Congenital disorders of glycosylation type IIb with MOGS mutations cause early infantile epileptic encephalopathy, dysmorphic features, and hepatic dysfunction

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Abstract

Aim: MOGS mutations cause congenital disorders of glycosylation type IIb (CDG-IIb or GCS1-CDG). The specific manifestations caused by the mutations in this gene remain unknown. We aimed to describe the clinical features of CDG-IIb and the effectiveness of urinary oligosaccharide analysis in the diagnosis of CDG-IIb.

Methods: Patient 1 was analyzed with whole-exome sequencing (WES) to identify the causative gene of intractable epilepsy and severe developmental delay. After detecting MOGS mutation in patient 1, we analyzed patients 2 and 3 who were siblings and had clinical features similar to those in patient 1. Urinary oligosaccharide analysis was performed to confirm CDG-IIb diagnosis in patient 1. The clinical features of these patients were analyzed and compared with those in eight published cases.

Results: Our three patients presented with early infantile epileptic encephalopathy, generalized hypotonia, hepatic dysfunction and dysmorphic features. In two cases, compound heterozygous mutations in MOGS were identified by WES. Isolation and characterization of the urinary oligosaccharide was performed in one of these cases to confirm the diagnosis of CDG-IIb. Although the isoelectric focusing of transferrin (IEF-T) of serum in this patient was normal, urinary excretion of Hex4 corresponding to Glc 3Man was observed by mass spectrometry.

Conclusion: This report provides clinical manifestations of CDG-IIb with MOGS mutation. CDG-IIb shows a normal IEF profile of serum transferrin and cannot be detected by structural analysis of the patient’s glycoproteins. Characterization of urinary oligosaccharides should be considered to detect this disorder.

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Keywords: Congenital disorders of glycosylation; CDG-IIb; MOGS; Early infantile epileptic encephalopathy; Dysmorphic features; Hypotonia; Hepatic dysfunction; Hearing impairment; Urinary oligosaccharides

1. Introduction

Congenital disorders of glycosylation (CDG) are caused by genetic defects in the synthesis and processing of glycoproteins that affect N-glycan assembly. Patients
|                     | Patient 1 | Patient 2* | Patient 3* | Patient 4 [5] | Patient 5 and 6** [6] | Patient 7 and 8 *** [7] | Patient 9 [8] | Patient 10 [9] | Patient 11 [10] |
|---------------------|-----------|------------|------------|---------------|-----------------------|--------------------------|---------------|----------------|----------------|
| Gender              | Male      | Female     | Male       | Female/Female | Early in life         | Male/Female              | Male          | Male           | Male           |
| Age of onset        | Neonatal  | Neonatal   | Neonatal   | Neonatal      | Early in life         | Early in life            | Neonatal      | Neonatal       | Neonatal       |
| Neurologic symptoms | Microcephaly | EIEE | EIEE | EIEE | + | + | + | + | + |
|                     | Seizures | EIEE | EIEE | EIEE | + | + | + | + | + |
|                     | Psychomotor disturbance | Profound | Profound | Profound | ND | Profound | ND | ND | ND |
|                     | Hypotonia | + | + | + | + | + | + | + | + |
|                     | Cerebral abnormality | Loss of white matter volume, delayed myelination | – | – | – | – | – | – | – |
|                     | Dysmorphic features | Broad nose | + | + | + | + | + | + | + |
|                     |          | High arched palate | + | + | + | + | + | + | + |
|                     |          | Retrognathia | + | + | + | + | + | + | + |
|                     |          | Short palpebral fissure | + | + | + | + | + | + | + |
|                     |          | Enlarged ears | + | + | + | + | + | + | + |
|                     |          | Overlapping fingers | + | + | + | + | + | + | + |
|                     |          | Arthrogryposis | + | + | + | + | + | + | + |
|                     |          | Hypertrichosis | + | + | + | + | + | + | + |
|                     |          | Hypoplastic genitalia | + | ND | ND | + | + | + | + |
|                     |          | Cardiac involvement | + | – | – | – | – | – | – |
|                     |          | Elevated transaminases (AST/ALT (IU/L)) | + (30-1547/9-1132) | + (median 64, 35-144/median 23, 7-83) | + (median 95, 36-226/median 50, 5-164) | + (80/34) | ND | + | ND |
|                     |          | Cirrhosis | – | + | + | ND | ND | ND | ND |
|                     |          | Hepatomegaly | + | + | + | + | + | + | + |
|                     |          | Hypogammaglobulinemia (mg/dL) | Low IgA (median 21, 10-451) | Low IgA (median 63, 49-102) | Low IgA (median 19, 11-27) | IgG (median 540, 495-584) | Low IgA, IgM | Low IgA, IgA, IgM |
|                     |          | IgG (median 535, 408-1380) | IgG (median 718, 348-1190) |
|                     |          | Recurrent infections | + | + | + | – | – | – | – |
|                     |          | Endocrine abnormality | Hyponatremia | ND | ND | ND | ND | ND | ND |

