Updated clinical and glycomic features of mannosyl-oligosaccharide glucosidase deficiency: Two case reports

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Abstract

BACKGROUND
Mannosyl-oligosaccharide glucosidase (MOGS) deficiency is an extremely rare type of congenital disorder of glycosylation (CDG), with only 12 reported cases. Its clinical, genetic, and glycomic features are still expanding. Our aim is to update the novel clinical and glycosylation features of 2 previously reported patients with MOGS-CDG.

CASE SUMMARY
We collected comprehensive clinical information, and conducted the immunoglobulin G1 glycosylation assay using nano-electrospray ionization source quadruple time-of-flight mass spectrometry. Novel dysmorphic features included an enlarged tongue, forwardly rotated earlobes, a birth mark, overlapped toes, and abnormal fat distribution. Novel imaging findings included pericardial effusion, a deep interarytenoid groove, mild congenital subglottic stenosis, and laryngomalacia. Novel laboratory findings included peripheral leukocytosis with neutrophil predominance, elevated C-reactive protein and creatine kinase, dyslip-
idemia, coagulopathy, complement 3 and complement 4 deficiencies, decreased proportions of T lymphocytes and natural killer cells, and increased serum interleukin 6. Glycosylation studies showed a significant increase of hypermannosylated glycopeptides (Glc3Man7GlcNAc2/N2H10 and Man5GlcNAc2/N2H5) and hypersialylated glycopeptides. A compensatory glycosylation pathway leading to an increase in Man5GlcNAc2/N2H5 was indicated with the glycosylation profile.

CONCLUSION

We confirmed abnormal glycomics in 1 patient, expanding the clinical and glycomic spectrum of MOGS-CDG. We also postulated a compensatory glycosylation pathway, leading to a possible serum biomarker for future diagnosis.

Key Words: Mannosyl-oligosaccharide glucosidase; MOGS-CDG; Congenital disorder of glycosylation type IIb; Mannosyl-oligosaccharide glucosidase gene; Glycomics of IgG1; Case report

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Core Tip: We updated the clinical and glycosylation features of 2 previously published patients with mannosyl-oligosaccharide glucosidase-congenital disorders of glycosylation (MOGS-CDG) by confirming abnormal glycomics and expanding the phenotypical and glycomic spectrum of MOGS-CDG. We also postulated a compensatory glycosylation pathway, leading to a possible serum biomarker for future diagnosis.

INTRODUCTION

Protein glycosylation is a process of glycoprotein or glycolipid biosynthesis and modification. Congenital disorders of glycosylation (CDGs) influence the properties and functions of glycoproteins or glycolipids, leading to multiple organ/system disorders[1]. The mannosyl-oligosaccharide glucosidase (MOGS) gene (OMIM#601336) encodes the first enzyme in the N-linked oligosaccharide processing pathway, namely MOG (also known as glucosidase I). This enzyme is responsible for removing distal alpha-1,2-linked glucose from Glc3Man9GlcNac2 (N2H12) (N, N-acetylglucosamine or N-acetylgalactosamine; H, hexaoses including galactose, glucose, and mannose) after its transfer from dolichyl diphosphate to a nascent polypeptide chain in the endoplasmic reticulum[2,3]. Mutations in the MOGS gene cause MOGS-CDG (previously known as CDG type IIb, OMIM#606056)[4-11], which is characterized by generalized hypotonia, infantile spasm, dysmorphism, hypogammaglobulinemia, and abnormal protein glycosylation.

The N-glycan profile of immunoglobulin G (IgG) from patients show an increased level of Glc3Man7GlcNAc2 (N2H10), whereas serum or skin fibroblast samples have increased levels of Glc3Man7GlcNAc2 (N2H10), Glc3Man8GlcNAc2 (N2H11), and Glc3Man9GlcNAc2 (N2H12)[5,12]. Urine analyses from patients have shown accumulation of tetrasaccharide Glc(a1-2)Glc(a1-3)Glc(a1-3)Man (Glc3Man1, H4)[4,9,10]. Isoelectric focusing of serum transferrin is suggestive of a normal[4,9,10] or type II pattern[6] with increased trisialotransferrin but normal mono-sialotransferrin or asialotransferrin.

