

Congenital disorders of glycosylation presenting as epileptic encephalopathy with migrating partial seizures in infancy

Carmen Barba,<sup>1</sup> Francesca Darra,<sup>2</sup> Raffaella Cusmai,<sup>3</sup> Elena Procopio,<sup>4</sup> Carlo Dionisi Vici,<sup>5</sup> Melania Falchi,<sup>1</sup> Diego Martinelli,<sup>5</sup> Gaetano Cantalupo,<sup>2</sup> Elena Parrini,<sup>1</sup> Lorenzo Ferri,<sup>1</sup> Amelia Morrone,<sup>1</sup> Andrea Bordugo,<sup>6,7</sup> Liesbeth Keldermans,<sup>8</sup> Sandrine Vuilleumier,<sup>9</sup> Dirk J Lefeber,<sup>10</sup> Bernardo Dalla Bernardina,<sup>2</sup> and Renzo Guerrini.<sup>1,11</sup>

<sup>1</sup>Pediatric Neurology Unit and Laboratories, A. Meyer Children's Hospital - University of Florence, Florence, Italy.

<sup>2</sup> Child Neuropsychiatry, University of Verona, Verona, Italy

<sup>3</sup> Neurology Unit, Bambino Gesù Children's Hospital, Rome, Italy

<sup>4</sup>Metabolic Unit, A. Meyer Children's Hospital Meyer-University of Florence, Florence, Italy

<sup>5</sup>Metabolic Unit, Bambino Gesù Children's Hospital, Rome, Italy

<sup>6</sup>Metabolic Disease Unit, Division of Pediatrics, University-Hospital of Verona, Verona, Italy

<sup>7</sup> Regional Centre of Neonatal Screening for Inborn Errors of Metabolism, University-Hospital of Verona, Verona, Italy

<sup>8</sup>Centrum Menselijke Erfelijkheid, UZ Leuven, Leuven, Belgium

<sup>9</sup>AP-HP, Bichat Hospital, Biochemistry and Genetic laboratory, Paris, France.

<sup>10</sup> Translational Metabolic Laboratory, Radboud University Medical Center, Nijmegen, The Netherlands and Department of Neurology, Radboud University Medical Center, Nijmegen, The Netherlands

<sup>11</sup> IRCCS Stella Maris, Pisa, Italy

Corresponding author:

Prof. Renzo Guerrini

Pediatric Neurology Unit and Laboratories, Children's Hospital Meyer-University of Florence,

viale Pieraccini 24, 50139, Florence, Italy

Phone: +390555662573

Fax: +390555662329

Email: [renzo.guerrini@meyer.it](mailto:renzo.guerrini@meyer.it)

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## ABSTRACT

Congenital disorders of glycosylation (CDG) are a group of genetic diseases caused by hypoglycosylation of proteins and lipids. Confirmation of clinical diagnosis relies on enzymatic studies in leukocytes, lipid-linked oligosaccharide (LLO) analysis in fibroblasts and MALDI-TOF spectrometry, followed by molecular genetic analysis. CDG are associated with a broad-spectrum clinical features, ranging from paucisymptomatic individuals to extremely severe phenotypes with multi-organ involvement. Epilepsy is commonly observed in CDG, often as an early manifestation, but no distinctive epilepsy phenotypes are recognised.

We described four children (three girls, one boy) with CDG who were first referred between the 1st and 4th month of life, after onset of epilepsy, soon manifested as an epileptic encephalopathy with migrating partial seizures. All patients eventually manifested developmental delay, microcephaly and multiorgan involvement. MRI disclosed cerebral and cerebellar atrophy. Isoelectrofocusing of transferrin (TIEF), enzymatic studies, lipid-linked oligosaccharide (LLO) analysis and spectrometry strongly indicated CDG-I. Genetic testing demonstrated either homozygous or heterozygous variants involving the *ALG3* gene in patient 1 [homozygous: NM\_005787.5:c.1A>G p.(Met1?)] and 3 [compound heterozygous: NM\_005787.5: c.1061G>A p.(Arg354His) and NM\_005787.5:c.165C>T p(.Gly55Gly)], the *RFT1* gene in patient 2 [homozygous: NM\_052859.3:c.454A>G p.Lys152Glu] and of the *ALG1* gene in patient 4 [compound heterozygous: NM 019109.4: c.773C>T p.(Ser258Leu) and NM 019109.4: c.866A>T p.(Asp289Val)]. At last follow up, patients 1 and 2 were 5 and 3.5 years old. Patients 3 and 4 had died due to respiratory failure at age 6 years and refractory status epilepticus at age 1 year. Migrating partial seizures in infancy are etiologically heterogeneous. Concomitant multisystem involvement should prompt investigations for CDG.