Notes:
- EIEE: Early in life
- ND: Not described
- ASD: Asymptomatic
- LVH: Left ventricular hypertrophy
- SIADH: Syndrome of inappropriate antidiuretic hormone secretion
- ASD, LVH: Asymptomatic,
- Dilated cardiomyopathy
- PFO, ASD: Patent foramen ovale, asymptomatic
- Hypertrichosis
- Hypogammaglobulinemia (mg/dL)
- Recurrent infections
- Endocrine abnormality
- Hyponatremia
- Microcephaly
- Seizures
- Psychomotor disturbance
- Hypotonia
- Cerebral abnormality
- Dysmorphic features
- Broad nose
- High arched palate
- Retrognathia
- Short palpebral fissure
- Enlarged ears
- Overlapping fingers
- Arthrogryposis
- Hypertrichosis
- Hypoplastic genitalia
- Cardiac involvement
- Elevated transaminases (AST/ALT (IU/L))
- Cirrhosis
- Hepatomegaly
- Hypogammaglobulinemia (mg/dL)
- Recurrent infections
- Endocrine abnormality
- Hyponatremia
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- Cirrhosis
- Hepatomegaly
- Hypogammaglobulinemia (mg/dL)
- Recurrent infections
- Endocrine abnormality
- Hyponatremia

R. Anzai et al. / Brain & Development 43 (2021) 402–410

403
|                              | Patient 1 | Patient 2* | Patient 3* | Patient 4 [5] | Patient 5 and 6 ** | Patient 7 and 8 *** [7] | Patient 9 [8] | Patient 10 [9] | Patient 11 [10] |
|------------------------------|-----------|------------|------------|---------------|-------------------|------------------------|----------------|----------------|-----------------|
| **Endocrine abnormality**    | Hyponatremia | ND | ND | ND | ND | Low blood sugar, electrolyte disturbance and central hypothyroidism/ – | SIADH | ND | ND |
| **Edema**                    | +         | ND | ND | + | ND | ND | + | ND | + |
| **Hearing impairment**       |           | No wave with ABR | Only I wave with ABR | Only I wave with ABR | Only I wave with ABR | Flat with ABR | Abnormal ABR | ND | – |
| **EEG**                      |           | Suppression burst pattern | Suppression burst pattern | Suppression burst pattern | Suppression burst pattern | ND | ND | ND | Atypical hypsarrhythmia |
| **IEF-T profile**            | Normal | Normal | Normal | Normal | ND | ND | Trisialotransferrin ↑ | Normal | Normal |
| **Urinary oligosaccharide**  | Abnormal | ND | ND | Abnormal | ND | ND | Abnormal | ND | ND |
| **MOGS gene mutations**      | p.Gln505del and p.Arg495Ter | ND | p.Gln505del and p.Arg495Ter | p.Arg486Thr and p.Phe652Leu | p.Ala22Glu, p.Arg110His and p.Gln124Ter | p.Asp414Leufs*17, p.Gly182Arg | p.Thr802Ile and p.Arg535Ter | p.Arg495Ter and p.Gly752Asp | p.Arg565Gln and p.Arg540His |
| **Prognosis**                | Alive (13 years) | Died | Died | Died (74 days) | Alive (11 years/ 6years) | Died (9 months/10 months) | Died (4 months) | Died (1year) | Alive (2 years 1 month) |

ND: no data available, EIEE: early infantile epileptic encephalopathy, ASD: atrial septal defect, LVH: left ventricular hypertrophy, SIADH: syndrome of inappropriate secretion of antidiuretic hormone, PFO: patent foramen ovale, IEF-T: Isoelectric focusing of transferrin

*, **, ***: siblings
with CDG were identified in the 1980s and were classified based on the clinical symptoms and biochemical deficiencies in multiple plasma glycoproteins [1]. CDG are divided into the following two major subgroups: CDG type I comprise defects in N-linked glycan synthesis, and CDG type II include defects in further processing on the sugar chains [2].

