Cardiovascular Endocrinology

PATHOPHYSIOLOGY OF CARDIOMETABOLIC DISEASE

Effect of Growth Hormone Replacement on Metabolic Profile and Vascular System in Adult Patients with Congenital Hypopituitarism

Isabela Peixoto Biscotto, MD, PhD candidate[1], Valeria Hong, MD, PhD[2], Luiz Bortolotto, MD, PhD[3], Luciani Renata Silveira Carvalho, MD,PHD[4].

[1]Unidade de endocrinologia do desenvolvimento, Disciplina de Endocrinologia, Departamento de Clínica Médica do Hospital das Clínicas da Faculdade de Medicina da Universidade São Paulo, Sao Paulo, Brazil, [2]Unidade de Hipertensão, Instituto do Coração, Hospital das Clínicas da Faculdade de Medicina da Universidade São Paulo., Sao Paulo, Brazil, [3]Unidade de Hipertensão, Instituto do Coração, Hospital das Clínicas da Faculdade de Medicina da Universidade São Paulo., Sao Paulo, Brazil, [4]Hosp das Clinicas, Sao Paulo, Brazil.

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Introduction: Growth Hormone (GH) stimulates two distinct processes: anabolic effect of GH on growth through IGF1, and catabolic effect of GH stimulating lipolysis. GH deficiency (GHD) in adulthood is characterized with abnormal body composition, impairment of physical capacity and lipid and glycemic metabolism, beyond increase cardiovascular risk (CVR) factors. While in acquired hypopituitarism, GHD is always associated with CVR in several studies and demonstrated human recombinant growth hormone replacement (hrGHr) improves CVR. In congenital hypopituitarism (CH), however, the consequences of GHD and hrGHr in adulthood are unclear. Objective: To evaluate daily hrGHr in metabolic profile and vascular system in adult patients with CH. Patients and Methods: Fifty-nine adults with CH were selected for the study. They were divided into 2 groups: 1- hrGHr: 15 male, 17 female with median age 35,8 yrs, hrGHr in adult life with 7.2 yrs median time in the dose of approximately 1U per day in order to keep IGF1 in the normal range for age and sex; 2- Without hrGHr: 12 male, 15 female with 38,4 yrs median age and without hrGHr in adult life of 10.6 yrs median time. Thirty-two healthy volunteers were selected as controls. Anthropometric parameters, dual-energy X-ray absorptiometry (DXA), lipid and glycemic profile, and structural and functional parameters of the arterial vessels (carotid intima media thickness, arterial stiffness and flow mediated dilation) were evaluated and compared between the groups. Results: In patients with rhGHr the abdominal waist/height (AW/H) ratio (0,49 ± 0,06), the fat percentage (30,7 ± 10,4) and fat index (7,6 ± 3,7) were lower than the group without replacement (p= <0,001, p= <0,001 and p= 0,028, respectively). The low values of the CA/H ratio, fat percentage and fat index were independent of the diagnosis ACTH deficiency with corticosteroid replacement. Higher triglycerides (111,7 ± 62,4) and lower HDLc (49,5 ± 19,1) levels in patients without hrGHr compared to controls (p= 0,020 and p= 0,005, respectively) were observed. There was no statistical difference between glycemic profile, metabolic comorbidities and structural and function parameters of the arterial vessels between groups and controls. Conclusions: GHD in CH does not lead to accelerated premature atherosclerosis and arteriosclerosis. The hrGHr in adults with CH have beneficial effects on lipid profile and body composition and hrGHr in adulthood should be individualized.

Genetics and Development (including Gene Regulation)

ENDOCRINE DISRUPTING CHEMICALS

Endocrine Disruption by Phthalate Exposure in the Pediatric Intensive Care Unit

An Jacobs, MD[1], Adrian Covaci, PhD[2], Govindan Malarvannan, PhD[2], Giulia Poma, PhD[2], Inge Derese, BSc[1], Pieter Wouters, MSc[1], Sascha Verbruggen, MD PhD[3], Gonzalo Garcia Guerra, MD MSc[4], Philippe G. Jorens, MD PhD[2], Koen Joosten, MD PhD[3], Greet Van den Berghe, MD PhD[1], Ilse Vanhorebeek, MEng PhD[1].

[1]KU Leuven, Leuven, Belgium, [2]University of Antwerp, Antwerp, Belgium, [3]Sophia Children's Hospital, Rotterdam, Netherlands, [4]University of Alberta, Edmonton, AB, Canada.

