This chapter on oncology and chronic disease has been integrated for the first time in the Yearbook of Pediatric Endocrinology. In developed countries, 1:250 of the adult population is a long-term survivor of childhood cancer. Thus, a dramatic paradigm shift has occurred in pediatric oncology during the last 40 years. For example, the meaning of ‘outcome’ after tumor therapy has changed and includes not only the counting of the number of therapy survival rates but also the importance of analyzing the consequences of tumor therapy or, in other words, the study of the late effects of tumor therapy. The identification and analysis of late effects, especially endocrine sequelae after cancer therapy, has generated many interesting publications during the last years. The topic ‘Chronic Disease’ will be regarded here from a different perspective, e.g. analyzing growth and pubertal development of affected patients and analyzing side effects of the respective therapy on the endocrine system.

Hypothyroidism following childhood cancer therapy – an underdiagnosed complication

Department of Endocrinology, The Christie NHS Foundation Trust, Manchester, UK
georg.brabant@manchester.ac.uk
Int J Cancer 2012;130:1145–1150

Objective: To determine the prevalence of hypothyroidism amongst most adult survivors of childhood cancer in Britain using the British Childhood Cancer Survivor Study (BCCSS). The BCCSS is a population-based cohort of individuals diagnosed with childhood cancer between 1940 and 1991, and who survived at least 5 years from diagnosis (n = 17,981). 10,483 (71%) of those survivors aged at least 16 years, returned a completed questionnaire, which asked if hypothyroidism had been diagnosed.

Results: Of the whole cohort, 7.7% reported hypothyroidism with the highest risk among patients treated for Hodgkin’s disease (HD) (19.9%), CNS neoplasms (15.3%), non-Hodgkin’s lymphoma (6.2%) and leukemia (5.2%). Survivors were more likely to develop hypothyroidism if they had received radiotherapy for HD (p = 0.0001) or a CNS neoplasm (p < 0.00005) but not leukemia (p = 0.3). In these three patient groups, the frequency of hypothyroidism was similar in men and women. Survivors of irradiated CNS tumors reported a prevalence of hypothyroidism, which was substantially lower if discharged to primary care compared with being on hospital follow-up and which declined substantially with increased follow-up in both primary care (p = 0.004) and hospital follow-up (p = 0.023) settings.

Conclusions: Hypothyroidism is a common finding amongst adult survivors of childhood malignancy. The substantial differences in reported hypothyroidism prevalence after irradiated CNS neoplasms suggests substantial underdiagnosis, which increased with increased follow-up, and which increased among those followed-up in primary care compared with hospital settings.

Patients of the British Childhood Cancer Survivor Study were asked by questionnaire if hypothyroidism had been diagnosed. The approach of the study to send the questionnaire at first to the primary care physician with a request to forward it on to the survivor was an excellent move as reflected by the impressive number of completed questionnaires. The authors confirm and extend
knowledge on hypothyroidism as a major endocrine complication after childhood cancer therapy. Survivors of Hodgkin’s lymphoma and CNS tumors had a two- to threefold greater risk of developing hypothyroidism than survivors of other cancers. Their data also suggest that hypothyroidism may be substantially underdiagnosed in childhood cancer survivors. Therefore, it is necessary to raise the awareness of hypothyroidism in the care of these patients, and periodically test for thyroid functions.

Clinical trial
Summary of endocrine outcomes

Endocrine health problems detected in 519 patients evaluated in a pediatric cancer survivor program
Patterson BC, Wasilewski-Masker K, Ryerson AB, Mertens A, Meacham L
Emory University School of Medicine, Department of Pediatrics, M.S., Emory Children’s Center, Atlanta, GA, USA
bcpatte@emory.edu
J Clin Endocrinol Metab 2012;97:810–818

Context: Survivors of pediatric cancer frequently develop endocrine conditions. National guidelines recommend surveillance of these patients for late endocrine effects after alkylating agents, steroids, methotrexate, and radiation. The study was conducted to analyze endocrine outcomes in surviving patients.