MOGS-CDG is an extremely rare disease with only 12 reported cases to date[4-11]. Its genetic, glycomic, and clinical features of MOGS-CDG are still expanding. In this study, we updated the clinical and glycosylation features of two patients with MOGS-CDG who were previously reported without solid functional or glycomic evidence[7].
CASE PRESENTATION

Chief complaints
Case 1: A newborn infant (the younger sister) had difficulties feeding and breathing.

Case 2: A newborn infant (the elder sister) had birth asphyxia, severe pneumonia, stridor, gastroesophageal reflux, and respiratory failure.

History of present illness
Case 1: The younger sister was born after 39 wk of gestation, with a birth weight of 3300 g. Apgar score was 7 at 1 min and 9 at 5 min after birth. She was found to have difficulties feeding and breathing during admission, and continued to be treated for persistent pneumonia (Figure 1A-C). At 5.6 mo and still on nasogastric tube feeding, she was admitted for breathing difficulties with recurrent seizures. However, parents decided to leave the hospital with oral antibiotics and home-based oxygen therapy.

Case 2: The elder sister was born after 40.1 wk of uncomplicated pregnancy with a normal birth weight (3450 g), but was immediately hospitalized for birth asphyxia, severe pneumonia, stridor, gastroesophageal reflux, and respiratory failure. At the age of 1.4 mo, she was admitted for severe pneumonia with frequent choking on oral feeding, and transferred to intensive care unit for respiratory failure. At the age of 1.8 mo, she was admitted to a regional pediatric hospital for pneumonia and recurrent seizure while on nasogastric tube feeding. After intensive antibiotic and ganciclovir therapies during more than 2 mo of in-patient stay, the parents took the baby to home care with nasogastric tube feeding and nasal oxygen therapy.

History of past illness
Both patients started having symptoms since birth.

Personal and family history
Both patients started having symptoms since birth, and non-consanguineous parents are healthy.

Physical examination
Case 1 (the younger sister): At 5.6 mo, vital signs, which included body temperature and blood pressure, were within their normal ranges. But respiration and heart rate were abnormal. Dysmorphic features, such as microcephaly, narrow forehead, hypertelorism, retrognathia, enlarged tongue, large ear lobes with forward rotation, hirsutism with long eyelashes, a birthmark, abnormal fat distribution surrounding the genital area, and overlapped toes on both feet, were noted on physical examination (Figure 1D-K). Liver was palpated 4 cm below the right costal margin and 3 cm below the xiphoid process.

Case 2 (the elder sister): At the age of 1.4 mo, she had slight hepatomegaly (liver was palpable 2 cm below the right costal margin) and failure to thrive (3500 g body weight, less than the 1st percentile by World Health Organization standards). At the age of 1.8 mo, significant umbilical and inguinal hernias, hepatomegaly (3 cm below the right costal margin), and malnutrition were noted on physical examination. Parents recalled she had similar facial features and a head as small as her younger sister, but a larger tongue and clenched fingers.

Laboratory examinations
Case 1: At the age of 3.5 mo, the younger sister was found to have high percentage of peripheral blood reticulocytes (5.58%) and slightly higher level of serum lactate levels (4 mmol/L, normal range: 0-2 mmol/L). At 5.6 mo and during admission for breathing difficulties with recurrent seizures, complete blood count showed significantly elevated white blood cell (WBC) count with a higher neutrophil percentage (62.9%, normal range: 20%-50%) and elevated C-reactive protein (CRP) level. Lactic acid level (2.9 mmol/L, normal range: < 2.0 mmol/L) and serum transaminase levels were slightly elevated (Table 1).

