5th World Conference on CDG for families and professionals

ONLINE EVENT, 13-16 MAY 2021

#WCCDG2021

Organised by the Portuguese Association for CDG (APCDG) and CDG & Allies Professionals and Patient Associations International Research Network (CDG & Allies PPAIN), and in collaboration with our Global CDG community (families, patient groups and professionals).

17:45 – 19:30 PM Lisbon, Portugal **(a break will be done)**	**Panel of discussion 9: How to best serve the CDG community across countries? Key challenges and solutions by stakeholders views.** **Talk Title and corresponding Speaker(s) 1 (15 minutes) :** How to best serve the CDG community across countries? Key challenges and solutions by stakeholders views, by Vanessa Ferreira (Portugal) **Lightning to Posters session** This is the chance for conference participants to listen about pioneering work in CDG. **Poster presentation (s) (3 minutes):** Clinical case with a new type CDG-Ix from Bulgaria, Malina Stancheva-Ivanova (Bulgaria). **Round table discussion with Panelists facilitated by Moderator (s) (~45 minutes):** Eleonora Passeri, Vanessa Ferreira (Portugal), Rita Francisco (Portugal) and Madalena Parrado (Portugal) **Moderators supported by:** Marta Falcao, Madalena Abade, Joana Grilo, Tiago Martins and Madalena Raposo from Sci and Volunteer Program FCT NOVA 2021. **Panelists & Special Rare Disease Expert:** **Poster presenters are also invited to share views during the round table.** Some experiences and views when living with CDG (or when working in the field of CDG/rare diseases) will be shared. • Family and/or Patient Group Perspective: Tata Tsintsadze (CDG Georgia) • Family and/or Patient Group Perspective: Juliana da Silva Ferreira (Brasil) • Family and/or Patient Group Perspective: Etienne Barrier (Estonia) • Family and/or Patient Group Perspective: Adamastor Kemmler (Brasil) • Family and/or Patient Group Perspective: Paul Collot (México)

Clinical case with a new type CDG-Ix

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Abstract

The authors report a 4 years and 6 months boy suspected of having congenital disorder in glycosylation because of an intrauterine growth retardation, failure to thrive, severe protein-caloric malnutrition, elevated liver transaminases, dyslipidemia, hypoalbuminemia and hypoglycemia, hypothyreoidism, nanism, facial dysmorphysm, muscle hypotonia, mental retardation, liver cysts, membraneous MCD, hypoplasia of corpus callosum, olfactory bulbs and cerebellar pons, dysmorphic frontal lobes.
The patient underwent a detailed analysis of blood serum *N*-glycoprofile by MALDI-TOF mass spectrometry because the result from the standard CDG-isoelectric focusing of serum transferrin glycoforms (IEF-TF) was ambiguous. MALDI-TOF analysis of permethylated serum *N*-linked glycans revealed the presence of a family of aberrant high-mannose *N*-linked glycans (HexNac1Hex5 – HexNac1Hex8) with only one *N*-acetylglucosamine (HexNac) in the N-glycan core. Further experiments with Endoglycosidase H, which cleaves *N*-linked glycans between the two *N*-acetylglucosamine residues, confirmed the hypothesis of a metabolic deficiency of the *N*-glycosylation pathway, presumably in the early stages of the endoplasmatic reticulum.
The whole exome sequencing identified variants for which the evidence is currently too limited to determine whether they can be pathogenic and are classified as variants of uncertain clinical significance.

Fig.1.3 year old boy with CDG-Ix **Fig.2.**

Fig.2. Result of IEF of serum transferrin. O-asialo-, 1-monosialo-,2-disialo-, 3-trisialo-, 4-tetrasialo-, 5-pentasialo-,6-hexasialotransferrin.

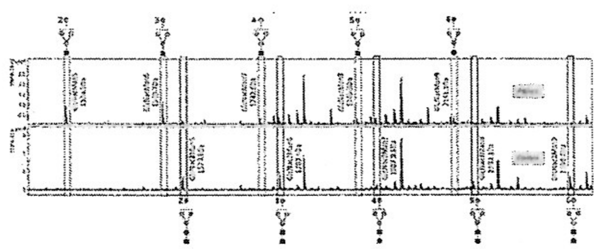

Fig.3.Analysis of patient blood serum N-glyocoprofile by MALDI-TOF of permethylated serum N-glycans determined:
- **a family of aberrant high-mannose N-linked glycans with only one N-acetylglucosamine (HexNac) in the N-glycan core,**
- **absence or low intensities of high-mannose N-linked glycans containing two N-acetylglucosamines in their core, which is usually reported in healthy controls**

Introduction

Congenital disorders of glycosylation (CDG) is a rapidly expanding group of more than 150 rare genetic, metabolic disorders due to defects in a complex biochemical process – glycosylation, discovered first by Jaak Jaeken. CDG can be associated with a broad variety of symptoms and can vary in severity from mild cases to severe, disabling or life-threatening cases. Transferrin and apolipoprotein CIII isoform analysis are the initial screening tests for CDG .Total N-glycan analysis by MALDI-TOF is used for global assessment of glycosylation. Even small differences in the glycan profile can be indicative of a different type of CDG.

