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RESEARCH REPORT

Electroclinical Features of Early-Onset Epileptic Encephalopathies in Congenital Disorders of Glycosylation (CDGs)

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Abstract Congenital disorders of glycosylation (CDG) are a constantly growing group of genetic defects of glycoprotein and glycolipid glycan synthesis. CDGs are usually multisystem diseases, and in the majority of patients, there is an important neurological involvement comprising psychomotor disability, hypotonia, ataxia, seizures, stroke-like episodes, and peripheral neuropathy. To assess the incidence, among early-onset epileptic encephalopathies (EOEE), of patients with identified congenital disorders of glycosylation (CDG), we made a review of clinical, electrophysiological, and neuroimaging findings of 27 CDG patients focusing on seizure onset, semiology and frequency, response to antiepileptic drugs (AED), and early epileptic manifestations. Epilepsy was uncommon in PMM2-CDG (11%), while it was a main concern in other rare forms. We describe a series of patients with EOEE and genetically confirmed CDG (ALG3-CDG, ALG6-CDG, DPM2-CDG, ALG1-CDG). Epileptic seizures at onset included myoclonic and clonic fits and focal seizures. With time, patients developed recurrent and intractable seizures principally tonic–clonic seizures, infantile spasms, and myoclonic seizures. Electrophysiological correlates included focal and multifocal epileptic discharges, slowed background rhythm, and generalized epileptic activity including burst suppression pattern and status epilepticus. We propose a diagnostic flowchart for the early diagnosis of CDG in patients presenting with EOEE and suggest to perform serum transferrin IEF (or capillary zone electrophoresis) as a first-line screening in early-onset epilepsy.

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The present study emphasizes the importance of increased awareness that among subjects with early-onset epileptic encephalopathies (EOEEs), patients with congenital disorders of glycosylation (CDGs) may be detected. We propose a diagnostic flowchart for the early diagnosis of CDG in patients presenting with EOEE.

Competing interests: None declared

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Introduction

Early-onset epileptic encephalopathies (EOEE) are challenging conditions in newborns and infants, characterized by recurrent seizures, with onset in the first year of life, and impaired cognitive and motor development (Holland and Hallinan 2010). They include Ohtahara syndrome, early myoclonic epileptic encephalopathy, malignant migrating partial seizures of infancy, and others. EOEE may have different origins (anoxic–ischemic events, intracranial bleeding, infections, brain malformations, genetic/metabolic defects, drugs abstinence) although the cause is not always identified. The incidence of inborn errors of

metabolism (IEM) causing epilepsy is rated differently in published series, ranging from 0.1 to 300/100,000 live births (Mastrangelo and Leuzzi 2012; Mastrangelo et al. 2012). Nevertheless, a significant bias can derive from the specific experience of caring physicians and the availability of diagnostic tests.

Among IEM, congenital disorders of glycosylation (CDG) are a rapidly growing group of genetic defects of glycoprotein and glycolipid glycan synthesis (Freeze 2006). Since their first description by Jaeken in 1980, some 80 CDG have been identified, classified as defects of protein *N*-glycosylation, protein *O*-glycosylation, lipid, and GPI anchor glycosylation and combined defects (Barone et al. 2014). The screening technique for *N*-glycosylation disorders is serum transferrin (Tf) isoelectric focusing (IEF), although in rare instances Tf IEF profile can be normal in the first weeks of life in affected subjects (Clayton et al. 1993). CDG with type 1 IEF pattern (increase of asialo- and disialoforms and decreased tetrasialoforms) (CDG-I) are defects of *N*-glycan assembly and/or transfer to the glycosylation site of a protein. CDG with type 2 IEF pattern (increase of asialo-, monosialo-, disialo-, and/or trisialoforms) are due to *N*-glycan processing defects (Jaeken 2010). After finding a type 1 pattern, further biochemical characterization can be performed by fibroblast dolichol-linked oligosaccharide analysis. In the case of type 2 pattern, mass spectrometry profiling of *N*-glycans from serum Tf or total serum glycoproteins may be performed. In both instances, the next step is mutation analysis of a panel of genes known to be involved in CDG. If the latter is normal, whole-exome/whole-genome sequencing is increasingly used.

CDG are usually multisystem diseases, and in the majority of patients, there is an important neurological involvement comprising psychomotor disability, hypotonia, ataxia, seizures, stroke-like episodes, and peripheral neuropathy. Seizures have been reported in almost all types of CDG, often without an accurate description of semiology, EEG patterns, and therapeutic response. In this study, we describe the electroclinical features of a series of patients with EOEE and genetically confirmed CDG. In addition, we propose a diagnostic flowchart for the early diagnosis of CDG in patients presenting with EOEE.