Blood samples were collected from the patient and parents for glycosylation analyses after written informed consent was obtained. Using the Waters Alliance 2695-2489 HPLC system (Waters Co., Waters, Manchester, United Kingdom) equipped with Waters Empower software[13], plasma samples collected from the younger sister and both parents were subjected to a standard peptidoglycan assay to examine the profile of conjugated oligosaccharides on IgG1. Compared to the pooled healthy controls, the profiles of conjugated oligosaccharides of the mother and the father were normal. However, an abnormal peak of N2H10 (Glc3Man7GlcNAc2) was detected in the patient’s sample (Figure 2A), and this result was further confirmed by normalizing N2 (GlcNAc2) serial oligosaccharides to controls (Figure 2B). The level of N2H10 (Glc3Man7GlcNAc2) in the younger sister was five-times higher than that in the pooled healthy controls and parents. Detection of abnormal levels of N2H10 (Glc3Man7GlcNAc2) was consistent with two previously reported cases of MOGS[4,5], and provided glycomic evidence for the diagnosis of MOGS-CDG. In addition to N2H10 (Glc3Man7GlcNAc2), a...
## Table 1 Blood test results

| Patient | Case 1 (younger sister) | Case 2 (elder sister) |
|---------|-------------------------|-----------------------|
| Age in mo | 1 | 1.5 | 3.5 | 5.6 | 1.4 | 1.8 | 3.9 |
| Complete blood count | White blood cell (4-10 × 10^9/L) | 24.4 | 21.8 | 27.0 | 32.2 | 20.9 | 23.9 | 8.8 |
| | Lymphocyte (45%-75%) | 50.6 | 44.5 | 65.5 | 32 | 37.8 | 25.5 | 47.8 |
| | Neutrophil (20%-50%) | 35 | 42.8 | 28.5 | 62.9 | 75.0 | 72.8 | 43.8 |
| | Red blood cell (4.0-5.5 × 10^12/L) | 4.3 | 3.8 | - | 4.0 | 4.1 | - | 3.0 |
| | Hemoglobin (110-160 g/L) | 143 | 124 | 100 | 110 | 125 | 108 | 84 |
| | Platelet count (100-300 × 10^9/L) | 506 | 509 | 303 | 308 | 418 | 357 | 464 |
| | C-reactive protein (< 8 mg/L) | < 8 | < 8 | 10.6 | 50 | 15 | 14 | 62 |
| Serum biochemistry | Albumin (35-55 g/L) | 37 | - | 39.5 | 39 | 41.8 | 35.8 | 38.7 |
| | Globulin (20-30 g/L) | 20.7 | - | 20.4 | 20 | 20.4 | 26.4 | 19.5 |
| | Alkaline aminotransferase (0-40 IU/L) | 14 | - | 81 | 51 | 17 | 56 | 29 |
| | Aspartate aminotransferase (0-40 IU/L) | 46 | - | 154 | 93 | 53 | 121 | 49 |
| | Total bilirubin (5.1-17.1 μmol/L) | 8.5 | - | 4.8 | - | 5.0 | 3.0 | - |
| | Direct bilirubin (0-6 μmol/L) | 2.4 | - | 0.2 | - | 1.1 | 0.8 | - |
| | γ-Glutamyl transpeptidase (7-50 IU/L) | 60 | - | 14 | - | - | - | 16 |
| | Total bile acid (0-10 μmol/L) | 9.6 | - | 10.2 | - | - | - | - |
| | Alkaline phosphatase (42-383 IU/L) | 265 | - | 259 | - | - | - | 113 |
| | Creatine kinase (25-200 IU/L) | 142 | - | 175 | 140 | 141 | 813 | 72 |
| | Creatine kinase-MB (< 25 IU/L) | 73 | - | 69 | 38 | 34 | 302 | 24 |
| | α-Hydroxybutyrate dehydrogenase (72-182 IU/L) | 452 | - | 342 | 297 | - | - | 274 |
| | Lactate dehydrogenase (180-430 IU/L) | 556 | - | 500 | 330 | - | 922 | 296 |
| | Glucose (3.9-5.8 mmol/L) | 4.3 | - | 4.9 | - | - | - | - |
| | Creatinine (31-52 μmol/L) | 27 | - | 23.9 | 24 | 19 | 15 | 17 |
| | Urea (2.5-6.5 mmol/L) | 5.0 | - | 6.6 | 7.1 | 2.3 | 1.4 | 3.6 |
| | Uric acid (90-420 μmol/L) | 168 | - | 338 | 301 | - | 281 | 167 |
| | Total cholesterol (3.1-5.2 mmol/L) | 5.0 | - | - | - | 4.4 | 4.3 | - |
| | Triglyceride (0.6-1.7) | 1.0 | - | - | - | 2.1 | 2.1 | - |
| Blood coagulation profiles | Activated partial thromboplastin time (28.0-44.5 s) | 35.8 | - | 37.1 | - | - | - | - |
| | D-dimer (0-0.3 mg/L) | 0.54 | - | 1.51 | - | - | - | - |
| | Fibrinogen (2.4 g/L) | 3.43 | - | 3.26 | - | - | - | - |
| | Fibrinogen degradation products (0.5 μg/mL) | 1.16 | - | 4.4 | - | - | - | - |
| | Thrombin time (14-21 s) | 18.5 | - | 17.9 | - | - | - | - |
| | International normalized ratio (0.8-1.2) | 0.99 | - | 1.37 | - | - | - | - |
| | Prothrombin time (12.0-14.8 s) | 13 | - | 17 | - | - | - | - |
| | Prothrombin time activity (80%-100%) | 103 | - | 62 | - | - | - | - |
| Immune function profiles | IgG (3.70-8.30 g/L) | - | 7.6 | - | - | 12.3^1 | 13.9^1 | - |
| | IgM (0.33-1.25 g/L) | - | 0.52 | - | - | 0.63 | 0.61 | - |
| | IgA (0.14-0.50 g/L) | - | 0.05 | - | - | 0.10 | 0.12 | - |
| | Complement 3 (0.67-1.76 g/L) | - | - | - | - | 0.45 | 0.49 | - |
| | Complement 4 (0.10-0.40 g/L) | - | - | - | - | < 0.06 | 0.10 | - |
| | Total T cells (CD3) (53%-84%) | - | - | - | - | 41.1 | 38.9 | - |
|                     | Before IVIG | After IVIG | Before IVIG | After IVIG |
|---------------------|-------------|------------|-------------|------------|
| Helper T cells (CD4) (35%-64%) | -           | -          | 34.7        | 29.8       |
| Cytotoxic T cells (CD8) (12%-28%) | -           | -          | 15.9        | 10.9       |
| Natural killer cells (CD16 + CD56) (4%-18%) | -           | -          | 2.3         | 9.9        |
| B cells (CD19) (6%-32%) | -           | -          | 36.3        | 43.6       |
| Procalcitonin (< 0.05 ng/mL) | -           | -          | 0.6         | 0.2        |
| Interleukin-6 (< 7 pg/mL) | -           | -          | 14.8        | -          |