Methods and Materials

Clinical methods: family history, history of disease, consultation with specialists.
Psychological methods: Denver II screening test, Developmental profile 3 test, CAB, RIAS-2 test,
Radiological methods: radiography of wrist for bone age, echography of abdomen, MRT of head,
Neurophysiological methods: EEG, Echocardiography,
Otoneurological methods: OAE testing,
Endocrinological methods-hormonal analysis,
IEF of serum transferrin and apolipoprotein C III
MALDI-TOF mass spectrometry,
Whole exome sequencing of proband.
Material: serum, fibroblast culture, EDTA blood

Results

The authors report a 4 years and 6 months boy suspected of having CDG because of:
► Intrauterine growth retardation, failure to thrive,
► Severe protein-caloric malnutrition,
► Elevated liver transaminases, dyslipidemia, hypoalbuminemia, hypoglycemia, hypothyreoidism,
► Nanism, facial dysmorphysm,
► Muscle hypotonia, vivid reflexes, Babinski (+) bilaterally, autonomous atactic gait, mental retardation, hypoplasia of corpus callosum, olfactory bulbs and pons, dysmorphic frontal lobes.
► Liver cysts, membraneous MCD.
Currently he is treated with L-Thyrox, Regulatius Pro kids kids, Aminocode jet glutathion spray.

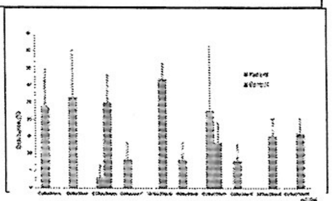

Fig.4. Relative percentage representation of high mannose N-glycan structures with GlcNac2Man3 core respectively with aberrant GlcNacMan3 calculated based on three replicates of patient`s serum sample and three age-matching negative controls.

The patient underwent a detailed analysis of blood serum *N*-glycoprofile by MALDI-TOF mass spectrometry because the result from the standard CDG-isoelectric focusing of serum transferrin glycoforms (IEF-TF) was ambiguous. MALDI-TOF analysis of permethylated serum *N*-linked glycans revealed the presence of a family of aberrant high-mannose *N*-linked glycans (HexNac1Hex5 – HexNac1Hex8) with only one *N*-acetylglucosamine (HexNac) in the N-glycan core. Further experiments with Endoglycosidase H, which cleaves *N*-linked glycans between the two *N*-acetylglucosamine residues, confirmed the hypothesis of a metabolic deficiency of the *N*-glycosylation pathway, presumably in the early stages of the endoplasmatic reticulum.
The whole exome sequencing identified the following variants for which the evidence is currently too limited to determine whether they can be pathogenic and are classified as variants of uncertain clinical significance: heterozygous variant c.2995A>G (NM_001846.2) in gene COL4A2, heterozygous variant c.2717 (NM_005270.4) in gene GLI2, heterozygous variant c.920C>T(NM-0011287223.1 in gene SCN11A), heterozygous maternally inherited variant c.2170G>A (NM_033004.3) in gene NLRP1 and maternally inherited variant c.790delT(NM_033004.3) which causes a frameshift at position 264 in aminoacid sequence coded by NLRP1.

Discussion

The authors report a clinical case with CDG-Ix with metabolic deficiency of the N-glycosylation pathway presumably in the early stages of the endoplasmic reticulum with prenatal onset of the disease. The child has nanism and hypotrophy with preserved growth velocity, delayed bone age (-2SD). He has slowly progressing intellectual development but delayed for the age. After the introduction of Regulatius pro Kids the hypoglycemia stopped and a normalization of liver transaminases was observed. NGS was withdrawed. The hypothyreoidism is compensated with L-Thyrox. The hypoechogenic lesions of the liver persist without worsening during treatment with hepatoprotector drug and glutathion.
The whole exome sequencing identified variants of uncertain significance in gene COL4A2, GLI2, SCN11A), The heterozygous maternally inherited variant c.2170G>A (NM_033004.3) (evidence category PM2, PP3) in gene NLRP1 and maternally inherited variant c.790delT (NM_033004.3) in gene NLRP1 with possible AD inheritance is predicted to result in a loss of function of the affected copy of the gene and has possible role in the pathogenesis of the disease. The NLRP1 protein is involved in the assembly of a inflammasome which is implicated in a variety of clinical conditions such as auto-inflammatory diseases, neuro-degeneration, metabolic disorders and the development of cancers. The role of inflammasome in protein glycosylation isn`t still elucidated.

Conclusions

1.The authors report a clinical case with CDG-Ix with metabolic deficiency of the N-glycosylation pathway presumably in the early stages of the endoplasmic reticulum.
2.Further discussion and evaluation of the necessity to use whole genome sequencing are needed to prove the clinico-genetic correlations of the candidate CDG genes.

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