## INTRODUCTION (1300 words)

Congenital disorders of glycosylation (CDG) are a group of genetic diseases caused by hypoglycosylation of proteins and lipids. Since their first description in 1980 several protein N- and O-glycosylation defects have been identified.<sup>1-4</sup> Isoelectrofocusing of transferrin (TIEF) is the screening test for N-glycosylation defects while isoelectrofocusing of apolipoprotein C-III (ApoC-III) is utilised to detect O-glycan synthesis disorders.<sup>1,2</sup> Based on the TIEF pattern, protein N-glycosylation disorders have been subdivided into two groups: CDG-I caused by defects in the assembly of glycans and their attachment to proteins (occurring in the cytosol and the endoplasmic reticulum), and CDG -II caused by defects in the processing of the glycans (in the endoplasmic reticulum and the Golgi).<sup>1,2</sup>

Confirmation of clinical diagnosis relies on enzymatic studies in leukocytes, lipid-linked oligosaccharide (LLO) analysis in fibroblasts and MALDI-TOF spectrometry followed by molecular analysis to detect underlying gene defects.<sup>2</sup>

Impaired glycosylation is associated with a wide range of clinical manifestations ranging from paucisymptomatic individuals to extremely severe phenotypes with multi-organ involvement.<sup>1,2</sup> As a consequence of their phenotypic variability, CDG represent a diagnostic challenge and are still largely under-diagnosed.

Epilepsy is commonly observed in CDG and is often a presenting symptom. Although infantile spasms, focal and generalised seizures are often mentioned,<sup>1-3</sup> no distinctive epilepsy phenotype is recognised. Identification of a characteristic presentation may help early diagnosis.

We report on four children with CDG and migrating partial seizures, describe their clinical course, electrographic, imaging, biochemical and genetic findings and suggest that CDG be considered in the differential diagnosis of disorders manifested as early EE with migrating partial seizures.

## METHODS

Based on the initial observation of an index case with migrating partial seizures, in whom we diagnosed CDG due to associated microcephaly, facial dysmorphisms, spastic quadriplegia, and severe cognitive impairment (patient 1, Table 1), we investigated whether this epilepsy phenotype pattern was a recurrent presentation of the disorder. We then evaluated a cohort of 16 additional children with CDG followed in three tertiary Pediatric Neurology Centers (Children's Hospital A. Meyer, Florence; Bambino Gesù Children's Hospital, Rome; Verona University Hospital) and analysed clinical course, biochemical and genetic findings, EEG and imaging features. Additional information on genetic testing is summarized in Supplementary Methods.

The ethical committee of Tuscany Region, Italy approved the study. Informed consent was obtained for all patients.

## RESULTS

### **Clinical, EEG and neuroimaging findings**

Four of 17 consecutively observed children with CDG had manifested migrating partial seizures as an early feature. There were three girls (patients 2-4) and one boy (patient 1); at last follow-up, patients 1 and 2 were 5 and 3.5 years old while patients 3 and 4 had died due to respiratory failure and refractory status epilepticus, respectively. All patients exhibited developmental delay, microcephaly and multiorgan involvement.

Migrating seizures appeared between the 1<sup>st</sup> and 4<sup>th</sup> month of life, involving clinically and electrographically either side, occurring in repeated clusters, with prominent clonic or tonic manifestations (Figure 1). In patients 1 and 4, partial seizures were at times accompanied by spasms.

MRI disclosed cerebral and cerebellar atrophy in all patients (Figure 2).

Additional clinical information on the four patients is summarised in Table 1.

### **Biochemical and genetic studies (Table 1)**

Metabolic screening (blood and cerebrospinal fluid [CSF] lactate, pyruvate and glucose, quantitative plasma and CSF amino acids, quantitative urine organic acids, plasma acylcarnitine profile, neurotransmitters) was normal in all patients.