Methods

Out of 3,700 samples referred for serum Tf IEF screening test to the Regional Center for Inborn Errors of Metabolism at the Pediatric Clinic, University of Catania, Italy, from 2005 to 2014, 29 showed a pattern compatible with the clinical diagnosis of CDG. Two subjects showed a type 2 IEF pattern suggesting a glycoprotein processing defect. In the 27 patients showing a type 1 pattern, PMM enzyme assay and/or PMM2 gene analyses were performed as PMM2-CDG is by far the most common *N*-glycosylation disorder. If PMM2-CDG was ruled out, dolichol-linked oligosaccharide (DLO) analysis was assessed in fibroblasts, and genetic testing for the putative CDG genes by Sanger was eventually performed. Thus, we reached a genetically confirmed diagnosis of PMM2-CDG in 17 out of 27 patients. Among the remaining ten non-PMM2-CDG subjects, ALG6-CDG, DPM2-CDG, and ALG3-CDG were each diagnosed in one patient. Furthermore, two ALG1-CDG patients were identified. In the other patients, including five CDG-I and two CDG-II subjects, we did not define yet the molecular defect, and whole-exome sequencing is ongoing.

The clinical records of all patients were reviewed with regard to the electroclinical features of epilepsy (onset, seizure semiology and frequency, response to antiepileptic drugs), EEG, and brain MRI findings. Seizures and epileptic syndromes were classified according to the International Classification (Commission on Classification and Terminology of the International League Against Epilepsy 1989).

Results

Epilepsy was uncommon in PMM2-CDG, as it was present in 2 (11%) out of the 17 genetically confirmed cases. Six patients experienced stroke-like episodes manifested as recurrent episodes of amaurosis, painful paresthesias, headache, and aphasia. Stroke-like episodes with transient hemiparesis or hemiplegia were initially diagnosed as partial crises followed by Todd paralysis for a few hours or days. On the contrary, epilepsy was the main complaint in patients with other CDG types. Four cases, each with a different CDG, were classified as having EOEE (Table 1).

Patient 1

This 7-year-old child of unrelated parents was born at the 38th week of gestation, after a pregnancy complicated by threats of miscarriage. Physical parameters were normal for his gestational age. He had respiratory distress and since his first week of life massive myoclonic jerks during sleep, hypotonia, and hypoglycemia. The boy presented sudden episodes of crying followed by apnea and cyanosis, lasting up to 15 min. Interictal electroencephalogram (EEG) showed slowed background and rare sharp waves over the posterior areas of the left hemisphere switching to synchronous and asynchronous epileptic discharges. The electroclinical picture was suggestive of early myoclonic encephalopathy of infancy (EMEI). Therapy with pheno-

Table 1 Clinical and molecular data of the present non-PMM2-CDG cases with EOEE

Case	1	2	3	4
Age/sex	7 y/M	30 m/F	22 m/F	10 m/F
Age at diagnosis (positive IEF test)	24 m	24 m	8 m	4 m
Type	ALG6-CDG	DPM2-CDG	ALG3-CDG	ALG1-CDG
Seizure onset	1st w	1st w	1st m	1st d
Seizure type	EMEI	EMEI	EMEI	Ohtahara syndrome
AED	PB, VGB, VPA	VPA, LTG	PB, VGB	PB, LEV, VPA, DZP, CLB
Current therapy/ outcome	LEV	Dead at age 30 m	Dead at age 22 m	Dead at age 10 m
Brain MRI	Cortical atrophy, thin corpus callosum	Periventricular and subcortical demyelination	Hypoplasia of corpus callosum	Delayed myelination, cortical subcortical atrophy

y year, *m* month, *w* week, *d* day, *M* male, *F* female, *EMEI* early myoclonic encephalopathy of infancy, *AEDs* antiepileptic drugs, *PB* phenobarbital, *VGB* vigabatrin, *VPA* valproate, *LTG* lamotrigine, *LEV* levetiracetam, *DZP* diazepam, *CLZ* clonazepam

barbital was started. At age 6 months, he started to experience daily tonic seizures with truncal hypertonia and sialorrhea, lasting more than 10 min. Treatment with vigabatrin and then valproate was unsuccessful.