1Values after IVIG therapy.  
< Not available. Reference ranges are presented in parentheses.

significantly high level of N2H5 (Man5GlcNAc2) compared to normal control was also detected (Figure 2A and B). To examine the collective impact of the mutations on the glycosylation process, we pooled all detected glycopeptides and calculated the fractions of fucosylated, galactosylated, sialylated, mannosylated, and bisected forms. The ratios of the family were normalized to those of the pooled healthy control (Figure 2C). The results indicated that, in addition to hypermannosylation, sialylation level was also significantly higher in the patient’s sample compared to the parents. Available blood test results throughout the disease course are provided in Table 1.

**Case 2:** The elder sister was tested positive for serum cytomegalovirus IgM and cytomegalovirus DNA (in serum, sputum, and alveolar lavage fluid) at the age of 1.8 mo. Blood test results revealed significant elevations of peripheral WBCs with neutrophil predominance, significant elevations of creatine kinase/creatinine kinase-MB/Lactate dehydrogenase, and abnormal immune function parameters (Table 1). At the age of 3.4 mo, alveolar lavage fluid culture was positive for multiple drug-resistant *Acinetobacter baumannii*. Parents recalled she had low levels of immunoglobulin requiring frequent use of intravenous immunoglobulin (IVIG), but the exact dates and dosages of IVIG therapy were unknown. Available blood test results of both patients throughout the disease course are provided in Table 1.