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Aim: Pediatric intensive care relies on plastic indwelling medical devices softened by phthalates. Phthalates leach into the circulation and concerns about toxicity were raised. Exceeding a certain threshold of di(2-ethylhexyl)phthalate (DEHP) exposure in the pediatric intensive care unit (PICU) has been associated with an attention deficit 4 years later (1). Moreover, DEHP and its metabolites have endocrine disrupting properties. Critically ill children reveal the non-thyroidal illness syndrome (2) and unexplained relatively low cortisol (3). Whether DEHP exposure in PICU has endocrine disruptive effects is unknown. We investigated whether DEHP exposure in the PICU, exceeding the previously identified "toxic" threshold for attention, is independently associated with thyroid- and HPA-axis alterations upon PICU discharge. **Methods**: In this preplanned secondary analysis of the PEPaNIC RCT (N=1440) (4), plasma DEHP metabolite concentrations (MEHP, 5OH-MEHP, 5cx-MEPP, 5oxo-MEHP) were quantified for all patients with a last PICU day sample (N=920). Minimal DEHP exposure was defined as the product of the total DEHP metabolite concentrations on the last PICU day and duration of PICU stay, with 0.551 µmol/L.days identified as "toxic" threshold (1). Serum TSH, total T4, total T3 and rT3 concentrations were quantified for patients with an available last day sample (N=913). For patients with a last day plasma sample and who did not receive corticosteroids (N=391), plasma ACTH, total cortisol, albumin and CBG concentrations were quantified and free cortisol calculated. Multivariable linear regression analyses, adjusted for baseline risk factors and for duration of PICU stay, assessed whether exceeding the previously determined threshold of toxic DEHP exposure was independently associated with the hormone levels on the last PICU day. **Main results**: Median total DEHP metabolite concentration was 0.101 (IQR 0.049 - 0.279) µmol/L on the last PICU day. Minimal DEHP exposure was 0.337 (IQR 0.161 - 0.880) µmol/l.days, and 328 patients (35.7%) exceeded the toxic threshold. Exceeding this threshold was independently associated with lower total T4 (P=0.002), total T3 (P=0.02) and total cortisol (P=0.001), and higher rT3 (P=0.01) concentrations on the last PICU day, but not with TSH, ACTH or free cortisol. **Conclusion**: Critically ill children

had DHEP metabolites in plasma upon PICU discharge and more than a third were exposed to toxic levels. Toxic DEHP exposure was an independent contributor to the severity of the non-thyroidal illness phenotype and to lower cortisol upon PICU discharge. Future research should assess whether such endocrine-disruptive impact of DHEP exposure in the PICU plays a role in the long-term developmental legacy of critical illness in children. 1 Verstraete et al Intensive Care Med 2016 2 Jacobs et al Thyroid 2019 3 Jacobs et al Intensive Care Med 2019 4 Fivez et al N Engl J Med 2016

Neuroendocrinology and Pituitary

PITUITARY TUMORS II

Soluble Alpha Klotho and IGF-I Before Surgery as Prognostic Factors to Acromegaly Long-term Remission

Junia Ribeiro de Oliveira Longo Schweizer, MD, PhD[1], Katharina Schilbach, MD[1], Michael Haenelt, M. A.[1], Xiao Wang, MD[1], Mariana Ferreira Bizzi, MD[2], Alexandre Varella Giannetti, MD, PhD[2], Jochen Schopohl, MD[1], Sylvère Stoermann, MD[1], Beatriz Santana Soares Rocha, MD, PhD[2], Antonio Ribeiro-Oliveira, MD, PhD[3], Martin Bidlingmaier, MD[1].
[1]Klinikum der Universitaet Muenchen - LMU-Ludwig Maximilians Universität, Munich, Germany, [2]UFMG- Federal University of Minas Gerais, Belo Horizonte, Brazil, [3]Ipsen, Boston, MA, USA.

