Raising awareness about Congenital Disorders of Glycosylation (CDG) Affordable tests and treatments exist

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INTRODUCTION

- Congenital Disorders of Glycosylation (CDG) are rare inherited diseases with aberrant protein glycosylation, initially described by Jaeken *et al.* in 1980 in Belgium [1].
- Every newly synthetized proteins will transit to the secretion pathway *i.e.,* the endoplasmic reticulum and the Golgi apparatus. Any disturbance of this highly regulated machinery can lead to a CDG.
- The majority has an autosomal recessive transmission,
- Mutations are mostly in genes coding for glycosylation enzymes, nucleotide-sugar transporters, cofactors, pH homeostasis of the secretory pathway.
- Currently, more than 160 different CDG have been characterized [2].

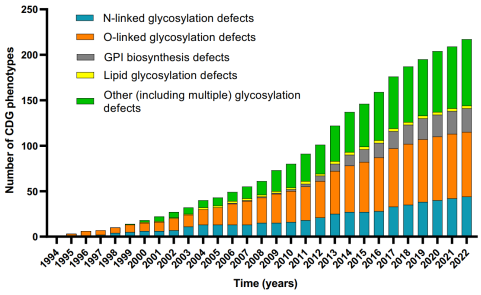

Fig.1 Exponential increase in CDG characterization over time [2]

- Clinical phenotypes are heterogeneous and hard to predict.
- Among them: hypotonia, developmental delay, cerebellar ataxia, intellectual disability, seizures, encephalopathy, microcephaly, facial dysmorphia, lipodystrophy, inverted nipples, failure to thrive, short stature, hepatomegaly, coagulation disorders, hypoglycemia, cardiomyopathy, strabismus, nystagmus, gastrointestinal signs, frequent infections, endocrine disorders (e.g., hypothyroidism, hypogonadism)…

Fig. 2 Various pictures of CDG patients (respectively PMM2-, SSR4-, TMEM165-CDG) [3-4]

BIOCHEMICAL SCREENING

- Diagnosis can be complex. Any patient with unexplained neurological signs, especially when others organs are affected can be suspected as CDG.
- They are classically identified using isoelectrofocalisation (IEF), HPLC or capillary electrophoresis (CE) of transferrin. These methods separate transferrin regarding to its glycosylation status.
- Compared to control serum **(A)**, the type 1 profiles **(B)** present an elevation of 2-sialotransferrin and 0-sialotransferrin fractions, while the type 2 profiles **(C)** present an elevation of 3- 2- 1-sialotransferrin fractions.

1) IEF

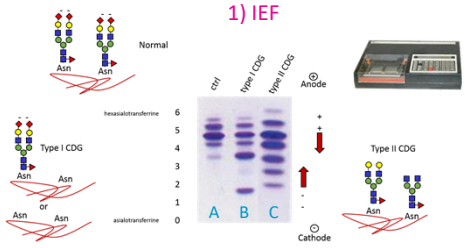

Fig. 3 Isoelectric focusing profiles of CDG

2) Capillary electrophoresis

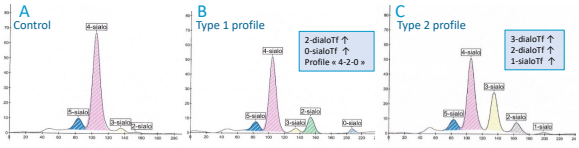

Fig.4 Capillary electrophoresis profiles of transferrin in CDG

→ Advantages: these analyzers can also be used for other analyses, such as the separation of other proteins and the screening and monitoring of chronic alcohol consumption

3) Western Blot

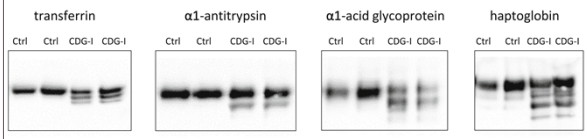

Fig. 5 Western patterns of serum N-glycoproteins

- Transferrin, α1-antitrypsin, α1-acid glycoprotein, and haptoglobin in CDG-I affected individuals typically display additional bands of decreased molecular weights on Western Blot (**fig.5**)
- Complementary biochemical methods exist, such as two-dimensional gel electrophoresis of N-glycoproteins
- Emerging markers such as O-glycosylated apolipoprotein C-III, Bikunin and Antithrombin can help refine the diagnosis [5]
- CDG-II affected individuals can be characterized by glycans mass spectrometry

→ The diagnosis is confirmed using genetic analysis
Panels, WES, WGS

CDG in Lebanon

- The worldwide prevalence is estimated to reach 1/20 000-50 000 births
- The prevalence of inborn errors of metabolism, including CDG, is potentially higher in country like Lebanon
- 67% of reported genetic diseases are associated with consanguinity
- In Lebanon, the overall consanguinity rate can reach up to 35.5%
- 1 case in a retrospective review of charts of patients referred to the Inherited Metabolic Diseases Program at the American University of Beirut Medical Center (AUBMC) between 2015 and 2018. **ALG12-CDG** (type 1) sent to Germany cf D.O Salman et al. (2022) [6]
- 1 family **RTF1-CDG** (type 1) reported in https://cdgcare.org/ worldmap

THERAPEUTICS

- The first French TMEM165-CDG treated by manganese supplementation since 2022 showed improved growth and glycosylation status [4].
- National guidelines for mannose supplementation for MPI-CDG patients are published in 2020 and today 15 patients are followed in France [6]. Mannose at low doses could be safe during pregnancy.
- The first French PGM1-CDG patient treated by galactose supplementation showed improvement of the transferrin glycosylation profile, transaminases and coagulation factors levels.
- PMM2-CDG (CDG-Ia) is the most common CDG that affects 1000 patients worlwide. The use of Acetazolamide DIAMOX® improves stroke-like syndrome. [7]

TAKE HOME MESSAGE

- Data about CDG are missing for many Mediterranean countries (as well as most countries in Africa, Asia and South America)
- Their prevalence is linked to consanguinity → underestimation
- Biochemical screening is easily implementable for most middle-income countries (IEF, WB)
- Patient affected by particular CDG subtype can benefit of simple and affordable treatments than can be life changing
- Samples can be sent to reference laboratories abroad for complementary analyses

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