**Imaging examinations**

**Case 1:** The younger sister had a serial X-rays showed persistent pneumonia (Figure 1A-C), and echocardiography showed patent foramen ovale (1.6 mm) with slight pericardial effusion (2.5-2.7 mm). At 5.6 mo, X-ray showed pneumonia with enlarged heart size and increased liver span (Figure 1L).

**Case 2:** The elder sister was admitted to a regional pediatric hospital for pneumonia at the age of 1.8 mo (Figure 1M). Serial X-rays afterwards showed recurrent exacerbations of pneumonia, progressive hepatomegaly, and enlarged heart size (Figure 1N-P).

Updated clinical (Figure 1 and Table 2), laboratory (Table 1), genetic (Table 2), glycomic (Figure 2 and Table 2) findings, and characteristics of all previously reported patients (Table 2) are summarized in the accompanying tables and figures within the manuscript.

**Genetic defects**

Clinical exome (which includes more than 4000 known disease-causing genes) sequencing and whole exome sequencing of the parents and both sisters were positive for three variants in the MOGS gene (c.1698C>A/p.Asp566Glu, c.544G>A/p.Gly182Arg, and c.1239-1240insCTTCTACGGAAGGCTG-GTATTGCCA/p.Asp414Leufs*17). Details of genetic testing and Sanger sequencing confirmation in family members were published by Li et al[7].

**TREATMENT**

**Case 1 (the younger sister):** Nasogastric tube feeding was started at the age of 5 d. Stridor was improved after laryngotracheoplasty, but feeding difficulty and choking were not improved even after 3 wk of intensive oral motor training. At 5.6 mo, seizure attacks were stopped and breathing difficulty was improved after treatment with antibiotics, nasal oxygen, and nasogastric tube feeding.

**Case 2 (the elder sister):** Supportive treatments such as mechanical ventilation, antibiotics, nasogastric tube feeding, intravenous immunoglobulin, ganciclovir, and anti-seizure medications (not specified).
# Table 2 Clinical, genetic, and glycomic features of all reported patients with mannosyl-oligosaccharide glucosidase deficiency[4]

| Patients in the order of publication date | 1[4] | 2/3[5] | 4[6] | 5[7] and present report | 6[7] and present report | 7[8] | 8[9] | 9[10] | 10[10] | 11[10] | 12[11] |
|------------------------------------------|------|--------|------|--------------------------|-------------------------|------|------|------|-------|-------|-------|
| Sex                                      | Female | Male/Female | Male | Female (younger) | Female (elder) | Female | Male | Male | Female | Male | Female |
| Age of onset                              | Neonatal | Early in life | Neonatal | Neonatal | Neonatal | Neonatal | Neonatal | Neonatal | Neonatal | Neonatal | Neonatal |
| Neurologic symptoms                       | EIEE | + | ND | + | + | ND | + | + | + | + | + |
| Seizures                                  | EIEE | + | ND | + | ND | Infantile spasm | + | EIEE | EIEE | EIEE | + |
| Psychomotor disturbance                   | ND | Profound | ND | Profound | Profound | + | ND | Profound | Profound | Profound | Profound |
| Hyptonia                                  | + | + | + | - | - | + | + | + | + | + | + |
| Cerebral abnormality                      | - | Small corpus callosum, optic-nerve atrophy | - | ND | Frontal gyrus stenosis, high T1W1 signal in anterior pituitary, and thin corpus callosum | Thin corpus callosum, wide cerebral sulcus | Agenesis of corpus callosum, septo-optic dysplasia | Loss of white matter volume, delayed myelination | Loss of white matter volume | Loss of white matter volume | Delayed myelination, cortical and subcortical atrophy |
| Dysmorphic features                       | + (ND) | + | + | + | + | + | + | + | + | + | - |
| Broad nose                                | + | + | + | + | + | + | + | + | + | + | ND |
| High-arched palate                        | + | + | ND | ND | + | + | + | + | + | ND |
| Retrognathia                              | + | + | + | + | + | + | + | + | + | + |
| Short palpebral fissure                   | + | + | + | + | + | + | + | + | + | + | - |
| Enlarged ears                             | + | ND | + | + | ND | + | + | + | ND |
| Overlapping finger/toe                    | + | + | ND | ND | + | + | ND | + | + | ND |
| Arthrogryposis                            | + | + | ND | ND | ND | ND | + | + | + | ND |
| Hypertrichosis                            | + | + | + | + | ND | + | + | + | + | + | + |
| Hypoplastic genitalia                     | + | + | ND | Abnormal fat distribution | - | - | Hypogonadism | + | ND | ND | ND |
| Cardiac involvement                       | - | - | ASD, LVH | ASD, PFO, heart failure, and pericardial effusion | PFO, heart failure | PFO, ASD | Dilated cardiomyopathy | + | - | - | ND |

