enveloped viruses despite hypogammaglobulinemia [6]. In MOGS-CDG, viral replication and cellular entry is thought to be impaired due to a glycosylation defects in human viral receptors and the viral envelope.

The clinical course of a patient with MOGS-CDG is expected to be grave, considering the very short life-span of the two patients including our case [5]. The longer survival observed in the other siblings [6] are associated with the reciprocal mitotic recombination between compound heterozygous alleles, which causes reversion to a wild-type allele in somatic cells. The survival or growth advantage of these cells with the wild-type allele ameliorates the phenotype of the siblings [13].

With rapid advances in human genome studies, multigene testing using next-generation sequencing techniques may help the genetic diagnosis of CDG. Although each subtype is extremely rare, CDG is now gaining recognition as an important group of diverse diseases affecting panethnic populations. As more cases are identified, the clinical characteristics of each subtype will be delineated as MOGS-CDG described here.

Acknowledgements We are grateful to the patient and his family for participating in this study. This work was supported by research funds from the National Research Foundation of Korea (NRF-2015K1A4A3046807).

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1 Freeze HH, Chong JX, Bamshad MJ, Ng BG. Solving glycosylation disorders: fundamental approaches reveal complicated pathways. Am J Hum Genet. 2014;94:161–75.
2 Varki A. Biological roles of glycans. Glycobiology. 2017;27:3–49.
3 Li, H. Aligning sequence reads, clone sequences and assembly contigs with BWA-MEM. 2013 arXiv:1303.3997v2 [q-bio.GN].
4 Van Scherpenzeel M, Willems E, Lefeber DJ. Clinical diagnostics and therapy monitoring in the congenital disorders of glycosylation. Glycoconj J. 2016;33:345–58.
5 De Praeter CM, Gerwig GJ, Bause E, Nuytinck LK, Vliegenthart JFG, Breuer W, et al. a novel disorder caused by defective biosynthesis of n-linked oligosaccharides due to glucosidase i deficiency. Am J Hum Genet. 2000;66:1744–56.
6 Sadat MA, Moir S, Chun TW, Lusso P, Kaplan G, Wolfe L, et al. Glycosylation, hypogammaglobulinemia, and resistance to viral infections. N Engl J Med. 2014;370:1615–25.
7 Jaeken J, Peanne R. What is new in CDG? J Inherit Metab Dis. 2017;40:569–86.
8 Scott K, Gadomski T, Kozicz T, Morava E. Congenital disorders of glycosylation: new defects and still counting. J Inherit Metab Dis. 2014;37:609–17.
9 Zuhlsdorf A, Park JH, Wada Y, Rust S, Reunert J, DuChesne I, et al. Transferrin variants: pitfalls in the diagnostics of Congenital disorders of glycosylation. Clin Biochem. 2015;48:11–13.
10 Guillard M, Morava E, de Ruijter J, Roscioli T, Penzien J, van den Heuvel L, et al. B4GALT1-congenital disorders of glycosylation presents as a non-neurologic glycosylation disorder with hepatointestinal involvement. J Pediatr. 2011;159:1041–3.e1042.
11 Macchia PE, Harrison HH, Scherberg NH, Sunthornthepfvarakul T, Jaeken J, Refetoff S. Thyroid function tests and characterization of thyroxine-binding globulin in the carbohydrate-deficient glycoprotein syndrome type I. J Clin Endocrinol Metab. 1995;80:3744–49.
12 Mohamed M, Theodore M, der Grinten HC-v, van Herwaarden AE, Huijben K, van Dongen L, et al. Thyroid function in PMM2-CDG: Diagnostic approach and proposed management. Mol Genet Metab. 2012;105:681–83.
13 Kane MS, Davids M, Adams C, Wolfe LA, Cheung HW, Gropman A, et al. Mitotic intragenic recombination: A mechanism of survival for several congenital disorders of glycosylation. Am J Hum Genet. 2016;98:339–46.