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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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CDG and the Cerebellum
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Functions of the Cerebellum (*Little Brain*)

- Motor control
- Learning new motor skills
- Higher cognitive functions
- Emotional reactivity
Structure of the Cerebellum

Spinocerebellum
Motor execution

Neocerebellum
Motor Planning

Vestibulocerebellum
Eye movements
Balance
Main cerebellar clinical signs

- Hypotonia
- Ataxia
- Dysmetria
- Nystagmus
Congenital Disorders of Glycosylation with Emphasis on Cerebellar Involvement

Rita Barone, MD, PhD¹  Agata Fiumara, MD, PhD¹  Jaak Jaeken, MD, PhD²

CDG
Genetic diseases of the synthesis of the glycan moiety of glycoproteins and glycolipids.

Nervous system affected in almost 80% CDG
Cerebellum affected in

PMM2-CDG
SRD5A3-CDG
Dystroglycanopathies (regularly affected)

Other CDGs
Cerebellar Atrophy (CA)
Normal cerebellar structure in presence of loss of cerebellar tissue

Brain MRI (normal cerebellum)  PMM2-CDG
<table>
<thead>
<tr>
<th>Onset</th>
<th>Disease</th>
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<tbody>
<tr>
<td>0–1y (infancy)</td>
<td>Pontocerebellar hypoplasia types 1 and 2</td>
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<tr>
<td></td>
<td>Infantile neuroaxonal dystrophy</td>
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<td>Pelizaeus–Merzbacher disease</td>
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<td><strong>Congenital disorders of glycosylation</strong></td>
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<td></td>
<td>Infantile-onset spinocerebellar ataxia</td>
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<td>Cockayne syndrome</td>
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<td></td>
<td>Neuronal ceroid lipofuscinosis (infantile)</td>
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<td></td>
<td>Spinocerebellar ataxia, autosomal recessive with axonal neuropathy</td>
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<td>Mevalonate kinase deficiency</td>
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<td>3-Methylglutaconic aciduria</td>
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<td>Salla disease</td>
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<td>Progressive encephalopathy with oedema, hypsarrhythmia, and optic atrophy</td>
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<td>1–2y (late infancy)</td>
<td>Hypomyelination with atrophy of the basal ganglia and cerebellum</td>
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<td>Ataxia telangiectasia</td>
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<td>Marineco–Sjögren syndrome</td>
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<td>Neuronal ceroid lipofuscinosis (late infantile)</td>
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<td>2–18y (early and late childhood)</td>
<td>Ataxia with oculomotor apraxia 1</td>
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<td>Ataxia with oculomotor apraxia 2</td>
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<td>Ataxia-telangiectasia-like disorder</td>
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<td>Spastic ataxia of Charlevoix–Saguenay</td>
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<td>Cerebrotendinous xanthomatosis</td>
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<td>Myoclonic epilepsy of Unverricht–Lundborg disease</td>
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<td>Coenzyme Q10 deficiency</td>
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<td>Episodic ataxia 1</td>
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<td>CACNA1A-related disorders</td>
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<td></td>
<td>Leukoencephalopathy with ataxia, hypodentia, and hypomyelination</td>
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<tr>
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<td>Juvenile-onset dentatorubral pallidolysian atrophy</td>
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<tr>
<td></td>
<td>Neuronal ceroid lipofuscinosis (late infantile/juvenile)</td>
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<td>Variable</td>
<td>Late-onset GM2 gangliosidosis</td>
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<td>Mitochondrial</td>
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<td>Spinocerebellar ataxia (s)</td>
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<td>Niemann–Pick disease type C</td>
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<td>Adrenoleukodystrophy</td>
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Radiological Appearance of Cerebellum in CDG

Cerebellar atrophy

«Bright cerebellum» appearance

Olivopontocerebellar atrophy

Dandy-Walker-like malformation
PMM2-CDG
The most frequent N-glycosylation disorder

Cerebellar signs in PMM2-CDG

Early signs
Unusual jerky, conjugate oscillation of the eyes

Later signs
Truncal titubation when sitting, dysmetria, slurred speech (dysarthria), gait ataxia

Cerebellar involvement is the most constant feature of PMM2-CDG
A nationwide survey of PMM2-CDG in Italy: high frequency of a mild neurological variant associated with the L32R mutation

