to guide management and take precautionary measures to alleviate negative outcomes.

Attention of these male patient should be paid to prevent the incidence of secondary osteoporosis.

Pediatric Endocrinology

PEDIATRIC ENDOCRINOLOGY: ADRENAL, THYROID, AND GENETIC DISORDERS

Impact of Male Hypogonadism on Bone Mineral Density in Childhood Hemato-Oncologic Disease

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Introduction: Patients with childhood hemato-oncologic diseases have many medical problems, not only due to disease itself, but also adverse effects of specific treatment that patients had. Osteoporosis, one of the most common side effects of the treatment, decreases quality of life when the disease progresses. Our study investigated the impact of male hypogonadism on secondary osteoporosis in childhood hemato-oncologic patients, using association between male sex hormone and bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA). **Methods:** This study collected BMD score (T-score) of 52 male subjects who were diagnosed with hemato-oncologic diseases in the past (average age of 22.3 years at DXA examination). All subjects measured serum testosterone and we divided them into two subgroups according to gonadal status. The first group, called hypogondal group, was a group of subjects with serum testosterone level less than 3.5 ng/ml. The other group was classified into eugonadal group, with serum testosterone level equal or more than 3.5 ng/ml. Mean BMD score of spine and hip were presented and compared between the two groups. Furthermore, relativity with other risk factors for osteoporosis was calculated using multiple regression analysis. **Results:** Overall, spine BMD in the hypogondal group did not significantly differ from the eugonadal group. However, hip BMD was significantly lower in the hypogonadal group (mean difference; 0.8, $p = 0.023$). Furthermore, testosterone level itself showed linear correlation with BMD score in hip ($p = 0.013$). When other risk factors for osteoporosis were taken into account, hemato-oncologic patients treated with total body irradiation also had significantly lower hip BMD ($p = 0.007$) compared with non-irradiation group. Hypogonadism still remained a significant factor for decreased bone mineral density in hip ($p = 0.022$). **Conclusions:** Hemato-oncologic patients with hypogonadism or previously treated with total body irradiation are at increased risk of decreased bone mineral density in both hips. Hypogonadism alone remains independent risk factor for osteoporosis in hip.

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Novel Pathogenic Variants in LHX3, LHX4 and GLI2 Identified in Pediatric Patients With Congenital Hypopituitarism: From Variant Calling To Variant Testing

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Congenital hypopituitarism (CH), septo-optic dysplasia (SOD), and holoprosencephaly (HPE) constitute an important group of structural birth defects that cause significant morbidity and life-long consequences for quality of life and care. The genetic causes are highly overlapping. As such, these disorders can be considered as a spectrum of related disorders. Improved insight into genetic causes would be valuable for patients, families, and medical geneticists. Very few systematic genetic screens have been carried out for patients with CH. We implemented genetic screening using single-molecule molecular inversion probes sequencing to identify causative mutations in a set of 67 genes previously reported in CH patients and the spectrum encompassing SOD and HPE. We captured genomic DNA from 170 Argentinean pediatric patients with CH, and 54% of the patients in this cohort have craniofacial, ophthalmologic, and/or central nervous system defects. We found candidate pathogenic, likely pathogenic and variants uncertain significance (VUS) in 23% of the cases. In order to evaluate the functional consequences of VUS in *LHX3, LHX4*, and *GLI2*, we performed *in-vitro* functional assays to study the activity of the mutated proteins. To test *LHX3/4* variants we co-transfected HEK293T cells with wild type (WT) or mutated *LHX3/4* variant plasmids and luciferase reporter genes driven by the α*GSU* promoter or *GH1* promoter and assayed for luciferase activity. For *GLI2* functional analysis we used the cell line NIH/3T3-CG, stably transfected to express GFP under the presence of GLI2 activated form. Endogenous *Gli2* was knocked out by CRISPR-Cas9 and

