Clinical manifestations and management in adults with congenital disorders of glycosylation.

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Adult CDG

- Patients diagnosed in infancy or childhood followed to adulthood
- Newly diagnosed CDG in adult age
PMM2 CDG 37 cases
– Age range 11-68 yrs
– 19/37 adults (19-68 yrs)

DPM2 3 pz
ALG1 2 pz (1 adolescent)
ALG 6 1
ALG3 1
Slc35 1
CDG Ix
CDG IIx
Adult CDG
main concerns

- Coagulation
- Eyes
- Skeletal
- Nervous System
• Eyes
  – Strabism
  – Retinitis pigmentosa
  – ERG
ASSESSMENT OF SKELETAL STATUS IN PATIENTS WITH CONGENITAL DISORDER OF GLYCOSYLATION TYPE IA

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Summary: Congenital disorder of glycosylation (CDG) type IA (phosphomannomutase deficiency) is the most common of a group of inherited metabolic disorders that are due to defective glycosylation of glycoproteins. CDG-IA is clinically characterized by major nervous system involvement and various organs are affected to a variable degree. Common clinical findings are skeletal changes including peculiar thoracic deformity and joint restriction, while a major radiological feature is diffuse osteopenia. The aim of this study was to measure bone density and biochemical markers of bone turnover in three patients with CDG-IA, whose age ranged between 14 and 27 years. We found that bone mass, as judged by standard densitometry, quantitative computed tomography and ultrasonography, was lower in patients than in age- and sex-matched healthy controls. Biochemical indexes of bone resorption including free pyridinoline levels in serum and pyridinoline and deoxypyridinoline urinary excretions were normal, whereas bone formation markers (serum osteocalcin and serum bone-specific alkaline phosphatase) activity were increased. These results suggest that low bone density is a component of CDG-IA, which should be considered among inherited metabolic diseases with decreased bone mass. We hypothesize that hypoglycosylation of noncollagenous bone proteins may contribute to the osteopenia observed in these patients. From a clinical point of view, our observation shows that bone density measurements can provide a quantitative assessment of bone involvement in such diseases.

Introduction

Congenital disorders of glycosylations (CDG), formerly known as carbohydrate deficient glycoprotein syndromes, are an expanding group of inherited metabolic diseases characterized by defective synthesis of the carbohydrate moiety of glycoproteins (1, 2). They are diagnosed biochemically by serum transferrin isoelectric focusing, which shows an increase of cathodal bands due to hypoglycosylated isoforms. CDG-IA, the most common of these disorders, is due to phosphomannomutase-2 enzyme deficiency. This leads to defective synthesis of GDP-mannose, which is required in the early N-glycan biosynthetic pathway (3). The phosphomannomu-

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Pre-OB

CaSR + Other?

↑ Replication

Osteoblasts

↑ Bone Matrix Synthesis

Pre-OC

↑ OPG

↓ RANKL

RANK

↓ Differentiation

Osteoclasts

↓ Activity

↑ Apoptosis

CaSR

Brennan, CTI, 2006 (ECTS 2006)
Bisphosphonates inhibit osteoclast activity, and promote osteoclast apoptosis.

Bisphosphonates may modulate signaling from osteoblasts to osteoclasts:
- Increased OPG production
- Decreased RANKL expression

Bisphosphonates are concentrated under osteoclasts during bone resorption.

New bone formation.
Bleeding stroke like thrombosis
Together, coagulation, anti-coagulation, and fibrinolysis maintain a delicate physiological balance.
NS in Adult CDG

Classic PMM2

- Gait ataxia 11/11
- Intellectual disability
  - Mild 1/11
  - Moderate 1/11
  - Severe 9/11
- Stroke like 6/11
- Cerebellar Hypoplasia 11/11
- Epilepsy 4/11
- Peripheral neuropathy 2/11

Milder phenotype L32R/-

- Walking unaided 6/8
- Intellectual disability
  - Mild 3/8
  - Moderate 5/8
- Stroke like 0/8
- Moderate 5/8
- Epilepsy 0/8
- Peripheral neuropathy 0/8
SYMPTOMATIC MANAGEMENT
OF PMM2-CDG (CDG-1a)

WHAT IS CDG?
Complex Glycogen Storage Disease (CDG) is a group of diseases among the rarest known genetic diseases. CDG is a group of disorders caused by
the breakdown of glycogen, a type of sugar found in the liver and muscles.

