Epilepsy and movement disorders in CDG: Report on the oldest-known MOGS-CDG patient

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Abstract
Congenital glycosylation disorders (CDG) are inherited metabolic diseases due to defective glycoprotein and glycolipid glycan assembly and attachment. MOGS-CDG is a rare disorder with seven patients from five families reported worldwide. We report on a 19-year-old girl with MOGS-CDG. At birth she presented facial dysmorphism, marked hypotonia, and drug-resistant tonic seizures. In the following months, her motility was strongly limited by dystonia, with forced posture of the head and of both hands. She showed a peculiar hyperkinetic movement disorder with a rhythmic and repetitive pattern repeatedly documented on EEG-polygraphy recordings. Brain MRI showed progressive cortical and subcortical atrophy. Epileptic spasms appeared in first months and ceased by the age of 7 years, while tonic seizures were still present at last assessment (19 years). We report the oldest-known MOGS-CDG patient and broaden the neurological phenotype of this CDG.

KEYWORDS
congenital disorders of glycosylation, long-term outcome, MOGS, movement disorders, spasms

1 | INTRODUCTION

Congenital disorders of glycosylation (CDG) are caused by defective glycosylation of glycoproteins, glycolipids and glycosylphosphatidylinositol anchor synthesis (Fiumara et al., 2016; Jaeken and van den Heuvel, 2014). CDG phenotypes are heterogeneous, and usually characterized by multi-organ involvement including neurological features such as psychomotor disability, hypotonia, ataxia, epilepsy, stroke-like episodes, and peripheral neuropathy (Fiumara et al., 2016). Dystonia and hyperkinetic movement disorders have only sporadically been described in CDG patients (Mostile et al., 2019).

MOGS-CDG is due to glucosidase I deficiency. Seven patients from five families have been reported worldwide (de Praeter et al., 2000; Sadat et al., 2014; Kim et al., 2018; Li et al., 2019; Peiwei Zhao et al., 2020). We describe a 19-year-old girl with MOGS-CDG, who showed a peculiar movement disorder in the first years of life followed later by global dystonia. To the best of our knowledge, the present patient is the oldest one reported with MOGS-CDG.
This girl was born via normal spontaneous vaginal delivery without complications after an uncomplicated full-term pregnancy.

At birth several dysmorphic features were noted, namely flat facial angiomata, narrow bifrontal diameter, mild retrognathia, a low hairline, and generalized hypertrichosis. In the first days of life she developed hypotonia, hyporeactivity, transient hypoglycaemia, and frequent tonic seizures, with poor response to treatment. EEG showed multifocal epileptic discharges with preserved background activity, and seizures spontaneously resolved at 2 months.

By age 12 months, generalized tonic seizures relapsed and flexor spasms without hypsarrhythmia appeared, in the context of a significant psychomotor impairment, including absent visual fixation, marked axial hypotonia, and secondary microcephaly. The video-polygraphic recordings at this age documented both (a) the recurrence of epileptic spasms, isolated or in series, and (b) a peculiar movement disorder characterized by repetitive periodic brief contractions of upper limb muscles, without paroxysmal EEG discharges (Figure 1a).

In the following years, the patient developed severe spastic tetraparesis associated with visual impairment, hypoacusia, and generalized dystonia, more evident on the left hemibody, with a distinctive dystonic posturing of the hands (Figure 1c).

From 3 years of age, the general condition was complicated by severe systemic involvement including respiratory (bronchospasms and recurrent infections caused by mycoplasma or respiratory viruses, requiring O2 supplementation), endocrinological (cortisol, progesterone, and androstenedione increase) and hematological problems (chronic lymphocytosis). Initially, she fed well orally with proper swallowing coordination, but after few years she required medical treatment for gastro-esophageal reflux and then enteral nutrition through PEG positioning and correction of gastric hernia. A lower concentration of plasma IgG2 was observed in the first years of life (13.71% of IgG total, normal range 19.4–31%). Plasma IgA and IgM remained normal. In addition, lymphoedema affecting the lower limbs and numerous yellow-orange scattered stains on the trunk appeared.

