Glossary dedicated to CDG Symptom Prioritization Questionnaire – (CDGSPQ)

WHO DEVELOPED THIS PROJECT?

This project is developed under the scope of **CDG & Allies – Professionals and Patient Associations International Network (CDG & Allies – PPAIN)** and led by Dr. Vanessa Ferreira, Prof. Dr. Paula Videira and Prof. Luísa Barros. We had the support of experts like Pf. Dr. Jaak Jaeken, Pf. Eva Morava, Dr. Mercedes Serrano, Andrea Miller (CDG Care), Merell Lidlle (CDG Australia), Claudia Vazquez (CDG USA) and CDG & Allies - PPAIN colleagues. CDG & Allies-PPAIN is a unique international patient-led network focused on increasing CDG knowledge and ultimately, contributing to future therapies and better management of CDG.

HELP CONTACT:

If you need help, please do not hesitate to contact us asking for help related to this survey at https://worldcdg.org/contact. We will be available to schedule a SKYPE, WhatsApp CALL, or Zoom meeting.

PMM2-CDG medication and food supplements
There is no specific treatment for **gastroenterological dysfunction** in PMM2-CDG patients. ● Antacids are used to avoid gastroesophageal reflux. More information HERE
There is no specific management for the **endocrine abnormalities** in PMM2-CDG patients. ● L-thyroxine supplementation only for patients with clinical **hypothyroidism** and biochemical hypothyroidism (elevated TSH, low free thyroxine and decreased FT4 levels). ● Oral diazoxide to treat **hyperinsulinemic hypoglycemia**. ● Hormonal replacement therapy (HRT) in case of **hypogonadism and delayed sexual development in women** can be initiated cautiously to decrease risk of **osteoporosis**, considering the thromboembolic risk associated with some of HRT. The preferential HRT to reduce this risk is natural estrogen by the dermal route. More information HERE
There is no specific treatment for **skeletal abnormalities** in PMM2-CDG patients. ● Treatment of **fractures** resulting of **osteopenia** and **osteoporosis**: calcium and vitamin D supplementation and consideration of treatment with bisphosphonate in case of vertebral compression fractures or recurrent low impact fractures. More information HERE
Seizures in PMM2-CDG patients are managed with anti-epileptic drugs. Most of the patients are treated with a single anti-epileptic drug. Examples of antiepileptic drugs are midazolam, lorazepam, levetiracetam, valproic acid, carbamazepine, and oxcarbazepine. More information HERE
There is no specific treatment for the **stroke-like episodes (SLE)** in PMM2-CDG patients. ● During acute phase of SLE antiepileptic drugs are used to improve seizures and focal deficits. In this phase, Benzodiazepines (midazolam, lorazepam) are recommended. During prophylactic phase of SLE, most common antiepileptic drugs such as levetiracetam, valproic acid, carbamazepine, and oxcarbazapine have been used. But there is no evidence for efficacy in preventing new SLE. ● During the acute phase of SLE, antiaggregants or anticoagulants are recommended. There is no evidence for the safe continuous use of antiaggregants (e.g. acetylsalicylic acid) to prevent SLE except in recurrent SLE. More information HERE.
Acetazolamide (AZA) has been suggested to treat stroke-like episodes in familial hemiplegic

migraine (FHM) patients with gain-of-function mutations in CACNA1A gene coding for the CaV2.1 channel and was repurposed for PMM2-CDG patients because they show gain-of-function in CaV2.1channel due to deficient N-glycosylation. AZA is a carbonic anhydrase inhibitor that probably changes the intracellular pH, and therefore the transmembrane potential. Lower pH values reduce the potassium conductance of the neuron membrane and inactivate the CaV2.1 channel showing a gain of function. AZA is safe and improves **cerebellar syndrome** in PMM2-CDG. Its ability to prevent stroke-like episodes and its long-term effects on kidney function should be addressed in PMM2-CDG. More information HERE.

Epalrestat is an oral formulation of an aldose reductase inhibitor (ARI) that has been used for the treatment of diabetic neuropathies. Due to its safety and ability to improve the symptoms of neuropathy this drug was repurposing for PMM2-CDG patients. Epalrestat is an activator of PMM2 enzyme activity with the potential to treat **peripheral neuropathy** and correct the underlying enzyme deficiency in a majority of pediatric and adult PMM2-CDG patients. More information HERE.

