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It is organized in partnership with several associations and/or country CDG patient advocates: CDG Australia, CDG Brazil, CDG Czech Republic, CDG Denmark, Foundation of Glycosylation (the FoG) Canada, CDG Denmark, CDG Italy/Ireland, CDG Israel, Les ptits CDG France, CDG Spain, CDG Sweden, CDG USA, CDG UK charity and CDG The Netherlands.

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Unraveling neurologic aspects from a cross-sectional study

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Spanish CDG Group
**A big challenge...**

**Intellectual disability**
- ALG3-CDG, ALG2-CDG, RFT1-CDG, ALG11-CDG, ST3GAL3-CDG, ALG13-CDG, DPM2-CDG, MPDU1-CDG, GCS1-CDG, SLC35C1-CDG, COG8-CDG
- PMM2-CDG and other
- ALG14-CDG, MPI-CDG, GNE-CDG, GFPT1-CDG, PMG1-CDG, DPM3-CDG, SEC23B-CDG, ATP6V0A2-CDG, SLC35D1-CDG, DHDDS-CDG

**Abnormal muscle tone**
- Hypotonia: ALG6-CDG, ALG8-CDG, DPAGT1-CDG, ALG1-CDG, ALG9-CDG, RFT1-CDG, ALG11-CDG, PMM2-CDG, DDOST-CDG, DPM2-CDG, DOLK-CDG, COG1-CDG and GCS1-CDG
- Extrapyramidal: ALG13-CDG
- Spasticity: ALG13-CDG, COG5-CDG
- Involuntary movements: NGLY1-CDG

**Skeletal muscle disease**
- Myopathy: DPM1-CDG, DPM2-CDG, DPM3-CDG (inclusion bodies) PG1-CDG, B4GALT1-CDG
- Myasthenic syndrome: GFT1-CDG, ALG14-CDG (both congenital), GT1-CDG
- Limb girdle dystrophy: GMPPB-CDG

**Ataxia**
- PMM2-CDG, ALG8-CDG, DPM1-CDG, DPAGT1-CDG.

**Peripheral neuropathy**
- DPM1-CDG, PMM2-CDG

**Abnormal head circumference**
- micro
  - GMPPB2-CDG, ALG3-CDG, ALG12-CDG, DPAGT1-CDG, ALG9-CDG, RFT1-CDG, ALG11-CDG, ALG13-CDG, DPM1-CDG, DPM2-CDG, DOLK-CDG, SLC35C1-CDG, COG1-CDG, COG2-CDG, COG4-CDG, COG5-CDG, COG8-CDG
- Macro
  - Man1B1-CDG

**Epilepsy**
- GMPPB-CDG, ALG3-CDG, ALG12-CDG, ALG13-CDG, DPM1-CDG, ALG9-CDG, GT1-CDG.

**Limb girdle dystrophy**
- GMPPB-CDG, ALG8-CDG, DPM1-CDG, DPAGT1-CDG.

**Abnormal muscle tone**
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**Ataxia**
- PMM2-CDG, ALG8-CDG, DPM1-CDG, DPAGT1-CDG.
CDG in Spain

- PMM2-CDG (67)
- DPMI-CDG (4)
- DPAGT1-CDG (4)
- ALG1-CDG (2)
- COG8-CDG (1)
- COG4-CDG (1)
- DOLK-CDG (1)
- PGM1-CDG (1)
- RFT1-CDG (1)
- SRD5A3-CDG (1)
- SSR4-CDG (1)

(Numerals indicate the number of cases for each condition.)
National network for PMM2-CDG

H Hospitals included in the project supported by the Spanish Ministry of Health

H Hospitals not included in the project supported by the Spanish Ministry of Health but participating in the network.

AIMS

1) To **develop and validate scales** designed for the quantification of severity of neurological symptoms in children and adults,
2) To validate a volumetric method for the study and **monitoring of cerebellar involvement** through magnetic resonance image
3) To **study of the correlations** among the diverse clinical, radiological, biochemical and molecular issues of patients suffering PMM2-CDG
4) To develop a professional national network to **unify clinical practice and share knowledge and guidelines**

2015-2017
Cerebellar syndrome

Cerebellar involvement is a regular feature of PMM2-CDG. At birth, most children have marked hypotrophy of the vermis and cerebellar hemispheres, followed by progression towards atrophy.