The patient was admitted to our department at age 24 months. He showed slowed growth of head circumference and facial dysmorphism (coarse face with high forehead, esotropia, hypertelorism, large ears, depressed nasal root, bulbous nose) and bilateral cryptorchidism. Psychomotor development was severely delayed: he had poor gaze fixation and pursuit eye movements, axial hypotonia (he did not sit unaided), and dyskinetic limb movements (Fig. 1a). Fundoscopy revealed initial signs of chorioretinal dystrophy and optic nerve atrophy. Blood investigation revealed increased prothrombin time (PT), decreased coagulation factor XI, and pseudocholinesterase; serum Tf IEF showed a type 1 pattern. PMM activity was normal in fibroblasts. Dolichol-linked oligosaccharide (DLO) analysis in fibroblasts suggested an ALG6 defect, and molecular investigation revealed a homozygous mutation (c.250G>A/p.A84T) in this gene. Levetiracetam was started with partial benefit. Follow-up brain MRI revealed delayed myelination, thinning of corpus callosum, and progression of cerebral cortical atrophy (Fig. 1b).

Patient 2

This 30-month old girl (Fig. 1c) has been previously reported (patient 1 in Barone et al. 2012) without describing electroclinical features of epilepsy. She started to present myoclonic jerks of the four limbs at 6 days of life. She showed facial dysmorphism (hypertelorism, small rounded nose, pronounced philtrum, thin upper lip, ogival palate, and micrognathia); keel thorax; multiple contractions of elbows, wrists, fingers, and knees; and mild hepatomegaly. Spontaneous movements as well as plantar and palmar reflexes were absent. Brain ultrasound showed periventricular matter abnormalities. She was admitted for respiratory distress at age 3 months. Blood investigation showed increased serum transaminases and CK and decreased AT-III levels. Her EEG showed slowed background and low-voltage spikes over the left fronto-central areas. Seizures were refractory to antiepileptic therapy with valproate and then lamotrigine. The electroclinical features suggested EMEI. At 20 months, the patient showed profound psychomotor disability with generalized severe hypotonia, and she still experienced daily tonic–clonic seizures and limb myoclonus. At age 2 years, fundoscopy showed optic atrophy. Brain MRI revealed loss of myelin in the periventricular and subcortical areas and widening of the lateral ventricles. She died at the age of 30 months. A type 1 pattern was found on serum Tf IEF. DLO analysis in fibroblasts showed an accumulation of the glycan assembly intermediate Dol-PP-$GlcNAc_2Man_5$. She was found to be compound heterozygous for two mutations in DPM2: c.68A>G (p.Y23C) of maternal origin and c.4-1G>C from the father.

Patient 3

This patient was born at the 35th week, with a birth weight of 2,550 g (50th centile) by natural delivery. Around the 12th gestational week, threats of miscarriage were pharmacologically treated. She had respiratory distress at birth, severe hypotonia, and arthrogryposis. At 1 month, she developed cyanotic spells. The EEG showed continuous, generalized, slow spike/waves and polyspike waves configuring a nonconvulsive status epilepticus. Vigabatrin and phenobarbital were started. With time she developed focal motor and tonic–clonic seizures with multifocal epileptic