To manage a **coagulopathy** during surgery, international clinical guidelines for PMM2-CDG suggests the prophylactic use of fresh frozen plasma or prothrombin complex concentrate (PCC) depending on:

- The levels of clotting factors and inhibitors and the hemorrhagic risk of the surgical procedure.
- The levels of protein C and protein S, as PCC contain these proteins. More information HERE

International clinical guidelines for PMM2-CDG suggests the use of a curative and prophylactic antithrombotic therapy for the **thrombotic event**:

- Individualized dose of low molecular weight heparin (LMWH).
- Antithrombin concentrate in case of antithrombin deficiency, when the dose adjustment of LMWH is difficult.
- Rivaroxaban as alternative prophylaxis in LMWH nonresponsive patients. More information HERE

Infections in PMM2-CDG patients must be treated according to good standards of care:

- Appropriate antibiotic administration, and close patient follow-up until infection remission.

- When infection is not responsive to antibiotic therapy considers intravenous administration of immunoglobulins.

Vaccines should be administered in PMM2-CDG patients, except in cases of medical history of adverse reactions or non-response to the vaccine. More information HERE

There is not a validate specific treatment for PMM2-CDG patients.

- The efficacy of dietary supplementation with mannose to treat **PMM2-CDG signs and symptoms** has been a controversy between CDG researchers and physicians. More information HERE, HERE and HERE.
- Mannose-1-phosphate pharmacological formulation using liposomes as the delivery system, to treat **PMM2-CDG signs and symptoms** (Clinical trials: Clinical Natural History Study Protocol in PMM2-CDG (CDG-Ia); ID number: NCT03173300).

MPI-CDG medication and food supplements

To treat **hypoglycaemia,** international clinical guidelines for MPI-CDG recommend:

- Oral mannose (isolated or in combination with other approaches).
- Hyperinsulinaemic hypoglycaemia can be managed by frequent feedings and by adding complex carbohydrates to the diet. It can also be treated by diazoxide (contraindicated in pregnancy).
- Severe acute hypoglycaemia should be treated with intravenous glucose to keep blood glucose over 4 to 6 mmol/L.
- Patients not fed orally and with acute states (e.g. gastrointestinal tract infections and perioperative time) should have continuous glucose infusion to keep blood glucose concentration above 4 mmol/L.
- In life-threatening situations must be considered to combine IV glucose and mannose, but with extreme caution due to the potential side effects. Note that is required high doses of glucose infusion to avoid neurological symptoms, due to hypoglycaemia. More information HERE.

To treat the **coagulopathy** and **other haematological complications,** international clinical guidelines for MPI-CDG recommend:

- Oral mannose (isolated or in combination with other treatments).

- Unfractionated heparin or low-molecular-weight heparin can treat thrombosis. Particularly in case of digestive ulcerations and/or oesophageal varices, treatment with vitamin K antagonist should be considered carefully, due to the risk of bleeding.
- For severe bleeding can be used in local haemostatic procedures. Moreover, reduced levels of coagulation factors can require fresh frozen plasma. Infusion of factor XI concentrate or recombinant factor VIIa (rFVIIa) is not recommended due to the high risk of thrombotic complications.
- The management of coagulopathy during surgery must consider the levels of clotting factors and inhibitors (especially AT and FXI), the hemorrhagic and the thrombotic risk of the procedure. In case of reduced plasmatic levels of AT and/or FXI can be necessary prophylactic use of fresh frozen plasma, or AT concentrate. Factor XI concentrate or rFVIIa infusion is not recommended due to the high risk of thrombotic events. More information HERE.

To treat **digestive signs and symptoms** (e.g. recurrent vomiting, diarrhoea, failure to thrive and protein-losing enteropathy (PLE) with hypoalbuminaemia), international clinical guidelines for MPI-CDG recommend:

- Oral mannose (isolated or in combination with other approaches). However, intravenous albumin supplementation may be needed before clinical and biochemical normalisation.
- Parenteral nutrition may be necessary for severely undernourished patients with chronic diarrhoea or recurrent vomiting. More information HERE.

Oral mannose does not treat the **liver signs symptoms** of the MPI-CDG (e.g. mild hepatopathy, hepatomegaly, hepatic fibrosis, portal hypertension with or without oesophageal varices and hepatopulmonary syndrome). Liver transplantation was performed in one patient and could be required in selected cases (e.g. patients with hepatopulmonary syndrome due to portal hypertension). More information HERE.