Array-CGH and targeted re-sequencing of a panel of 95 epilepsy related genes were negative in three children (1-3).

TIEF indicated CDG I in all four patients. Enzymatic studies, lipid-linked oligosaccharide (LLO) analysis and spectrometry confirmed the diagnosis in three tested children (1-3). In the remaining patient (4) these analyses were not performed.

In patient 1, a new homozygous variant [NM\_005787.5:c.1A>G p.(Met1?)] was identified in the *ALG3* gene using a 25 CDG I gene panel and subsequently confirmed by Sanger sequencing. Bioinformatic analysis predicted the amino acid substitution to be probably pathogenic (Polyphen2 score: 0.713, Mutation Taster score: 1, SIFT score: 0.00). In patient 2, a homozygous variant in the *RFT1* gene [NM\_052859.3:c.454A>G p.(Lys152Glu)] was detected by whole exome sequencing (WES) and confirmed by Sanger sequencing. This variant was previously described as causative<sup>5</sup>. Patient 3 was compound heterozygous for two variants in the *ALG3* gene [NM\_005787.5:c.1061 G>A p.(Arg354His) and NM\_005787.5:c.165C>T p.(Gly55Gly)] as demonstrated using a 79 CDG I, II and congenital muscular dystrophy-dystroglycanopathy genes panel, and confirmed by Sanger sequencing. The new variant c.1061 G>A p.(Arg354His) was predicted to be pathogenic (Polyphen2 score: 1, Mutation Taster score: 1, SIFT score: 0.00). p.Arg354 is a phylogenetically conserved amino acid mapping in an ALG3 loop, which protrudes to the cytosolic side of the endoplasmic reticulum membrane<sup>6</sup>. A disease-causing variant in the same codon [NM\_005787.5:c.1060C>T p.(Arg354Cys)] was previously reported.<sup>7</sup> The synonymous

variant c.165 C>T in the *ALG3* gene has been reported to affect splicing.<sup>8</sup> Patient 4 was compound heterozygous for two variants in the *ALG1* gene [NM\_019109.4:c.773C>T p.(Ser258Leu) and NM\_019109.4:c.866A>T p.(Asp289Val)] as demonstrated using a 79 CDG I, II and congenital muscular dystrophy-dystroglycanopathy genes panel, and confirmed by Sanger sequencing. The variant p.(Ser258Leu) was previously reported as causative.<sup>9</sup> The new variant p.(Asp289Val) in *ALG1* was predicted to be pathogenic (Polyphen2: score 1, Mutation Taster score: 1, SIFT score: 0.00). p.Asp289 is a highly conserved amino acid and there is a large physiochemical difference between Asp and Val.

Parents of all children were asymptomatic heterozygous carriers of the segregating familial variants.

## DISCUSSION

Epilepsy is commonly observed in infants with CDG. Infantile spasms, generalised and focal seizures have been variably reported<sup>1-3</sup>, but no distinctive epilepsy phenotype has been identified.<sup>1-3</sup>

Migrating partial seizures of infancy are considered to be a distinctive phenotype and the hallmark of a severe form of early onset epileptic encephalopathy (MPSI also known as EIEE14, OMIM: #614959)<sup>10,11</sup>, now recognised as a new syndrome entity<sup>12</sup> (Epilepsy of infancy with migrating focal seizures - EIMFS).<sup>13</sup> EIMFS has been associated with variants of different genes (*SCN1A*, *SCN8A*, *PLCB1*, *KCNT1*, *SCN8A*, *SLC25A22*, *QARS*, *TBC1D24*, *SLC12A5*)<sup>11,13,14</sup> and with 16p11.2 duplication.<sup>15</sup>

*KCNT1* gene mutations are the most frequent genetic cause of EIMFS<sup>11</sup> and have been associated with a particularly pharmacoresistant migrating partial seizures, arrest of psychomotor development, and normal MRI at onset.<sup>11,14</sup>

In our patients, migrating partial seizures were part of a complex clinical picture characterised by early developmental delay, quadriparesis, microcephaly, dysmorphic facial

features, multi-organ involvement and accompanied cerebral and cerebellar atrophy as demonstrated by MRI. Biochemical and spectroscopy prompted by the above clinical features led us to the diagnosis of CDG which was genetically confirmed in all patients. We could not find co-occurring abnormality in any of the genes previously associated with EIFMS.<sup>11,13,14</sup>

CDG pose considerable diagnostic challenges, due to their high phenotypic variability, and should be ruled out in any unexplained clinical condition in which multiorgan dysfunction is associated with neurological involvement.<sup>3</sup> Limited awareness of CDG is the main reason why they are still under-diagnosed.<sup>1</sup>

Our findings suggest that in children with EE with migrating partial seizures, concomitant multisystem involvement should prompt investigations for CDG.