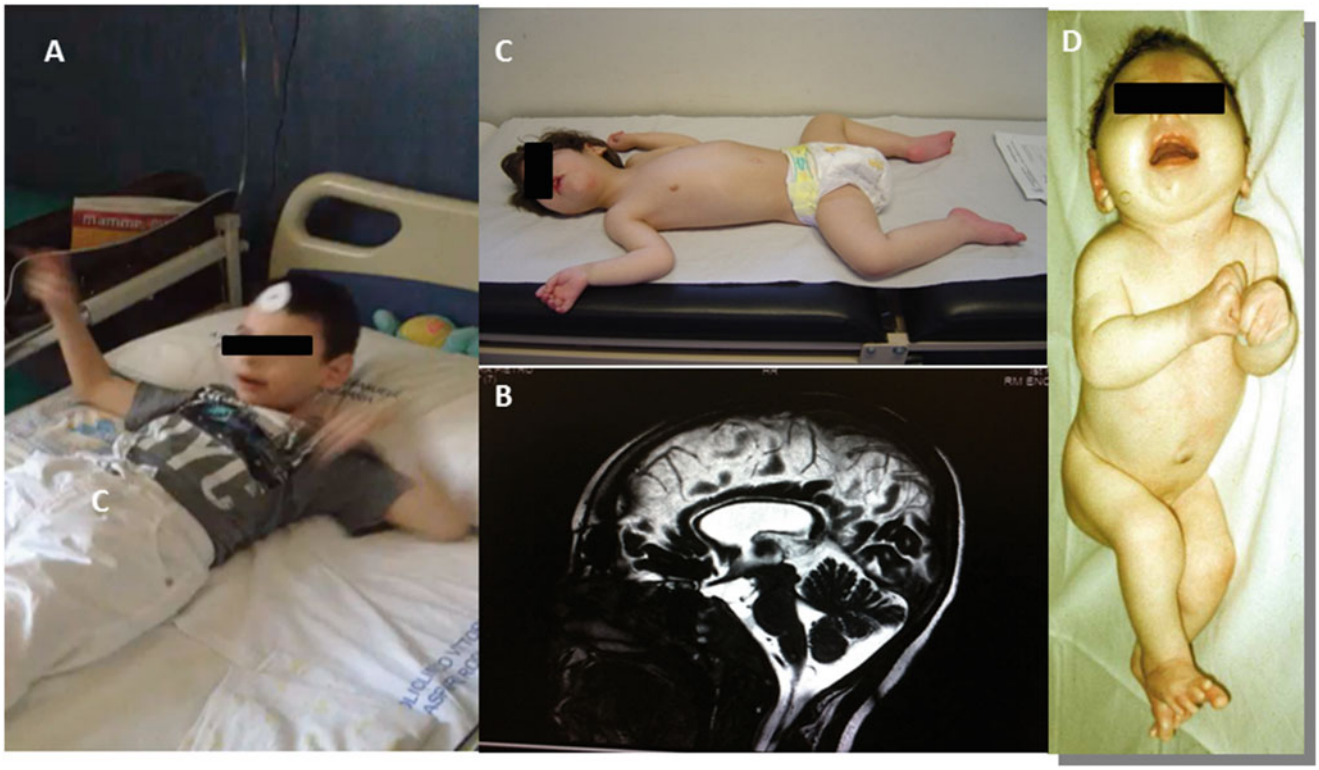

Fig. 1 Clinical and neuroimaging features of present patients with CDG and EOEE. (**a**) Case # 1 ALG6-CDG. (**b**) Case #1 MRI showing thin corpus callosum. (**c**) Case # 2 DPM2-CDG. (**d**) Case # 3 ALG3-CDG

abnormalities at the EEG compatible with early-onset multifocal epileptic encephalopathy. Brain MRI showed hypoplasia of the corpus callosum.

At age 8 months (Fig. 1d), she showed stunted growth, poor eye contact and head control, hypomotility, microcephaly, and craniofacial dysmorphism (plagiocephaly, short neck, low-set hairline, sparse hair, depressed nasal root, flat philtrum, large mouth with down-slanting lips, high-arched palate and micrognathia, and large and dysmorphic earlobes). There were also severe scoliosis, camptodactyly of hand and arm joints, pes cavus, and arthrogryposis of elbows, knees, ankles, and toes. Laboratory investigation showed increased serum transaminases and gamma-GT. Serum Tf IEF showed a type 1 pattern, and genetic testing revealed two ALG3 mutations: the c.564_566del CCT mutation and the combination of mutations c.1125G>A (p.Met375Ile) plus c.1127delC. She died at age 22 months with pulmonary infection and respiratory failure.

Patient 4

This girl was born to unrelated healthy parents after a 37 weeks pregnancy. The birth weight was 2,560 g (50th centile); length was 46 cm (50th centile); head circumference was 31 cm (<3rd centile); and APGAR at 1′ and 10′ was 9 and 10. From day 1 of life, she experienced daily clonic seizures, with cyanosis and oxygen desaturation (<92%) and burst suppression EEG pattern indicative of Ohtahara syndrome. Different AEDs were used (levetiracetam, valproate, diazepam, and clonazepam) without benefit.

At 3 months of age, neurological examination showed axial muscle hypotonia, weakness, hyperreflexia, and severe dysphagia; there were some dysmorphic features, as frontal bossing, short philtrum, and inverted nipples. The head circumference was 34 cm (<3rd centile). At that time, she suffered daily motor partial complex seizures, often with secondary generalization and oxygen desaturation. EEG showed multifocal anomalies, mainly on anterior areas, and brain MRI impaired myelination. Profound psychomotor disability, microcephaly, severe axial hypotonia, and intermittent dystonia of the arms were present. Swallowing impairment requested nose tube feeding since age 6 months. She died at age 10 months with pulmonary infection and respiratory failure. Because of a positive screening test for CDG by serum Tf IEF, mutation analysis of putative CDG genes showed a compound heterozygosity of ALG1 gene c.1076C>T (p.S359L) c.1250_1251insTG: (p.A418Efs*18).