MON-327

Background: Transsphenoidal surgery is the cornerstone of acromegaly treatment. However, cure is obtained in only ~50% of the cases. Until today, no biochemical marker has been identified to preoperatively predict surgical outcome and long-term remission. Recently, soluble alpha klotho (αKL) was proposed as new biomarker for diagnosis and follow-up of acromegaly. Therefore, we aimed to evaluate the potential of pre-surgery αKL concentrations as a prognostic factor to predict remission by surgery alone. **Methods:** We measured αKL concentrations (IBL-ELISA) and classical biomarkers (IGF-I and GH_{random}, both by IDS-iSYS, GH_{nadir} measured by IDS-iSYS (n=13) or DiaSorin-Liaison® (n=7)) in samples from a prospective study in treatment-naïve patients with acromegaly (total n=25). Patients were then followed for at least 6 months after surgery (median (range) 30.1 (6–142) months). Outcome was evaluated and classified as non-remission (NR: IGF-I>1.2xULN (n=2) or continued need for medical treatment with somatostatin analogues (n=10)) or remission (R: improvement on clinical signs and symptoms and IGF-I<1.2xULN without medical treatment, n=13). **Results:** Before surgery, all patients had elevated IGF-I (>1.2xULN), GH_{nadir} (>0.4 ng/mL) and GH_{random} (>1.0 ng/mL). As expected, αKL (pg/mL) was also high (>1.2xULN) in 92% patients. Before surgery, αKL was significantly higher in NR compared to R [6648 (4408–13951) vs. 3389 (2132–6837); p<0.05), as was IGF-I (ng/mL) [NR: 879.7 (771.8–961.5) vs. R: 640.2 (448.6–862.6); p<0.05). There was no difference in GH_{nadir} and GH_{random} (ng/mL) [10.42 (6.35–16.40) vs. 5.19 (1.19–10.70) and 12.39 (8.24–24.87) vs. 8.94 (4.24–15.55); p>0.05 for both comparisons). ROC analysis indicated that concentrations of αKL>4470pg/mL (~3.5xULN) (75% specificity, 62% sensitivity, AUC=0.72) and IGF-I>3.8xULN (67% specificity, 85% sensitivity, AUC=0.79) indicate lack of long-term remission. **Conclusion:** High αKL (>4470pg/mL, ~3.5xULN) and IGF-I (>3.8xULN) concentrations before surgery are significantly associated with persistent disease activity after surgery. However, both biomarkers alone or in combination have insufficient specificity (though acceptable sensitivity) as predictors of surgical outcome.

Tumor Biology

TUMOR BIOLOGY: DIAGNOSTICS, THERAPIES, ENDOCRINE NEOPLASIAS, AND HORMONE DEPENDENT TUMORS

Growth Hormone-Releasing Hormone (GHRH) Deficiency Promotes Inflammation Associated Carcinogenesis.

Lucia Recinella, PharmD, PhD[1], Sheila Leone, MD[1], Annalisa Chiavaroli, PharmD, PhD[1], Claudio Ferrante, PharmD, PhD[1], Giustino Orlando, PharmD, PhD[1], Roberto Salvatori, MD[2], Luigi Brunetti, MD,PhD[1].
[1]G d'Annunzio University, Department of Pharmacy, Chieti, Italy, [2]Johns Hopkins University, School of Medicine, Baltimore, MD, USA.

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The somatotropic axis, in addition to its well-known metabolic and endocrine effects, plays a pivotal role in modulation of inflammation. Additionally, GH-releasing hormone (GHRH) has been involved in the regulation of the growth of various human tumors. In this work, we aimed to investigate the consequences of GHRH and GH deficiency on the development of inflammation-associated colon carcinogenesis in a mouse model of isolated GH deficiency due to generalized ablation of the GHRH gene [GHRH knock out (GHRHKO)]. Homozygous GHRHKO (-/-) male mice and wild type (C57/BL6, +/+) male mice as control group were used.

After azoxymetane (AOM)/dextran sodium sulfate (DSS) treatment GHRHKO-/- mice displayed higher Disease Activity Index (DAI) score, and more marked weight loss compared to +/+ animals. Additionally, -/- mice showed a significant increase in total colonic tumors, in particular of large size and predominantly localized in distal colon. In colonic tissue of AOM/DSS-treated -/- mice we found the presence of invasive adenocarcinomas, dysplasia and colitis with mucosal ulceration. Conversely, AOM/DSS-treated +/+ mice showed only presence of adenomas, without invasion of sub-mucosa. Treatment with AOM/DSS significantly increased prostaglandin (PG)E2 and 8-iso-PGF2α levels along with cyclooxygenase-2 (COX-2), tumor necrosis factor (TNF)-α, nuclear factor kappa B (NFkB) and inducible nitric oxide synthase (iNOS) gene expression, in colon specimens of both groups. However, the degree of increase of all these parameters was more marked in -/- than +/+ mice.

In conclusion, generalized GHRH ablation increases inflammatory response and colon carcinogenesis in male mice. Whether this results from lack of GH or GHRH remains to be established.