CDG type IIb (CDG-IIb or GCS1-CDG) is a less frequently reported type of CDG and results from defective mannosyl-oligosaccharide glucosidase (glucosidase I, GCS1) expressed in the endoplasmic reticulum that removes the distal α-1,2-linked glucose from Glc3Man9GlcNAc2 glycan after its transfer to the nascent polypeptide (Supplementary Fig. 1) [3,4]. In 2000, De Praeter et al. [5] reported the first case of CDG-IIb with mutations in MOGS encoding GCS1. Moreover, they described the pathological findings including cholangiobifidosis, myelin-like lamellar in the cytoplasm of hepatocytes, ballooning in neurons, and empty-looking vacuoles in the neuronal perikaryon; they detected tetrasaccharides in the urine specimen as a degraded product of unprocessed N-glycans [5]. Recently, a total of 8 cases of CDG-IIb with MOGS mutations have been reported (Table 1) [6–10]. IEF-T was performed in four patients, and three of four patients had a normal IEF-T profile.

Here, we present three patients of CDG-IIb in whom exome sequencing revealed the mutations in MOGS gene, and summarize the clinical features of CDG-IIb, including early infantile epileptic encephalopathy, characteristic dysmorphism, and hepatic dysfunction.

2. Patients and methods

Patient 1 was analyzed using whole-exome sequencing (WES) to identify the causative gene of intractable epilepsy and severe developmental delay. After the diagnosis of MOGS mutation in patient 1, we analyzed patient 2 and 3 who were siblings and had clinical features similar to those in patient 1. The clinical characteristics of these patients were analyzed and compared with those of eight published cases. WES analysis was performed on patient 1 and 3 using peripheral blood and liver tissue as the samples, respectively. IEF-T was analyzed using the patient’s serum specimen. Urinary oligosaccharide analysis was conducted on patient 1 by matrix-assisted laser desorption/ionization (MALDI) time-of-flight (TOF) mass spectrometry (MS) as follows. Aliquots (1 mL) of urine were loaded on a column containing 0.5 mL AG501-X8 cation/anion mixed resin (Biorad, Hercules, CA) for deionization, and the eluent was collected. After 10-fold concentrated, a 0.5 μL sample solution was mixed with the same volume of dihydroxybenzoic acid (20 mg/mL in 50% acetonitrile), and spotted on a MALDI sample plate. A Voyager DE-Pro MALDI-TOF-MS instrument (Applied Biosystems, Foster City, CA) was used for measurements, using a N2 laser system (337 nm). Samples were analyzed in the positive linear mode.

This study was approved by the institutional review boards of Kanagawa Children’s Medical Center and Yokohama City University Faculty of Medicine. Informed consent was obtained from the parents for WES, IEF-T, urinary oligosaccharide analysis, and publication including a photograph of patient’s clinical features.

3. Results

The clinical and dysmorphic features of the three patients are summarized in Table 1. Patient 1, a 13-year-old boy, is the second child of a healthy nonconsanguineous couple. During the early trimester of gestation, a fetal ventricular extrasystole was noticed. He was born full term with normal delivery. He presented with microcephaly (head circumference at birth was 33 cm, −0.2 SD and 44.2 cm and that at 8 years of age was −4.1 SD), cryptorchidism, and dysmorphic features (Fig. 1). He also noted hypotonia with normal deep tendon reflexes. Developmental milestones were severely delayed, with no head control. Electroencephalogram (EEG) at 16 days of age showed a suppression burst pattern and small spikes at the O-pT area.