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|                  | Elevated AST/ALT (IU/L) | Cirrhosis  | Hepatomegaly | Hypogammaglobulinemia | Recurrent infections | Endocrine abnormality | Edema | Hearing impairment | EEG | Isoelectric focusing of transferrin | Urinary oligosaccharide | IgG or serum glycan analysis | MOGS gene mutations | Prognosis |
|------------------|-------------------------|------------|--------------|-----------------------|---------------------|----------------------|-------|------------------|-----|---------------------|------------------------|------------------------|---------------------|-----------|
|                  | *(80/34)*               | ND         | ND           | Low IgA               | +                   | ND                   | +     | Flat with ABR     | ND  | Normal              | Abnormal               | ND                     | p.Arg486Thr and p.Phe652Leu | Died (74 d)          |
|                  | *(46-154/14-81)*       | ND         | ND           | Low IgA, IgA, IgM     | ND                  | ND                   | +     | Suppression burst pattern | ND  | Increased trisialo-transferrin | Increased N2H10 in IgG; Increased N2H10, N2H11 and N2H12 in serum | ND                     | p.Ala22Glu, p.Arg110His, and p.Gln124Ter | Died (4 mo)          |
|                  | *(49-121/17-56)*       | +          | ND           | Low IgA               | ND                  | ND                   | +     | Abnormal ABR      | ND  | Normal              | Increased N2H10 and N2H5 in IgG | ND                     | p.Thr802Ileand p.Arg535Ter | Died (9 mo)          |
|                  | *(30-1547/9-1132)*     | ND         | ND           | Low IgA, Normal IgG and IgM after IVIG | ND                  | ND                   | +     | Hearing impairment | ND  | Normal              | Normal                 | Normal                 | p.Asp414Leufs*17, p.Gly182Arg, and p.Asp566Glu | Died (10 mo)         |
|                  | *(35-144/23-83)*       | ND         | ND           | Low IgA               | ND                  | ND                   | +     | -                | ND  | Normal              | Normal                 | p.Arg565Gln and p.Arg540His | p.Arg565Gln and p.Arg540His | Died (2 yr 1 mo)     |
|                  | *(36-226/50.5-164)*    | ND         | ND           | Low IgA               | ND                  | ND                   | +     | No wave with ABR  | ND  | Normal              | Normal                 | Normal                 | p.Arg495Ter and p.Arg495Ter | Died (1 yr)         |
|                  |                         | ND         | ND           | Low IgA               | ND                  | ND                   | ND    | Only I wave with ABR | ND  | Normal              | Normal                 | p.Gln505del and p.Arg353Ter | p.Gln505del and p.Arg353Ter | Died              |
|                  |                         | ND         | ND           | Low IgA and IgG       | ND                  | ND                   | ND    | Only I wave with ABR | ND  | Normal              | Normal                 | p.Pro513Ser and p.Gly824Asp | p.Pro513Ser and p.Gly824Asp | Died              |
|                  |                         | ND         | ND           | Low IgG2              | +                   | ND                   | +     | Hypoglycemina; elevated cortisol, progesterone, and androstenedione levels | ND  | Abnormal             | Abnormal               | ND                     | ND                   | Alive (19 yr)       |

1 Siblings.
2 Siblings.
3 Siblings.
4 Updated on the basis of Anzai et al [10].

ASD: Atrial septal defect; EEG: Electroencephalogram; EIEE: Early infantile epileptic encephalopathy; LVH: Left ventricular hypertrophy; N2H5: Man5GlcNAc2; N2H10: Glc3Man7GlcNAc2; N2H11: Glc3Man8GlcNAc2; N2H12:...
Glc3Man9GlcNAc2; ND: No data available or not determined; PFO: Patent foramen ovale; SIADH: Syndrome of inappropriate secretion of antidiuretic hormone.