Brain MRI showed a delayed myelination and at 10 years a progressive diffuse cortical and subcortical atrophy; spectroscopy

![Figure 1](wileyonlinelibrary.com)

**FIGURE 1** (a) Video-polygraphic recording at 2 years (EEG and EMG: R-Delt, right deltoid; L-Delt, left deltoid; R-Flex, right flexor carpi; R-Ext, right extensor carpi) documenting epileptic spasms (arrow) without hypsarrhythmia, and the peculiar motion pattern, characterized by repetitive, pseudoperiodic short phasic contractions (1 s in duration), synchronous on antagonists (asterisks), and asynchronous between the two hemibodies (circles, right; triangles, left), at the frequency of 40–50 events per minute. (b) At 18 years, EEG shows a poorly organized and asymmetric background activity, with multifocal epileptiform discharges and tonic seizures. (c) At 18 years, several dysmorphic features are evident: thick eyebrows and eyelashes, retrognathia, prominent cheeks, low-set ears with rotated helix, monomorphic teeth, and flat angiomata. It is also evident a dystonic posture of the head, forcedly turned to the left side, and of both hands, resembling the "main d’accoucheur" (or "obstetrician’s hand") posture. (d) At 10 years, brain MRI documents a diffuse cortical–subcortical atrophy, particularly involving lateral portions of cerebellar hemispheres [Color figure can be viewed at wileyonlinelibrary.com]
showed a reduction of NAA and choline (Figure 1d). Epileptic spasms clusters, which were mainly triggered by tonic seizures, persisted until the age of 7. Since 7 years of age there were no major respiratory tract infections.

Serum Tf IEF profile was normal. The diagnosis of MOGS-CDG was made at age 15 years by means of trio exome sequencing, revealing compound heterozygous MOGS gene variants: maternal p.Pro513Ser (NM_006302.2:c.1537C>T; gnomAD MAF 0) and paternal p.Gly824Asp (NM_006302.2:c.2471G>A; gnomAD total MAF 2/249252 - European [NF] 2/113038). Urine thin layer chromatography showed the typical tetrasaccharide associated with MOGS-CDG (de Praeter et al., 2000). IgG N-glycan analyses by MALDI mass spectrometry revealed the typical increases of Glu3Man7GlcNAc2 and Glu3Man8GlcNAc2 (data not shown).

At last assessment (19 years), height was 135 cm (<<3rd percentile) and weight 33 kg (<<3rd percentile). She had a profound intellectual disability with visual inattention, severe central hypotonia, no head control, and absent language. Routine use of PEEP mask reduced infections, and PEG positioning helped and reduced respiratory problems related to possible aspiration. She was supplemented with calcium and vitamin D as bone scans revealed markedly reduced bone density. Muscular retraction were treated with botulinum toxin. Short multi-day tonic seizures continued, sometimes recurring in clusters for a few hours. They were characterized by repeated vomiting or gagging, often hardly distinguishable from the numerous accesses of gastroesophageal reflux. EEG background activity was asymmetric, with multifocal epileptic discharges (Figure 1b).

3 | DISCUSSION

This is the oldest reported MOGS-CDG patient documented so far. The huge chromosomal distance of the two heterozygous variants found (more than 900 nucleotides) can facilitate the mitotic intragenic recombination mechanism, leading to an advantage of cells with the wild-type allele (as demonstrated in CDG by Kane and coworkers in 2016; Kane et al, 2016), and in turn possibly contributing to the prolonged survival of this patient. This hypothesis deserves further study.

Seven MOGS-CDG patients have been reported; age at last examination ranged from a few months to 11 years (de Praeter et al., 2000; Sadat et al., 2014; Kim et al., 2018; Li et al., 2019; Peiwei Zhao et al., 2020). Three patients died in their first years of life (Li et al., 2019; de Praeter et al., 2000; Kim et al., 2018). Despite showing some typical characteristics of congenital glycosylation defects (prominent CNS involvement, multisystem disease, and severe psychomotor disability) (Fiumara et al., 2016; Jaeken and van den Heuvel, 2014), patients with MOGS-CDG are distinguished by some peculiar features.