International clinical guidelines for MPI-CDG recommend that the **secondary seizures** (e.g. hypoglycaemic convulsions) must be treated according to the underlying aetiology, and highlight that chronical antiepileptic treatment is usually not necessary. More information HERE.

International clinical guidelines for MPI-CDG recommend regular administration of IV or SC immunoglobulins in patients with **hypogammaglobulinaemia**. More information HERE.

Note:

- The **main side effects of mannose therapy** were abdominal pain and diarrhoea (in 40% of patients) and improved either spontaneously or with a dose adjustment. **Intravenous mannose** treatment caused in severe haemolysis in one patient and severe neurological symptoms in another. More information HERE.

PGM1-CDG medication and food supplements
There is no specific management for **congenital malformations** in PGM1-CDG patients. For **cleft palate** and **Pierre-Robin sequence** should be followed the standard care procedures (e.g. surgical repair). More information HERE.
There is no specific treatment for the **psychomotor delay** and/or **learning disabilities** in PGM1-CDG besides early physical and speech therapy. International consensus guidelines for PGM1-CDG suggest diet or treatments to prevent **central nervous system (CNS) damage secondary to hypoglycemia (e.g. secondary seizures)**, although this relationship is not clear. More information HERE.
Ophthalmologic abnormalities (e.g. strabismus, abnormal eye movements, nasolacrimal duct obstruction, and/or epiphoria) are rare in PGM1-CDG and should be treated individually, including surgery, if necessary. More information HERE.
There is no specific management for **endocrine dysfunction** in PGM1-CDG patients (e.g. hyperinsulinemic, and also with ketotic hypoglycemia, hypogonadotropic hypogonadism, hypocortisolism, and delayed puberty). To manage the **hypoglycemia** the International consensus guidelines for PGM1-CDG recommend: ● Frequent feedings and complex carbohydrates. ● Intravenous bolus of 10% dextrose followed by a continuous glucose infusion, in case of acute hypoglycemia. ● D-Galactose supplementation ● Continuous tube feeding in young infants. ● The oral administration of uncooked corn starch before bedtime between 6 months and 3 years age, and use of modified cornstarch (Glycosade) in children over 3 years.

- Oral diazoxide therapy, in case of hyperinsulinemic hypoglycemia.

D-galactose supplementation has a positive impact in **hypogonadism**, **delayed puberty** and in the **low level of serum follicle-stimulating hormone (FSH)**, in PGM1-CDG patients.

Growth hormone therapy can improve **growth problems** from some PGM1-CDG patients. More information HERE.
L-thyroxine is recommended to treat clinical **hypothyroidism**.

Cortisol supplements are indicated for **hypocortisolism** treatment. More information HERE.

There is no specific treatment for **cardiac problems** in PGM1-CDG (e.g. cardiomyopathy, specifically dilated cardiomyopathy). Treatment of cardiac manifestations is based on current clinical practice and guidelines. More information HERE.

D-Galactose treatment decreases **high levels of serum transaminases**, associated with liver problems, in PGM1-CDG patients. Also, to prevent this and other **liver involvement** (e.g. steatosis, cholestasis, fibrosis, and episodes of acute hepatic failure) should be avoided hepatotoxic (damaging or destructive to liver cells) medication. More information HERE.

There is no standard specific treatment for **coagulation anomalies** in PGM1-CDG (e.g. antithrombin III deficiency, factor VII, IX, X, XI, and XIII deficiency, reduced protein C and S as well as increased PT and prolonged aPTT).

- Standard protocols should be followed, considering the clinical status and history of the patient.
- D-Galactose treatment normalizes **antithrombin III levels** in some patients. More information HERE.

Dietary D-galactose supplementation has a positive effect on following **skeletal muscle manifestations**: **exercise intolerance**, **fatigability**, **reduction of creatine kinase elevation** and **rhabdomyolysis**. The rhabdomyolysis treatment should be focused at prevention of kidney failure and electrolytes abnormalities. More information HERE.

Note:

- The International consensus guidelines for PGM1-CDG recommend the use of **anesthetic agents** with caution, particularly depolarizing muscle relaxants and

volatile anesthetic agents, as the halothane was associated with malignant hyperthermia.