Discussion

Epilepsy is reported in almost one-third of patients with PMM2-CDG (Monin et al. 2014), and it is generally controlled with one or more AEDs. On the other hand, the retrospective evaluation of this series of CDG patients shows that epilepsy can be the first and prominent sign of non-PMM2-CDG. They presented with epileptic encephalopathy within the first weeks of life. In the same 9-year period, we observed 122 EOEE patients, and thus these four account for the 3.3% of them. On the other hand, if we consider also the five cases of CDG-Ix still without a definitive molecular diagnosis, the incidence of CDG among EOEE in our center increases to 5%. In the present four CDG patients, epileptic seizures at onset included myoclonic and clonic fits and focal seizures with desaturation, apneic spells, and bradycardia. With time, all patients developed recurrent and intractable seizures, principally tonic–clonic seizures, infantile spasms, and myoclonic seizures. Electrophysiological correlates included focal and multifocal epileptic discharges, slowed background rhythm, and generalized epileptic activity including burst suppression pattern and status epilepticus. Associated neurological findings were severe developmental disability, acquired microcephaly, generalized hypotonia, and, in some, dyskinetic limb movements. Three out of four subjects died at an early age ranging from 6 to 30 months.

Among the *N*-glycosylation disorders, ALG6-CDG is the most frequent type, after PMM2-CDG. Fifty four cases have been described (review in Jaeken et al. 2015a). Although in most patients the neurological/epileptic phenotype is reported as a unique entity, it appears that most patients have epilepsy with early onset (between 5 months and 2 years). As illustrated by patient 1, ALG6-CDG epilepsy is difficult to treat and has variable features including tonic–clonic, partial complex, atonic, as well as myoclonic seizures. MRI brain findings frequently include corpus callosum hypoplasia; cerebellar involvement was described in one-third of cases (Barone et al. 2014).

The patient with DPM2-CDG started epileptic myoclonus on the sixth day of life, passing to generalized tonic fits associated with myoclonic jerks when she was 20 months old. Two other DPM2-CDG patients were reported so far: they both had severe epilepsy with focal and/or generalized seizures at 3 and 5 months, respectively (Barone et al. 2012).

The ALG3-CDG patient started to present epilepsy at age 1 month. She had been initially labeled with Pena–-Shokeir syndrome because of her peculiar dysmorphisms with arthrogryposis. She was the first reported CDG-Ix patient with a malformation syndrome (Fiumara et al. 2002). Since the first description, in 1999, ALG3-CDG was identified as a severe epileptic syndrome with neonatal onset and absent psychomotor development. Moreover, microcephaly; skeletal malformations, resembling those observed in the present patient; and ophthalmological anomalies were described (Korner et al. 1999). Nine patients have been reported (review in Riess et al. 2013). They all presented microcephaly, neonatal-onset intractable seizures with multiple patterns (West syndrome, tonic–clonic seizures, or combined types), and various degrees of corpus callosum involvement. Cerebral and/or cerebellar atrophy can be present.

Our ALG1-CDG patient had epileptic encephalopathy with electroclinical features of the Ohtahara syndrome. Severe hypotonia, dystonic posture of limbs, and swallowing impairment were additional features. At the time of writing, 19 ALG1-CDG patients have been reported (review in Jaeken et al. 2015b). Their clinical spectrum ranges from early-onset severe cases with rapid fatal outcome to milder, long-surviving cases. Most reported patients experienced intractable epilepsy with onset between birth and 8 months. Multifocal EEG activity and sharp wave pattern were observed. Stupor, probably masking status epilepticus, was also described in terminal patients (Rohlfing et al. 2014).