All reported patients showed a decrease of serum immunoglobulins that appeared to be related with a shortened half-life (Sadat et al., 2014). Our patient showed only a decreased serum IgG2, and only in the beginning. In some patients immunoglobulin deficiency is associated with a resistance to viral infections, which has been explained by the fact that the impaired N-linked glycan processing compromises intrinsic abilities to support efficient replication and cellular entry of viruses (Sadat et al., 2014). Our patient may not have shown resistance to viral infections as she suffered from recurrent episodes of respiratory illness. Episodes mostly started with rhinorrhea and cough, whom clinical course and laboratory parameters suggested a viral etiology such as lymphocytosis, low-grade fever, and absence of purulent discharges. Unfortunately testing that confirmed the presence of a viral etiology such as viral PCR analysis or viral culture were not performed.

Serum sialotransferrin profiles were normal in one reported patient (de Praeter et al., 2000), as well as in the present one, while an increase of trisialotransferrin was found in another (Kim et al., 2018). Recurrent dysmorphic features include: narrow forehead, hirsutism, light-colored hair, short palpebral fissures, hypertelorism, long eyelashes, broad nose, and retrognathia (Kim et al., 2018); some of these features were also present in our patient (see Figure 1c).

Neurological features of reported patients were only briefly illustrated. Dystonia, which strongly characterizes the condition of our patient, was not described in the reported patients, even if a "clenched" aspect of the hands is described in some instances (Kim et al., 2018; Li et al., 2019), potentially attributable to a dystonic posture rather than to a deformity.

Dystonia is not usually reported among the main neurological features of CDG (Jaeken and van den Heuvel, 2014). Cervical dystonia was described in two sisters with PMM2-CDG, one also with dystonic hands posture (Rossi et al., 2017).

In our patient, a distinctive movement disorder was characterized by nonepileptic pseudo-periodic dystonic phenomena involving upper limbs. Interestingly, Fiumara and colleagues described "intermittent dystonia of the arms" and "dyskinetic limbs movements" in ALG3-CDG and ALG6-CDG (Fiumara et al., 2016). Furthermore, dystonic hand movements were reported also in another patient with PMM2-CDG (Neumann et al., 2003). In addition, stereotypical dystonic hand movements were described in a 17-month-old girl with CDG-x (later diagnosed with SRD5A3-CDG; Prietsch et al., 2002; Jaeken et al., 2020), and "abnormal movements" are mentioned in MGAT2-CDG (Mostile et al., 2019).

More recently, Mostile and colleagues found hyperkinetic movement disorders affecting all of eight reported CDG patients, including dystonia and choreo-athetosis in PMM2-CDG (n:4) and ALG6-CDG (n:1), thus suggesting that movement disorders in CDG may be present more often than reported (Mostile et al., 2019).

4 | CONCLUSION

This oldest reported MOGS-CDG patient presents with early-onset hypotonia and drug-resistant epilepsy. The patient had an early onset hyperkinetic dystonic movement disorder with a rhythmic/repetitive pattern, not previously reported in MOGS-CDG. In addition, drug-resistant epilepsy with tonic seizures persisted over the years. Infantile spasms without hypsarrhythmia also characterized the clinical
course, as previously described in other CDG. Finally, it should be noted that MOGS-CDG cannot be excluded on the basis of a normal serum sialotransferrin profile.

**CONFLICT OF INTEREST**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**AUTHOR CONTRIBUTION**

Tommaso Lo Barco (first author): collected and interpreted clinical data, wrote the first draft and revised the manuscript. Elisa Osanni, Andrea Bordugo, Giulia Rodella, and Bernardo Dalla Bernardina: collected and interpreted clinical data, and revised the manuscript. Rita Barone: performed and interpreted metabolic analysis, interpreted genetic data and revised the manuscript. Romano Tenconi and Maria Iascone: performed genetic test, interpreted genetic data, and revised the manuscript. Gaetano Cantalupo (last author, corresponding author): collected and interpreted clinical data, wrote and revised the manuscript. Andrea Bordugo, Giulia Rodella, and Bernardo Dalla Bernardina: collected and interpreted clinical data, and revised the manuscript. Elisa Osanni, Tommaso Lo Barco (first author): collected and interpreted clinical data, wrote the first draft and revised the manuscript. Gaetano Cantalupo: performed the figure.

**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.

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