Rita Barone · M. Carrozzi · R. Parini · R. Battini · D. Martinelli · M. Elia · M. Spada · F. Lilliu · G. Ciana · A. Burlina · V. Leuzzi · M. Leoni · L. Sturiale · G. Matthijs · J. Jaeken · M. Di Rocco · D. Garozzo · A. Fiumara

37 subjects studied with PMM2-CDG: all have cerebellar involvement

Severe phenotype (N: 21)

Mild phenotype (N: 16)
A novel cerebello-ocular syndrome with abnormal glycosylation due to abnormalities in dolichol metabolism

Eva Morava,¹,²,³, Ron A. Wevers,¹,³,⁴, Vincent Cantagrel,⁴ Lies H. Hoefsloot,⁵ Lihadh Al-Gazali,⁶ Jeroen Schoots,⁵ Amo van Rooij,¹ Karin Huijben,³ Connie M. A. van Ravenswaaij-Arts,⁷ Marjolein C. J. Jongmans,² Jolanta Sykut-Cegielska,³ Georg F. Hoffmann,⁹ Peter Bluemel,¹⁰ Maciej Adamowicz,¹¹ Jeroen van Reeuwijk,⁵ Bobby G. Ng,¹² Jorinde E. H. Bergman,⁷ Hans van Bokhoven,⁵ Christian Kömer,¹⁰ Dusica Babovic-Vuksanovic,¹³ Michel A. Willemsen,¹⁴ Joseph G. Gleeson,⁴,† Ludwig Lehle,¹⁵,† Arjan P. M. de Brouwer⁵,† and Dirk J. Lefeber¹,³,¼

- Developmental delay
- Visual impairment
- Cerebellar atrophy

Mild to severe cerebellar abnormality

SRD5A3-CDG
MALDI-TOF analysis of permethylated N-glycans from serum glycoproteins

**Deficiency of Golgi-localized UDP-galactose transporter SLC35A2**

**Galactosylation deficiency**

- Developmental Delay
- Epilepsy
- Systemic involvement
- Cerebral/Cerebellar atrophy
SLC35A2-CDG

Courtesy Dr. P. Striano, Genoa
Cerebellar Atrophy (CA)

Predictors of Outcome

- Isolated CA better than CAplus (other brain malformations)
- Progression of CA
- Transverse Cerebellar Diameter
Clinical Assessment of Cerebellar symptoms/signs in patients with CDG

Ataxia
ICARS (International Cooperative Ataxia Rating Scale) (Serrano et al., 2015)

Motor disability
SDFS (spinocerebellar degeneration functional score) (Monin et al., 2014)

Ability of daily living (ADL)
Clinical Assessment of Cerebellar symptoms/signs in patients with CDG

Ability of daily living (ADL) scale*

Domains
Speech, swallowing, ability to feed self, dressing, sitting, walking, frequency of falls, bladder function, and self-hygiene.

Scores
Range from 0, indicating normal function, to 36, indicating very severe functional disability

*Subramony et al., 2005
Radiological assessment of the Cerebellum (biometry) in PMM2-CDG

1. Transverse Cerebellar Diameter

2. Tegmento vermian angle

3. Craniocaudal height of the vermis

4. Anteroposterior measurements
Larger size of the transverse cerebellar diameter was correlated with better functional outcome in children with cerebellar atrophy.

Al-Maawali et al., 2013
Natural history of cerebellar volume loss in CDG

- Rare documentation of “normal” cerebellum in the prenatal/newborn period
- Cerebellar volume regresses within the first months or years of life and remains almost unchanged over many years

![Images showing cerebellar volume change from 9 months to 7 years](Image)

9 months  7 years
Pathological studies of the cerebellum in PMM2-CDG show a loss of cerebellar cells (green circle).

Glycosylation is important both for cerebellar neuronal development and for neuronal survival.
Outcome of development in CDG patients with cerebellar hypotrophy

**Natural history studies in patient cohorts with CDG**

Almost half of patients with PMM2-CDG acquires an independent walking

Clinical assessment tools should be defined

Systematic application of biometric cerebellar measures

Genotype and glycophenotype association studies
Children's Hospital

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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](http://www.thefog.ca/main.html)

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