Many key neurological symptoms found in PMM2-CDG patients can be explained by this cerebellar syndrome:

- ataxia,
- dysmetria,
- tremor,
- abnormal eye movements,
- dysarthria, slurred speech and
- cognitive deficits or low intelligence quotient (IQ)

Motor disturbance assessment

Neuroimaging evaluation

Is this neuroimaging progression real?
Does it correlate with a measurable clinical worsening?
Is this progression pointing toward a therapeutic window?

Psychometric evaluation

Do PMM2-CDG patients show a well-defined cognitive profile?
Is there a cognitive or behavioural phenotype to be described?

Is the motor phenotype improving with time?
Does motor disturbance correlate with a measurable clinical worsening?
Can we measure and detect changes due to a potential therapy?
The cerebellum, while once considered a brain region principally involved in motor control and coordination, is increasingly associated with a range of neuropsychological and neuropsychiatric presentations.

Do PMM2-CDG patients show a well-defined cognitive profile? Is there a cognitive phenotype to be described?
Why clinical assessment?

• Because we need to **quantify and detect improvements or worsening** of the condition with time.

• **Therapeutic agents** are under development, and clinical evaluation will require a standardized score of cerebellar dysfunction.

• The problem: Ataxia rating scales have been **developed and normed on adults**.

• The nervous system of the young child is still developing, and age-dependent achievement of fine motor skills, coordination, concentration, and muscle force can influence the interpretation of rating scale scores in a manner unrelated to the actual disease itself.

• Brandsma et al *Dev Med Child Neurol*. 2014;56(6):556-63) showed that the ataxia scores may be useful in **children older than 4**, taking into account that scores improve with age in the young, healthy child...

• **But the very young child (<4) cannot complete** all the components of the larger battery of tests, and the young child with an immature nervous system does not yet have a fully coordinated motor system.
Ataxia assessment in children older than 4

ICARS and ICARS subscores were significantly different between patients and controls.

To evaluate inter-observer agreement in patients’ ICARS ratings, intraclass correlation coefficients (ICC) were calculated. Interobserver agreement of ICARS was “almost perfect” (ICC=0.99),

ICARS internal consistency was evaluated using Cronbach’s alpha and resulted “good” (Cronbach’s-α=0.72).
ICARS evaluation in patients and controls

Figure 1a:
ICARS: Patients' mean 41.1 vs Controls' mean 1.3 (p<0.01)
Postural gait subscore: Patients' mean 16.3 vs Controls' mean 0.4 (p<0.01)
Kinetic subscore: Patients' mean 20.2 vs Controls' mean 0.8 (p<0.01)
Dysarthria subscore: Patients' mean 3.5 vs Controls' mean 0.1 (p<0.01)
Oculomotor subscore: Patients' mean 1.7 vs Controls' mean 0.1 (p<0.01)
Ataxia assessment in children younger than 4?

Aim 2016:

To develop and validate an ataxia rating score for infants and toddlers

Big efforts from the Ataxia Foundation (US) during the last years... no scale at the present time
Volumetric MRI available in 13 children

- Comparison between age-matched controls and patients

MRI: Male patient. 7 years
ICARS 18/100 (mild)
Volume: 40.4 cm³

MRI: Healthy control. 7 years
Volume: 119 cm³
Volumetric MRI: cerebellar atrophy progression

MRI Saggital & Coronal. 15 months

Cerebellar volume 15 months: **62.2 cm³**
Age matched control: **75.5 cm³**

MRI Saggital & Coronal. 8 years ICARS 16/100

Cerebellar volume 8 years: **55.1 cm³**
Age matched control: **121.5 cm³**
Volumetric MRI: cerebellar atrophy progression

- In all the PMM2-CDG patients with MRI at different time, a progression in the cerebellar atrophy was observed.
- The progression of the atrophy was evidenced even after the age of ten.