The association of CDG and migrating partial seizures represents a form of early onset genetic EE due to an 'interposed' structural abnormality.<sup>12</sup> Neuropathological studies of the whole brain in CDG has revealed loss of Purkinje and granule cells, white matter depletion in the cerebellum, and neuronal loss in pontine nuclei, inferior olives and cerebral cortex.<sup>16,17</sup>

Widespread brain damage and the important role of glycans in cell–cell interactions and intracellular signalling<sup>1,3</sup> might explain seizure onset from multiple brain sites in a same individual.

In this study, two patients (1 and 3) harboured causative *ALG3* variants, one (Patient 2) a causative *RFT1* variant and one (Patient 4) a causative *ALG1* variant (Patient 3). Our patients exhibited most of the general clinical features described in previous reports on the above mentioned CDG.<sup>1,2</sup>

Further studies including a greater number of patients with CDG might identify more precise correlations between genotype and the epilepsy phenotype.

“Supplementary information is available at European Journal of Human Genetics website”

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## Titles and legends to figures

Figure 1: Ictal EEG accompanying migrating partial seizures in the four patients. Arrows indicate seizure onset. (A) Patient 1: Left parieto-occipital (red arrow), right fronto-central (red arrowheads) and right temporo-occipital (black arrow) ictal activity. (B) Patient 2: Left fronto-centro-temporal and vertex (red arrows), left parieto-occipital (red arrowhead) and right fronto-central (black arrows) ictal activity. (C) Patient 3: Right centro-parietal (red arrow), right temporal (black arrow) and vertex (red arrowhead) ictal activity. (D) Patient 4: Right parieto-occipital (red arrowhead), right temporal (red arrow) and left temporo-occipital (black arrow) ictal activity.

Figure 2: Brain MRI of the four patients included in the study. Patient 1: Axial T2 (A), sagittal T1 (B) and coronal T2 (C) sequences showing cerebral atrophy with ventricular dilatation, thin corpus callosum, brainstem and cerebellar atrophy. Patient 2: Axial T2 (D), sagittal T1 (E) and coronal T2 (F) sequences showing cerebral atrophy with ventricular dilatation and cerebellar atrophy. Patient 3: Axial Flair (G), sagittal T1 (H) and coronal T2 (I) sequences showing severe cerebral atrophy with thin corpus callosum, brainstem and cerebellar atrophy. Patient 4: Axial (J) and sagittal (K) T2 and coronal (L) T1 sequences showing cerebral and cerebellar atrophy and a thin corpus callosum.

Table 1. Summary of information on four patients with CDG and migrating partial seizures