- As **high doses of galactose treatment** might not be tolerated in all patients, should be carefully administered/monitored.
- The effect of Galactose supplementation was studied in nine PGM1-CDG patients in a pilot study (clinicaltrials.gov NCT02955264). More information HERE.

CAD-CDG medication and food supplements
Uridine supplementation in CAD-CDG patients has ceased **seizure**, improved **alertness**, **communication**, and **cognitive and motor development**, and normalized of **biochemical parameters**. More information HERE.

MAGT1-CDG medication and food supplements
A MAGT1-CDG patient has been reported to be on oral Mg2+ therapy, but unfortunately, no patient follow-up has yet been reported. More information HERE.

PIGM-CDG medication and food supplements
The administration of sodium butyrate in a PIGM-CDG patient ceased **seizure** and allow the acquisition of previously lost capabilities. More information HERE.

PIGO-CDG medication and food supplements
Oral administration of vitamin B6 (pyridoxine) has made a PIGO-CDG patient **seizure**-free. More information HERE.

SLC35A2-CDG medication and food supplements
Galactose supplementation normalized the **transferrin glycosylation profile** in a SLC35A2-CDG patient. More information HERE.

SLC35C1-CDG medication and food supplements
Fucose therapy in SLC35C1-CDG patients, characterized by Bombay blood type due to lack the α1,2-fucosylated H-antigen, induced the expression of the **H antigen** in one of two patients. Furthermore, some patients have not shown any therapeutic benefit. These differences in therapy response could depend on the mutational background, residual enzymatic function, overall clinical severity or cellular mislocalization. More information HERE.

TMEM165-CDG medication and food supplements
Daily intake of Galactose led to improved **biochemical parameters** and **N-glycosylation** in two TMEM165-CDG patients harboring the same homozygous mutation and with normal Mn2+ levels. However, two different mutations R126H and E108G exhibited altered Mn2+ sensitivity, suggesting the potential impact of distinct genetic alterations on therapy responses. More information HERE.

SLC39A8-CDG medication and food supplements
Combined treatment with Galactose, Uridine, and Mn2+ in two SLC39A8-CDG patients improved **glycosylation** after 2 weeks. A treatment only with Galactose and uridine in a SLC39A8-CDG patient, with a severe phenotype, also showed considerable normalization of the **glycosylation** profile. Mn2+ monotherapy for over 12 months in two SLC39A8-CDG patients showed significantly improved **biochemical and clinical manifestations**. More information HERE.

CCDC115-CDG medication and food supplements
Two CCDC115-CDG siblings with hepatosplenomegaly, elevated serum transaminases and alkaline phosphatase performed liver transplantation. One of them rejected the transplant twice and died, while the other normalized of **serum aminotransferase levels** and **transferrin glycosylation** profile.

Liver transplant is an approved therapy in Europe for CCDC115-CDG patients. More information HERE.

ATP6VAP1-CDG medication and food supplements
Liver transplant is an approved therapy in Europe for ATP6VAP1-CDG patients. More information HERE.

DOLK-CDG medication and food supplements
DOLK-CDG patients with **mild dilated cardiomyopathy** either have been treated with supportive heart failure therapy (ACE inhibitors, β blockers and diuretics) or received heart transplants, because of rapid deterioration. Heart transplantation is an approved therapy for DOLK-CDG patients. More information HERE.

PGM3-CDG medication and food supplements
Hematopoietic stem cell transplantation from cord blood and bone marrow has been described as a treatment for two PGM3-CDG affected children with severe **immunodeficiency**. This therapy is approved for these patients in the USA. More information HERE.

GNE-CDG medication and food supplements
The effect of N-acetylmannosamine (ManNAc) in GNE-CDG patients has been studied in phase 1 and 2 clinical trials (clinicaltrials.gov NCT01634750 and NCT02346461). The administration of Aceneuramic Acid Extended-Release (Ace-ER) Tablets with a proper formulation has been studied in phase 1, 2 and 3 clinical trials (clinicaltrials.gov NCT01359319, NCT01517880 and NCT02736188). The phases 1 and 2 showed an increase

of **serum-free SA levels**, with significant improvement of **muscle strength in the upper extremities** and no serious adverse effects.

The therapeutic effects of immune globulin were studied in 4 GNE-CDG patients (clinicaltrials.gov NCT00195637). Patients only improved for approximately three weeks. More information HERE.