Volume= $29.1\,\text{cm}^3$.  

Volume= $27.5\,\text{cm}^3$. 
Midsaggital vermis versus volumetric

Spearman’s rank correlation coefficient test: $(0.64, p<0.05)$ between MVRD and cerebellar volume ($cm^3$) in PMM2-CDG patients.
The cerebellar atrophy was more evident in those with higher ICARS.
The cerebellar atrophy was more evident in those with higher ICARS.

Inverse correlation between midsagittal vermis relative diameter and ICARS ($r_s -0.85$, $p=0.003$)
A prospective design was performed. We developed two protocols:

### For children older than 5 years...
- WISC-IV (Wechsler Intelligence Scale for Children, 4th Ed)
  - Also including optional test: arithmetic and incomplete figures
  - Span direct digits
  - Span invers digits
- K-BIT (Kaufman Brief Intelligence Test)
- Simbol digits modalities test
- FACES: Perception of differences.
- Visual Motor Integration (VMI)
- Tomal: Test of Memory and Learning
- Stroop Test
- Child Behavior Checklist (CBCL)
- Behavior Rating Inventory of Executive Function® (BRIEF®)

### Younger patients
(less than 5 years old):
- Battelle Developmental Inventory, Second Edition (BDI-2)
- Vineland adaptive behavior scale
Higher ICARS was correlated with more intellectual disability.

Negative correlation between ICARS and IQ

\( r_s = -0.94, \ p = 0.005 \)
Cognitive aspects


Executive functions: plans, abstract rational, verbal fluency, working memory and cognitive flexibility.

Lack of attention, impulsivity, mood disturbances: indifference, disinhibition, quick changes of mood, lack of affection

Language abnormalities rather than those due to the dysarthria: aprosodic, agramatism and anomia.

Slow procession velocity

Memory disturbances

In our limited experience (6 patients older than 5):

  - Lack of attention
  - Slow processing
  - Fatigability

The definition of a cognitive profile in CDG patients will help to adapt academic materials and improve psychological resources for the families.
Families of patients suffering rare diseases share large amount of information about the disease in groups of families and social networks. Unfortunately, big part of this valuable information is not available to be used by doctors/researchers to improve knowledge on that rare disease.

Conversely, doctors use congresses or professional meetings or their e-mail to share experiences and difficulties when treating patients with rare diseases. However, we they do not have a tool to share reflections or doubts with other colleagues in a secure manner or perform group discussions. Many doctors treating rare diseases need help in their process of taking decisions from those doctors with more professional experience. Moreover, clinical guidelines are not always unified or published.
RareCommons is an open website for both patients/families and doctors. It requires registration and an informed consent.

The methodology used in RareCommons is based in the so called «crowdsourced health research studies».

Rare diseases with very low prevalence need the coordination among patients, patients’ associations, health professionals and researchers through the world.

For some of them achieving a critical mass to increase knowledge seems impossible with the traditional approaches.
Families

Benefits & commitments

1. Cooperating in the investigation, providing clinical data
2. Suggesting topics & questions: it will help us to identify the real needs of children and to prioritize our research
3. Providing access to your physicians, so that we can develop a working medical community

1. Improve competence in the management of diseases with information that is accessible, simple, clear but rigorous
2. Close monitoring of the evolution of each child.
3. Improve care of children by facilitating consensus among doctors.
4. Interact and collaborate with other families, participating in a community and creating a genuine support group
¡Hola! Yolanda Scott

How we work

The dynamics of collaboration in Rare Commons

1. The process begins with the reading of a chapter about the origin of the disease. All of the chapters may be read, and each one concludes with a summary of the most important information.

3. While filling in the questionnaire, you will access to support and advice, both from main investigators and from community. They will work with you to help resolve any uncertainties, providing guidelines for contributions.

5. Once your questionnaire is completed, you have the possibility to read the next chapter. Some of the questions in the same always available to complete them with information allowing the monitoring of the condition. For instance, that will be the case of treatments.