clones were selected for absence of GFP expression upon activation of the sonic hedgehog pathway. We tested the ability of transfected WT or mutated GLI2 expression plasmids to restore GFP fluorescence. We concluded that variants *LHX3*:p.Pro187Ser *LHX4*:p.Arg84His, p.Gln100His and p.Trp204Leu and *GLI2*:p.1404Lfs impair activation of the reporter gene, while the *LHX3*:p.Leu220Met and *GLI2*:p.L761P have WT activity on their respective assays. Identification of disease-causing variants in CH is complicated by phenotypic variation, incomplete penetrance, and VUS. Functional testing of potentially pathogenic variants is critical to arrive at a definitive molecular diagnosis. A full catalogue of variant effects in known causative genes would be invaluable for clinicians in order to simplify the interpretation of novel variants and reduce the diagnostic odyssey that families often experience.

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Prevalence and Risk Factors of Hypothalamic-Pituitary Dysfunction in Infant and Toddler Brain Tumor Survivors

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Background: Childhood brain tumor survivors (CBTS) are at risk for hypothalamic-pituitary (HP) dysfunction, mainly caused by radiation exposure or tumor involvement of the HP-region. The risk for HP dysfunction (HPD) may vary between different age groups due to maturation of the brain and differences in oncologic treatment protocols. The aim of this study was to determine the prevalence and risk factors of HPD in infant (IBTS) and toddler brain tumor survivors (TBTS) compared to older childhood brain tumor survivors (OCBTS).
Patients and Methods: A retrospective analysis in a nationwide cohort of CBTS was performed. Prevalence and risk factors for HPD were compared between IBTS (aged 0-1 years at diagnosis), TBTS (aged 1-3 years at diagnosis) and OCBTS (aged >3-18 years at diagnosis).
Results: In 718 included CBTS, with a median follow-up time of 7.9 years, overall no differences in percentage of HPD were found between the three age groups. Treatment with radiotherapy (RT) (OR 15.41; 95%CI 8.33 to 28.48), suprasellar tumor location (OR 46.62; 95%CI 19.64 to 110.66) and younger age (OR 1.09; 95%CI 1.02 to 1.15) were associated with HP dysfunction. Because IBTS were significantly less often treated with RT, subanalyses were performed for all CBTS not treated with radiation (n=459). In non-irradiated CBTS, IBTS and TBTS were significantly more frequently diagnosed with TSH-, ACTH- and ADH deficiency, compared to ECBTS. IBTS and TBTS showed significantly more weight gain (p<0.0001) and smaller height SDS (p=0.001) during follow-up.
Conclusion: Infant and toddler brain tumor survivors seem to be more vulnerable to develop HP dysfunction than when compared to older children. These results emphasize the importance of special infant and toddlers brain tumor treatment protocols and endocrine surveillance in children treated for a brain tumor at young age.

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Prevalence Trends of Metabolic Syndrome Among Korean Children and Adolescents From 2007 to 2018

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Background: The prevalence of metabolic syndrome (MetS) in adults is increasing worldwide. The change of cardiovascular structure associated with metabolic syndrome appears from childhood, it is crucial to detect MetS early, and control associated risk factors to protect future health. **Methods:** We used data of children and adolescents (8,718 subjects aged 10-18) from the National Health and Nutrition Survey IV-VII (KNHANES 2007-2018) to estimate the recent prevalence of MetS, and identify related nutritional factors. The definition of MetS used modified NCEP-ATP III and IDF criteria. **Results:** The prevalence of MetS among Korean adolescents in 2007-2018 was 4.6% using the modified NCEP-ATP III criteria, and the trend of MetS increased significantly (P trend=0.02). In the overweight and obese groups, the risk of MetS increased 7.079 (95% CI, 5.188-9.793) and 27.131 (95% CI, 20.896-35.240) compared to the normal-weight group. During KNHANES IV-VII, overall caloric intake increased, carbohydrate and sodium intake decreased, but fat intake increased (KNHANE-IV; 21.3% to VII; 24.0%, P <0.001). These fat intakes were significantly correlated with an increase in systolic blood pressure, fasting blood glucose, and waist circumference.
Conclusion: The prevalence of MetS is also increasing in Korean adolescents, and changes in dietary habits are related. In the future, it is also necessary to study the relationship with lifestyle.