Fig. 1. Clinical features of patient 1 at 13 years of age. Note the dysmorphic features including a broad nose, retrognathia, short palpebral fissures, upslanting palpebral fissures, enlarged ears, hypertrichosis, thick eyebrows, malocclusion, a long face, and a pointed chin.
He developed recurrent myoclonic seizures at 2 months of age and generalized brief tonic seizures and myoclonic jerks at 13 years of age. The antiepileptic drugs were VPA and ZNS for patient 1. Since infancy, he had had repeated episodes of severe infections accompanied by hyponatremia, thrombocytopenia, and generalized edema. A non-fatal transient atrioventricular block appeared during medical treatment for pneumonia at 8 years of age. After he had recovered from pneumonia, the atrioventricular block was not identified by holter ECG. Motor nerve conduction velocities (MCV) of median nerve was 35.9 m/s. Motor nerve conduction study yielded findings of possible demyelination in the median nerve (Supplementary Fig. 2). Auditory brainstem response (ABR) revealed no wave. Laboratory work up showed mild elevation of transaminases. A brain MRI at 8 years of age revealed reduction of cerebral white matter volume, cerebellar atrophy, and delayed myelination of the cerebral white matter (Fig. 3).

Patients 2 and 3 were siblings born to a healthy non-consanguineous couple. The head circumference of patient 2 was 33.5 cm (0.4 SD) at birth and 41 cm (−4.6 SD) at 3 years of age; the head circumference of patient 3 was 33 cm (−0.2 SD) at birth and 39.5 cm (−3.6 SD) at 8 months of age. Patient 2 was a female who presented with generalized tonic-clonic seizures at 17 days of age and myoclonic jerks at 7 months of age. The EEG showed a suppression burst pattern. MCV of median nerve was 30.1 m/s and ulnar nerve was 40.1 m/s. She developed hepatic cirrhosis at 4 years of age. At 9 years of age, she died from hepatic and renal insufficiency. No autopsy was performed. Patient 3 was male and born full term with a cesarean section for breech presentation. After birth, he required mechanical ventilation for 3 h. At 32 days of age, he presented generalized tonic seizure and the EEG showed a suppression burst pattern. Clonazepam, vitamin B6, Zonisamide, and Phenobarbital were used in patient 2 and 3. At 6 months of age, hepatic insufficiency progressed. At 9 months of age he died from respiratory failure associated with aspiration pneumonia.

Postmortem examination of patient 3 revealed enlargement of the liver and hepatic fibrosis with bile duct proliferation and cholestasis. The weight of his whole brain was 611 g, which was smaller and lighter than that of a normal brain (approximately 900 g) at 9 months. Especially, the volume of the white matter

![Fig. 2. Electroencephalogram (EEG) of patient 1 at the age of 16 days, 7 months, and 7 years. Note a suppression burst pattern and small spikes at the O-pT area at 16 days of age.](image-url)
was decreased. Myelination of the cerebral white matter was incomplete and delayed. In addition, diffuse gliosis - so-called “dissociation gliomyelinique” - was seen in the entire white matter (Fig. 4). Microscopic observation showed swelling of the neuronal perikarya, mainly in the pyramidal cell layer, and ultimately, neuronal cell loss that led to a diffuse spongy state in the cerebral gray matter, mainly in the pyramidal cells layer, which caused neuronal cell degeneration and loss. Ultrastructurally, many cytoplasmic organelles in the neuronal cell were enlarged (Fig. 4).

WES analyses were performed on patient 1 (peripheral blood) and patient 3 (liver tissue) as previously described [8]. Two rare heterozygous mutations of MOGS were detected in the WES data, which were confirmed as compound heterozygous by Sanger sequencing using trio samples: c.1514_1516del (p.Gln505del) from the father and c.1483C > T (p.Arg495Ter) from the mother in patient 1 and c.1514_1516del (p.Gln505del) from the father and c.1603C > T (p.Arg535Ter) from the mother in patient 3 (Supplementary Fig. 3). These mutations were not found in our 575 in-house control exomes, in the Human Genetic Variation Database (http://www.hgvd.genome.med.kyoto-u.ac.jp/). The c.1514_1516del is absent in the ExAC database (http://exac.broadinstitute.org/), and the c.1483C > T and c.1603C > T are found in one of 119,942 and two of 120,696 alleles, respectively. The c.1514_1516del may affect the function because it deletes a conserved glutamine residue.