Defectos congénitos de la glicosilación (CDG)

1. Los CDG desde el punto de vista celular y molecular
2. Los CDG, la sangre y las alteraciones de la coagulación
3. Los CDG desde el punto de vista neurológico I
4. Los CDG desde el punto de vista neurológico II
5. Gastroenterología y hepatología en el síndrome de CDG
6. Problemas endocrinos y ginecológicos en el síndrome de CDG
7. Problemas renales en el síndrome de CDG
8. Problemas osteoarticulares en el síndrome de CDG
9. La cardiopatía en los CDG
10. Manifestaciones oftalmológicas en los CDG
11. Trastornos inmunológicos en los CDG
12. Problemas de conducta y aprendizaje en los CDG
13. La piel en los CDG
Cuestionario de neurología

Parto

Datos antropométricos al nacimiento

- **Peso**: 400 g
  - Introduce el peso en gramos.

- **Longitud**: 40.0 cm
  - Introduce la altura en centímetros.

- **Perímetro craneal**: 40.0 cm
  - Introduce el perímetro de la cabeza en centímetros.

Problemas de prematuridad

- **Problemas de prematuridad (<37 semanas)**
  - Ninguno
  - Distrés respiratorio
  - Hemorragia periventricular
  - Enterocolitis necrotizante
  - Displasia broncopulmonar
  - Otro...

GUAÑAR BONITAS | PÁGINA SIGUIENTE →
Clinicians

Benefits & commitments

1. Cooperate in the research of the disease by providing clinical data and personal experiences in your clinical practice.
2. Suggest new questions or work areas based upon hypotheses and personal clinical experience.
3. Enable access to your patients so that we may construct samples that are large enough to be statistically relevant.

1. Register of your patients
2. A close structured work forum in which questions and uncertainties may be addressed, hypotheses may be discussed.
3. Bibliography and documentation of interest: up-to-date listings of scientific articles published in the relevant domains, organized and classified by affected organs and bodily systems.
4. The opportunity to develop scientific papers resulting from the analysis and interpretation of the data gathered in the project.
DOCTORS COMMUNITY

- Online Library specialized on rare diseases
- Work forum for sharing and discussing on clinical cases
- Patient questionnaires
- Medical information
CDG Community: 56 patients and their doctors (invited by patients)

54 PMM2-CDG patients (52 from Spain)

1 COG8-CDG patient

Congenital Disorders of Deglycosylation
1 NGLY1-CDG patient
First symptoms

- Neurological
- Gastrointestinal
- Ophtalmological
- neurol. and gastroent.
**Liver disease**

- **Stroke-like**
  - Sí: 30%
  - No: 70%

- **Trombosis y hemorragias**
  - Sí: 13%
  - No: 87%

**HALLAZGOS RENALES**

- No
- Proteinuria
- Quistes
- Nefromegalia
- Nefrocalcinosis
- Ectasia pielélica
ENDOCRINOLOGY

- **Subclinical hypothyroidism**
  - **Sí**
  - **No**

- **Cryptorchidism**
  - **Sí**
  - **No**

- **Hypoglycemia**
  - **Sí**
  - **No**

- **Delayed puberty**
  - **Sí**
  - **No**
Social Network and comments/questions area

Secure place to share experiences, doubts and feelings with other families
TEAM TOGETHER EVERYONE ACHIEVES MORE
Foundation Glycosylation (FoG) is the official sponsor of the videos targeted to the “SSIEM Official Satellite Symposia – Second World Conference on Congenital Disorders of Glycosylation (CDG): a challenging story of sugar trees”:

The Foundation Glycosylation (FoG) founded by Duncan Webster (Canada), is the official sponsor of the videos of all oral session that will be given during the conference. This material will be available in the Youtube channel dedicated to “SSIEM Official Satellite Symposia – Second World Conference on Congenital Disorders of Glycosylation (CDG): a challenging story of sugar trees” at:

For more information about the work of this organization which is focused on research to ALG9 -CDG (CDG -1L), visit the following link: http://www.thefog.ca/main.html

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