Treatment in Congenital Disorders of Glycosylation

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Multisystem involvement in CDG

Congenital anomalies
Intellectual disability
Neuropathy
Balance problems
Low tone/weakness
Spasticity
Developmental delay
Seizures
Stroke like events

Cardiomyopathy
Pericardial effusion
Bleeding disorder
Thrombosis

Osteopenia
Joint contractures
Kyphosis/scoliosis

Recognizable face
Abnormal eye movements
Retinal pigmentation
Blindness
Squint
Cataract
Progressive myopia

Hypothyreodism
Hyperinsulinism
Hypogonadism

Failure to thrive
Protein-losing enteropathy
Liver dysfunction
Cirrhosis

Skin disease
Renal tubulopathy
Nephrotic syndrom
Treatment: still symptomatic

- Physical therapy
- Occupational therapy
- Speech therapy
- Seizure control

- Adequate hydration
- Albumin supplement
- Cardiac drugs

- Hormone supplements
- Vitamin supplements
- Tube feeding
- Special diets

- Bleeding and thrombosis prevention
- Osteoporosis prevention
Glycans are sugar chains

- \(\text{Glc}\) = Glc
- \(\text{Gal}\) = Gal
- \(\text{Man}\) = Man
- \(\text{GlcNAc}\) = GlcNAc
- \(\text{Fuc}\) = Fuc
- \(\text{Sia}\) = Sia

**Cell membrane**

**Protein**

**Glycoproteins**
CDG disorders: two types

Missing glycan chains

SUGAR CODE

Galactose
Mannose
Sialic acid

Missing sugars
Glycosylation: Sugar by sugar building the "glycan" chain

Blood

Glucose (cane sugar)  Mannose (cranberry sugar)

Sugar activation is essential for sugar chain synthesis
MPI-CDG (CDG Ib)

MPI

CDG Ib

PMM2

CDG Ia

Mannose supplementation
Clinical presentation in MPI-CDG

- Low blood sugar
- Chronic diarrhea
- Liver disease
- High insulin

Mannose 1 g/kg/day
- No diarrhea
- LFTs normalized
- Normal sugars
- No bleeding anomalies
Galactose therapy
1 g/kg/day
(oral)
Coagulation and anticoagulation factors improve in patients rapidly.

- Normal Antithrombin III: 75-135%
- Normal Factor XI: >70%
- Normal Factor XIII: 75-155%
UDP-Galactose Transporter SLC35A2

shortened extremities
growth failure
developmental delay
cerebellar hypoplasia

D-galactose 1-1.5 g/kg/day
## Laboratory analysis

<table>
<thead>
<tr>
<th>Test</th>
<th>Nov 2015</th>
<th>Jan 2016</th>
<th>March 2016</th>
<th>April 2016</th>
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<tbody>
<tr>
<td>ALAT (&lt;39 U/L)</td>
<td>13</td>
<td>23</td>
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<tr>
<td>ASAT (&lt;56 U/L)</td>
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<tr>
<td>Antithrombin III (101-131%)</td>
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<td>106</td>
<td>101</td>
<td>116</td>
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<tr>
<td>PT (&gt;70%)</td>
<td>91</td>
<td>112</td>
<td>120</td>
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</tbody>
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Significant improvement in seizure control
Treatment in CDGs with decreased galactose (milk)sugar in the sugar chain

- PGM1-CDG
- SLC35A2-CDG
- SLC39A8-CDG
- TMEM165-CDG
CDG galactose study in CDGs

Hormone abnormalities
Abnormal liver function
Coagulation defects

Balance problems
Seizures
Stroke-like episodes
Methods

• Every 6 weeks F/U:
  - Liver Function tests
  - Metabolic labs
  - Coagulation and anticoagulation studies
  - Endocrien Labs., Lipids
  - TIEF, MS/MS, urine gal
• Clin. control
• Liver US

- 18 patients enrolled (PMM2, ALG6, SRD5A3, SLC35A2-CDG, TMEM165-CDG)
- Two TMEM165 patients show biochemical improvement
- One patient ALG6 patient, one PMM2 and 2 SLC35A2-CDG show significant clinical improvement
Sialic acid treatment in GNE

Hereditary inclusion body myopathy

Decreased sialylated glycans in muscle

One months course of iv immunoglobulines containing sialic acids

• Increased muscle strength


Sialic acid treatment in NANS
PMM2-CDG or CDG Ia

Glucose (cane sugar)  Mannose (cranberry sugar)

Blood

Activated mannose

Sugar activation is essential for sugar chain synthesis.
PMM2-CDG (CDG 1a)

- Low muscle tone
- Balance problems
- Squint
- Speech delay
- Seizures

- Feeding difficulties
- Diarrhea/vomiting
- Cardiac disease

- Hormonal abnormalities

- Spasticity
- Balance problems
- Neuropathy

- Constipation
- Thrombosis
- Osteoporosis
- Scoliosis
CDG la: mannose phosphate tx

Abnormal hormones
Liver function and coagulation problems
Balance problems
Epilepsy
Stroke-like episodes
Glycomine’s Approach to Therapy for CDG-la

- Mannose-1-Phosphate (Man-1-P or M1P), the missing substrate, is not cell membrane permeable
- Glycomine delivers M1P into cells via liposomes, hence the name Lipo-M1P
- Liposomes are nano-vehicles composed of lipids that resemble the cell membrane
- Liposomes enclose the hydrophilic (water loving) M1P for intracellular delivery into affected tissues
Lipo-M1P Restores GDP-Man Deficiency in CDG-Ia Fibroblasts

CDG-Ia fibroblasts w/ R141H/F119L mutation

GDP-Manose Enhancement (times)

CDG-Ia, untreated
Normal, untreated
CDG-Ia, treated w/ free M1P
CDG-Ia, treated w/ Lipo-M1P
Lipo-M1P Preliminary Safety Assessment in Rats

- A study on maximum tolerated dose in rats was conducted.
- The highest allowable volume did not elicit any signs of toxicity.
- Glycomine is currently conducting repeated dose studies in rats.
- 9-month long IND-enabling safety and toxicology studies in rats and dogs are scheduled to begin in early 2018.

NATURAL HISTORY TRIALS WILL START ALL OVER THE WORLD
Examples for organ transplantation

DOLK1-CDG: heart

MPI-CDG: liver

CCDC115-CDG: liver

PGM3-CDG: bone marrow
Examples for organ transplantation

- DOLK1 - CDG: heart
- MPI - CDG: liver
- TMEM198 - CDG: liver
- PGM3 - CDG: bone marrow

Nonalcoholic cirrhosis

Focusing on quality of life in CDG