RECOMMENDED ANNUAL SURVEILLANCE
(for more information when indicated):
- Eye examination:
  - Complete visual assessment by a specialist
  - Field assessment (if visual fields tested, report for abnormalities)
- Renal function tests: Serum creatinine, serum uric acid, electrolytes

AGENTS/CIRCUMSTANCES TO AVOID
Acetaminophen and other agents metabolized by the liver should be used with caution.
Avoid Reassurance (less of severe side effects).

HOW MANY PMM2-CDG PATIENTS ARE KNOWN?
Since many cases are unrecognized or misdiagnosed, it is difficult to determine the real number of patients. PMM2-CDG (CDG-1a) is the most common.

The prevalence may be as high as:
1 in 20,000

WHAT ABOUT PMM2-CDG TREATMENT?
Currently, there is no specific treatment for PMM2-CDG but research into the illness is ongoing in various centers.

SYMPTOMATIC TREATMENTS
Below, the scheme summarizes the symptomatic treatments for CDG.

POSSIBLE INTERVENTION BY A PHYSICIAN
- Consider managing the diet of patients with CDG to reduce the severity of chronic diarrhea, feeding issues, and other gastrointestinal symptoms.
- Consider using a formula instead of milk products.
- Glasses, patching, or other vision therapy.
- Speech therapy.
- Counseling consultation with a speech therapist, gastroenterologist, or nutritionist.
- Bisphosphonate therapy in severe forms.
- Corticosteroids and/or calcium, peptic acid drainage.
- Surgical treatment in severe forms.
- L-Tyrosine supplementation.

CDG FAMILIES AND PROFESSIONALS UNITED
TO BOOST RESEARCH AND ACHIEVE THERAPIES

This resource is brought to you by the PMM2-CDG Association (CDG-1a) and requires a rare metabolic disease expert.

For more information or to get involved, visit www.PMM2CDG.org. Contact: info@PMM2CDG.org. Help support research by donating on the website. Thank you for your support. PMM2-CDG Association (CDG-1a).
Keep assistance in Pediatrics?

- Bureaucratic complication (unappropriate admissions)

Transfer patients to Adults Medicine?

- Patient and family disappointment (feeling of abandon, broken sameness)
- Worse compliance to therapies and prescriptions
Adolescents

- Physical changes, Emotional feelings
- Isolation → depression
- Increased risk of inappropriate behaviour
- Poor compliance → feeling different from peers
- Low self esteem
Hampers in Transition

- **Sanitary system:** Inactivity due to stability.
  - Rosen DS Cancer 1993, Johnson CP P Annals 1995

- **Pediatrician:**
  - Doesn’t want to lose the patient *(even doesn’t think about)*

- **Adults Physician:**
  - No specific experience: the new “hard to handle patient”
    requests much time and availability
    - AAP 2000; Earl DT Prim Care 1998

- **Patient/ Family/care givers:**
  - Anxiety, missing referral doctor, feeling of being dropped
    - Viner R Hosp Med 2000
Why Start preparing?

• Changing is difficult
• Be informed helps
• Start talking in advance
• Every patient should be assured an assistance
  – Warranting safety
  – Age appropriated
  – Targeted to the maximum benefit
Transition pitfalls

- Identify adult specialist able to take care of the CDG patient based on his/her specific ability and knowledge
- Involve him/her early in follow up
- Arise interest (showing that, although rare, CDG can present for the first time in adult medicine without being recognized)
- Organize meetings on CDG cases
- Give all information about the clinical history of the patient
Transition as seen by the patient: main concerns

- **Adult Physicians might have no experience and scarce knowledge on metabolic diseases starting in infancy.**
- Feeling unsafe
- Hardly recognized psychological troubles
- Need for highly specialized Physicians
- Adult Doctors often do not like to care adolescents
- Feeling of life end
- Patients and their families request the same degree of assistance they had in Pediatrics

- Peter et al, 2009
Ideal transition

- Adults Physician goes to see the new patient in Pediatrics
- The Pediatrician follows the patients in the moment of his first enrollement in the Adult medicine dept.

The Pediatrician takes part of the new team
The new caring Doctor takes part of the old team
• Have we official guidelines?
• In order to prevent or foresee
  – Known complications, evolution
  ✓ Adolescent troubles, sexuality, nutrition, physical activity
May offer separate paediatric, (adolescent), adult services - in one primary care unit.