Pt	Age	Sex	Pregnancy and	NE	Additional clinical features	Age	Sz type and	AEDs at	Interictal	Brain MRI	Biochemical studies	Genetic findings
1	5 y	M	Uneventful	Poor eye contact, absent trunk control, spastic quadripareisis, severe delay	Acquired microcephaly (< 4SD), high-arched palate, micrognathia, saddle nose, thin lips, prominent columella, aplasia cutis congenita, failure to thrive, gastrointestinal problems	1 mo	Focal sz with tonic and clonic manifestations (either side), at times preceded by spasms/daily	PHT, LEV	Slow background activity, absent sleep stages, multifocal spike and SW discharges	Cerebral atrophy, thin corpus callosum, cerebellar and brainstem hypoplasia/atrophy	A) TIEF: increased disialotransferrins and absent asialotransferrins B) MALDI-TOF spectrometry: abnormal glycosylation as in CDG I C) PMM and MPI enzyme analysis in leucocytes: not performed D) LLO analysis in fibroblasts: not performed	Homozygous <i>ALG3</i> gene mutation [NM_005787.5: c.1A>G p.(Met1?)]
2	3.5 y	F	Threatened abortion in the first trimester of pregnancy, caesarean section for breech birth, dark amniotic fluid	Poor eye contact, no head and trunk control, diffuse hypotonia, severe cognitive impairment	Congenital microcephaly (< 3 SD), sensorineural deafness, coagulation abnormalities	2.5 mo	Hemiclonic (either side), hypomotor sz/daily	LEV, RFN, TPM	Slow background activity, absent sleep stages, multifocal spike and SW discharges	Cerebral atrophy, thin corpus callosum, cerebellar atrophy	A) TIEF: increased disialotransferrins and absent asialotransferrins. B) MALDI-TOF spectrometry: not performed. C) PMM and MPI enzyme analysis in fibroblasts: normal D) LLO analysis in fibroblasts: increased amount of Man5	Homozygous <i>RF71</i> gene mutation. [NM_052859.3: c.454A>G p.(Lys152Gln)] <sup>§</sup>
3	Deceased at 6 y for respiratory failure	F	IUGR at 20 <sup>th</sup> mo, reduced fetal movements, dystocic delivery	Poor eye contact, no head and trunk control, spastic quadripareisis, severe cognitive impairment	Acquired microcephaly (<4 SD), plagiocephaly, high-arched palate, thin lips, micrognathia, saddle nose, prominent columella, flattened philtrum, synophrys, low set dysmorphic ears, severe scoliosis with mediastinal shift, distal arthrogryposis, camptodactyly, failure to thrive, hepatomegaly	2 mo	Focal sz with tonic and clonic manifestations (either side) /daily	PB, LEV	Slow background activity, absent sleep stages, multifocal spike and SW discharges	Cerebral atrophy, thin corpus callosum, cerebellar and brainstem hypoplasia/atrophy	A) TIEF: increased disialotransferrins and absent asialotransferrins B) MALDI-TOF Mass spectrometry: abnormal glycosylation as in CDG I C) PMM and MPI enzyme analysis in leucocytes: normal D) LLO analysis in fibroblasts: increased amount of Man3 and Man5 (Gly55Gly)] <sup>7</sup>	Compound heterozygous <i>ALG3</i> gene mutation [NM_005787.5: c.1061 G>A p.(Arg354His) and NM_005787.5: c.165C>T p.(Gly55Gly)] <sup>7</sup>
4	Deceased at 1 y during refractory status epilepticus	F	IUGR since 24th week, and reduced foetal movements; urgent caesarean section for foetal bradycardia during expulsion stage	Poor eye contact, nystagmus, no head and trunk control, hypotonia, dystonic movements, erratic myoclonus, severe delay	Small head size (-1.5 SD), inverted nipples, convergent strabismus, gastrointestinal problems, coagulation abnormalities	3.5 mo	Focal sz with tonic manifestations (either side), at times preceded or followed by spasms/daily	VPA, TPM, PB, MDZ, KET, KBr	Slow background activity, absent sleep stages, multifocal spikes	Cerebral atrophy, thin corpus callosum, cerebellar and brainstem hypoplasia/atrophy	A) TIEF: increased disialotransferrins and reduced tetrasialotransferrins B) LLO analysis in fibroblasts: not performed C) MALDI-TOF spectrometry: not performed D) PMM and MPI enzyme analysis in leucocytes: not performed	Compound heterozygous <i>ALG1</i> gene mutations [NM_019109.4: c.773C>T p.(Ser258Leu)] <sup>8</sup> and NM_019109.4: c.866A>T p.(Asp289Val)]

AEDs: antiepileptic drugs; Dev: development; F: female; FU: follow-up; IUGR: Intrauterine growth restriction; KBr: potassium bromide; KET: ketamine; LEV: levetiracetam; LLO: lipid-linked oligosaccharide; M: male; Man3: Man3GlcNAc2-PP-Dolichol; Man5: Man5GlcNAc2-PP-Dolichol; MDZ: midazolam; Mo: months; MPI: mannosephosphate isomerase; MRI: magnetic resonance imaging; NA: not available; NE: neurological examination; PB: phenobarbital; PHT: phenytoin; PMM: Phosphomanno-mutase; Pt: patient; RFN: rufinamide; SD: standard deviation; Sz: seizure; SW: spike and waves; TIEF: isoelectrofocusing of transferrin; TPM: topiramate; VPA: valproic acid; Y: years.