In patient 1, significant excretion of a tetrasaccharide species (Hex4) in the urine was demonstrated by MS (Fig. 5). IEF-T showed a normal profile in all patients (data not shown). No abnormalities of transferrin were detected by MS (data not shown).

4. Discussion

We reported novel three cases of CDG-IIb with MOGS mutations, summarized the clinical features of CDG-IIb in Table 1 and described the usefulness of oligosaccharide analysis in urine.

Based on our findings and those previously reported in eight patients, we defined a recognizable phenotype in CDG-IIb that comprised neurological symptoms including intractable seizures as early infantile epileptic encephalopathy, severe developmental delay, generalized hypotonia and microcephaly, hepatic dysfunction, and dysmorphic features, such as a broad nose, high arched palate, coarse face, arthrogryposis, overlapping fingers, hypertrichosis, and hypoplastic genitalia (Table 1) [5–10]. We noted that most patients had hearing impairment, potentially representing an additionally recognizable clinical feature of CDG-IIb.

IEF-T is a simple and reliable biochemical screening tool for CDG associated with deficient sialylation [11]. Based on whether the defect is localized to the cytoplasm, the endoplasmic reticulum or the Golgi apparatus, IEF-T offers characteristic, recognizable patterns. However, CDG including type IIb, type IIc, and type...
If that do not result in a hyposialylation of transferrin, present with a normal IEF-T pattern, leading to an under diagnosis of these subtypes [11–14]. MS of isolated serum N-glycans is the next step in the identification of the subtypes. MS is capable of specifying some types of CDG-II, while most CDG-II are associated with non-specific glycan profiles. A previous report indicated that CDG-IIb cannot be detected using structural analysis, including MS, of the glycoproteins because the unprocessed N-glycans are cleaved by the enhanced endo-α-1,2-mannosidase activity [14]. As a consequence, CDG-IIb shows a normal IEF profile of serum transferrin and cannot be detected by structural analysis of the patient’s glycoproteins [2]. Alternatively, the accumulation of tetrasaccharides in the patient’s urine, corresponding to Glc3Man, enables the detection of CDG-IIb [5]. In fact, urinary excretion of this tetrasaccharide was demonstrated in patient 1 although the IEF-T profile was normal. The combination of neurological symptoms, including intractable seizures, dysmorphic features, and hepatic abnormalities, might suggest CDG-IIb.

Microscopic findings of patient 3 showed hepatic fibrosis with bile duct proliferation and cholestasis in the liver as well as spongy gray matter degeneration and leukoencephalopathy with dissociation gliomyelinique in the brain. Progressive cholangiofibrosis with cholestasis in the liver and abnormal intraneuronal vacuoles in the cerebral cortex were consistent with a previous report on CDG-IIb [5].

Moreover, the siblings with CDG-IIb were reported to have a paradoxical immunologic phenotype characterized by severe hypogammaglobulinemia but limited clinical evidence of an infectious diathesis [6]. The causative mechanism for hypogammaglobulinemia remains uncertain; however, altered N-glycosylation of immunoglobulin may alter the binding to certain Fc receptors such as the neonatal Fc receptor, a process controlling immunoglobulin half-life [3]. A shortened immunoglobulin half-life has been reported as the mechanism
underlying the hypogammaglobulinemia, and impaired viral replication and cellular entry are hypothesized to be associated with decreased susceptibility to infections [6,15]. Furthermore, previous studies strongly suggest that N-glycosylation defect in patients with CDG-IIb is responsible for reduced susceptibility to infection caused by glycosylated enveloped viruses. [3] In our patients, serum IgGs were mildly, but not extremely, low (535–718 mg/dL, Table 1), and we consider that they experienced recurrent episodes of infection other than those caused by glycosylated enveloped viruses.

In conclusion, we described three patients with early infantile epileptic encephalopathy, in two of which we detected mutations in the MOGS gene. They had similar clinical characteristics, such as severe neurological symptoms, dysmorphic features, and hepatic abnormalities. For the patients with these clinical features, even if IEF-T is normal, isolation and characterization of urinary oligosaccharides should be considered to diagnose CDG-IIb.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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