OUTCOME AND FOLLOW-UP

Case 1 (the younger sister): At the age of 7.5 mo, parents stopped nasogastric tube feeding and refused to follow our medical advice on intensive anti-microbial therapy with immune-supportive measures to contain the infection. The patient later died of multiple organ (respiratory, heart, and renal) failure at a local hospital at the age of 9 mo.

Case 2 (the elder sister): At the age of 10 mo, she died of multiple organ failure at a local hospital.

DISCUSSION

Since the first report of MOGS-CDG in 2000[4], 12 patients have been reported to date[4,11]. Previously reported dysmorphic features include prominent occiput, short palpebral fissures, long eyelashes, broad nose, retrognathia, high-arched palate, generalized edema, hypoplastic genitalia, clenched hands with overlapped fingers, alopecia, and thoracic scoliosis. Updated dysmorphic features in our patients included enlarged tongue, large and forwardly rotated earlobes, birthmark, abnormal fat distribution around external genitalia, and overlapped toes. Contrary to previous findings of hypoplastic genitalia, we observed abnormal fat distribution surrounding genital area suggestive of hyperplastic genitalia in the younger sister. We observed persistent respiratory infection with progressive hepatomegaly and cardiomegaly during the course of disease (Figure 1). Updated laboratory findings included significantly elevated peripheral WBC count with neutrophil predominance, elevated CRP, significant but transient elevations of creatine kinase and lactate dehydrogenase, elevation of serum triglyceride, and coagulopathy. As observed in previous studies in MOGS-CDG[4-11], immune profiles were abnormal with low levels of IgM and IgA, and with increased percentage of B lymphocytes. We observed additional evidence of immune deficiency or dysregulation such as complement 3 and complement 4 deficiencies, decreased proportions of T cell subtypes and natural killer cells, as well as elevated levels of serum interleukin 6. Our findings indicated abnormalities in both innate and adaptive immune responses. Since glycans expressed on the surface of immune cells are essential for cell development and function[14], abnormal glycosylation caused by MOGS gene mutation may have caused immune deficiency leading to persistent pneumonia in these siblings. Contrary to previous findings of resistance to infection by glycosylation-dependent enveloped viruses[5,15], the elder sister in our report had evidence of cytomegalovirus (CMV, also an enveloped virus) infection. Although some glycosylated proteins (i.e., gpUL37 and UL55) are involved during CMV replication[16,17], our case seems to suggest CMV replication was not affected by MOGS gene mutation. Further studies are needed to confirm whether CMV replication is dependent on MOGS-mediated glycosylation.

Sadat et al[5] first reported the presence of Glc3Man7GlcNAc2 (N2H10) when analyzing N-glycans in IgG from 2 siblings with MOGS-CDG. Using RapiFluor mass spectrometry, Messina et al[12] recently confirmed the presence of N2H10 in the IgG of an unspecified patient with MOGS-CDG. Consistent
with the previous glycan analyses on MOGS-CDG\cite{5,12}, an abnormal peak of 12-saccharide (N2H10, Glc3Man7GlcNAc2) was detected in IgG1 of the younger sister. In addition, abnormal accumulation of N2H5 (Man5GlcNAc2) was detected in serum sample, which could be another biomarker for MOGS-CDG. Endo-α-1,2-mannosidase might be hyperactivated in MOGS-CDG to partially compensate for MOGS deficiency. Messina et al\cite{12} also reported the presence of fucosylated and unfucosylated hybrid N-glycans in serum IgG, but we did not observe similar changes in our analyses.