In addition to ALG6- (OMIM: 603147), ALG3- (601110), ALG1- (608540), and DPM2-CDG (603564), other *N*-glycosylation disorders in which epilepsy is usually severe and difficult to treat are DPM1- (603503), MPDU1- (608799), ALG2- (607906), DPAGT1- (608540), ALG12- (607143), ALG8- (608104), ALG9- (608776), ALG11- (613666), and RFT1-CDG (612015). They all are defects of *N*-glycan assembly located in the endoplasmic reticulum, leading to underoccupancy of *N*-glycosylation sites of glycoproteins (Clayton and Grünewald 2009). In addition, seizures have been reported in patients with dolichol biosynthesis defect SRD5A3-CDG (62379) and DOLK-CDG (610768) and in CDG-II including GCS1- (606056), SLC35C1 (266265), B4GALT1- (607091), COG1- (611209), COG4- (613489), COG5- (613612), COG6- (606977), COG7- (608779), COG8- (611182), and ATP6V0A2-CDG (219200). Recently, SLC35A2-CDG (de novo mutation in X-linked UDP-galactose transporter) due to defective galactosylation of glycoconjugates in the Golgi was identified by whole-exome sequencing (WES) in patients with West syndrome, dysmorphic features, and absence of hepatic and coagulation features usually observed in CDG (Ng et al. 2013; Kodera et al. 2013).

Pathophysiology of epilepsy in CDG is undoubtedly complex (defective glycosylation of signal transducers such as receptors, ion channels, etc.) and will not be discussed here. In early-onset epilepsy, a CDG has to be considered particularly in the presence of dysmorphic features and/or

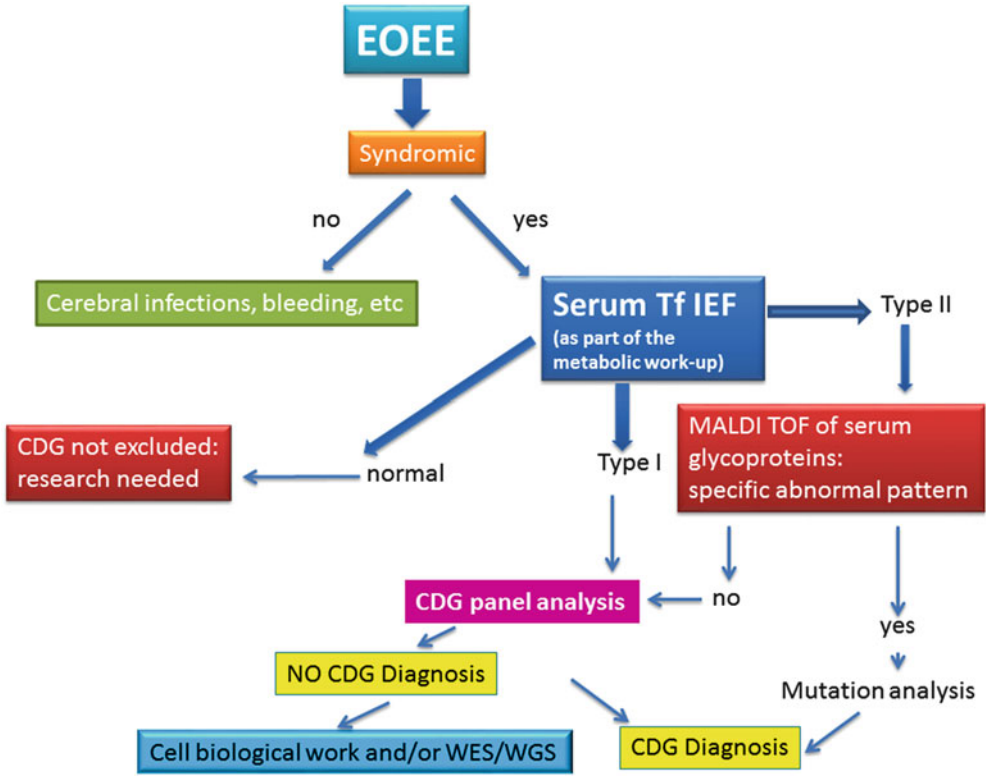

Fig. 2 EOEE diagnostic flowchart for CDG

signs of multisystemic involvement. We propose to perform serum Tf IEF (or capillary zone electrophoresis) as a first-line screening. The further differential diagnostic approach is depicted in Fig. 2. When serum transferrin IEF is not readily available, the decrease of other glycoproteins, such as haptoglobin, thyroxine-binding globulin, antithrombin III, protein C, and factor XI, can provide a hint to a glycosylation defect.

Compliance with Ethics Guidelines

Conflict of Interest

Agata Fiumara, Rita Barone, Giuliana Del Campo, Pasquale Striano, and Jaak Jaeken declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Details of the Contributions of Individual Authors

Prof. Fiumara wrote the report with the contribution of Prof Barone.

Prof. Jaeken critically revised the manuscript and added his own data.

Dr. Del Campo collected all patients' data and wrote their case reports.

Prof. Striano cared for the electrophysiological aspects and contributed to the manuscript elaboration.

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