The presence of N2H10 detected in MOGS-CDG suggests the activation of a distal α-1,2-mannosidase. The detection of N2H5 (Man5GlcNAc2) but not N2H6 (Man6GlcNAc2) indicated that in addition to H4 (Glc3Man1), endo-α-1,2 mannosidase might be able to remove H5 (Glc3Man2) and from N2H10...
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Figure 2 Abnormal glycoforms detected on immunoglobulin G1 in the serum of the younger sister and proposed compensatory pathway in mannosyl-oligosaccharide glucosidase-congenital disorder of glycosylation. A: Representative mass spectrums generated from the younger sister, parents, and pooled healthy controls by nano-electrospray ionization quadrupole time-of-flight mass spectrometry; B: N2 serials of oligosaccharides on immunoglobulin G1 (IgG1) normalized by the control. Abnormal enrichment of N2H10 and N2H5 were detected; C: Fractions of IgG1 with fucosylation, galactosylation, sialylation, mannosylation, and bisection showing significantly high levels mannosylation and sialylation in the patient sample; D: Proposed mannosyl-oligosaccharide glucosidase-independent pathway leading to increased levels of N2H10 and N2H5 (M5) in vivo. N: N-acetylglucosamine and/or N-acetylgalactosamine; H, hexaose (galactose, glucose, or mannose); GANAB: α-Subunit of glucosidase II; PRKCSH: β-Subunit of glucosidase II; MAN1B1: Endoplasmic reticulum mannosyl-oligosaccharide α-1,2-mannosidase; MAN1A, MAN1A2, and MAN1C1: Mannosyl-oligosaccharide α-1,2-mannosidase; MANEA: Endo-alpha-1,2-mannosidase.

(Glc3Man7GlcNAc2) as well. Based upon all of the collected glycomic results of MOGS-CDG by De Praeter et al[4], Sadat et al[5], Messina et al[12], and our cases, a MOGS-independent pathway through N2H10 (Glc3Man7GlcNAc2) to N2H5 (Man5GlcNAc2) is proposed (Figure 2D). Several groups[4,9,10] have detected an H4 (Glc3Man1) oligosaccharide in urine samples collected from patients with MOGS-CDG, but urine samples were not available from our patients.

When the saccharide-specific profile of glycopeptides in the younger sister was compared to parents and healthy controls, fractions of fucosylation, galactosylation, and bisection were similar. However, fractions of mannosylation (> 1.5 times the normal controls) and sialylation (about 1.2 times the normal controls) were increased compared to parents (Figure 2C). Although N2H10 (Glc3Man7GlcNAc2) accumulation has been previously reported[5,12], higher levels of N2H5 (Man5GlcNAc2) glycans and hypersialylation of IgG1 have not been reported in MOGS-CDG. The hypermannosylation of proteins may have secondary effects on inflammation or infection through mannose-recognizing C-type lectin receptors and mannose-recognizing antibodies[18]. However, hypersialylation is related to neurodegeneration[19] and abnormal immune modulation[20] that could partly explain developmental delay, seizure, and immune deficiency in patients with MOGS-CDG. Our findings may not only provide a potential serum biomarker but may also shed some light on the pathogenesis and subsequent treatment.
CONCLUSION

In conclusion, we confirmed the presence of glycomic abnormality in a patient, expanded the clinical and glycomics spectrum of MOGS-CDG, and postulated a compensatory glycosylation pathway in MOGS deficiency. Updated clinical and glycomics features may provide a better understanding of MOGS-CDG, leading to better identification and management of future patients.

FOOTNOTES

Author contributions: Wang JS and Chen L designed the study and approved the final submission; Abuduxikuer K collected and analyzed the clinical data and collected blood samples for further glycosylation studies; Wang L, Cao CY, Zou L, Yu L, Liang XM and Chen L analyzed the glycosylation data and proposed the MOGS-dependent glycosylation model; Wang JS and Abuduxikuer K clinically managed the patient; Guo HM provided in-patient information from the provincial level hospital; Abuduxikuer K, Wang L and Zou L co-wrote the manuscript and contributed equally to this study; Wang JS and Chen L agreed to serve as contacts for future correspondence.

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