Methods: The study included pediatric and young adult survivors of noncentral nervous system childhood malignancies followed up in the Comprehensive Cancer Survivor Program, an academic pediatric oncology program based on national screening guidelines, from January 1, 2001, until December 15, 2005. Patients were evaluated with history, physical examinations, and evaluations recommended in the Children’s Oncology Group’s Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers. Their medical records were reviewed for the types and frequencies of endocrine conditions.

Results: In total, 519 survivors were included in the analysis and 480 endocrine conditions were observed in 299/519 (57.6%) survivors. The most common endocrine conditions were problems with weight and gonadal function. A Cox regression model identified stem cell transplant, radiation, and older age at cancer diagnosis as being associated with higher hazard of an endocrine condition. Radiation, stem cell transplant, and sarcoma diagnosis were associated with growth problems.

Conclusion: Endocrine disorders were common sequelae of pediatric cancers. Endocrinologists should be aware of national guidelines, anticipate referral of pediatric cancer survivors, and participate in further research to optimize screening for, and treatment of, endocrine effects of cancer therapy.

In the past decades there has been a marked increase in the survival rates of pediatric cancer patients. However, survivors are at risk for long-term complications of cancer therapy throughout their lives. The authors add further evidence in support of the association between radiation and stem cell transplantation therapy and the occurrence of endocrine conditions. In this study, radiation therapy was independently associated with the development of classical endocrine disorders, including thyroid disease, short stature, and gonadal problems. The study did not allow for stratification of subjects by radiation site or radiation dose. Limitations of the study included selection bias in that not all survivors were evaluated in the program. Moreover, some endocrine conditions might be underrepresented due to defining the presence of disease by the need for hormonal replacement. Thus, Sertoli cell dysfunction and small testicular volume were not represented in this study cohort.
Antimüllerian hormone is a marker of gonadotoxicity in pre- and postpubertal girls treated for cancer: a prospective study

Brougham MF, Crofton PM, Johnson EJ, Evans N, Anderson RA, Wallace WH
Department of Paediatric Oncology (M.F.H.B., E.J.J., W.H.B.W.), Department of Paediatric Biochemistry (P.M.C.), Royal Hospital for Sick Children, Edinburgh, UK; Medical Research Council Human Reproductive Sciences Unit (N.E.), Edinburgh, UK, and Medical Research Council Centre for Reproductive Health (R.A.A.), University of Edinburgh, Edinburgh, UK

J Clin Endocrinol Metab 2012;97:2059–2067

Background: Cytotoxic treatment may accelerate depletion of the primordial follicle pool, leading to impaired fertility and premature menopause. Assessment of ovarian damage in prepubertal girls is not currently possible, but antimüllerian hormone (AMH) is a useful marker of ovarian reserve in adults.

Objective: The objective of the study was to prospectively evaluate AMH measurement in children as a marker of ovarian toxicity during cancer treatment.

Design and Setting: This was a prospective, longitudinal study at a university hospital.

Patients: 22 females (17 prepubertal), median age 4.4 years (range 0.3–15), were recruited before treatment for cancer.

Main Outcome Measures: AMH, inhibin B, and FSH at diagnosis, after each chemotherapy course and during follow-up, were measured. Risk of gonadotoxicity was classified as low/medium (n = 13) or high (n = 9) based on chemotherapy agent, cumulative dose, and radiotherapy involving the ovaries.

Results: Pretreatment AMH was detectable across the age range studied. AMH decreased progressively during chemotherapy (p < 0.0001) in both prepubertal and pubertal girls, becoming undetectable in 50% of patients, with recovery in the low-/medium-risk groups after completion of treatment. In the high-risk group, AMH became undetectable in all patients and showed no recovery. Inhibin B was undetectable in most patients before treatment and, with FSH, showed no clear relationship to treatment.

Conclusions: AMH is detectable in girls of all ages and falls rapidly during cancer treatment in both prepubertal and pubertal girls. Both the fall during treatment and recovery thereafter varied with risk of gonadotoxicity. AMH is therefore a clinically useful marker of damage to the ovarian reserve in girls receiving treatment for cancer.

Inhibin B and antimüllerian hormone as markers of gonadal function after treatment for medulloblastoma or posterior fossa ependymoma during childhood

Université Paris Descartes and AP-HP, Hôpital Bicêtre, Unité d’endocrinologie pédiatrique, Le Kremlin Bicêtre, France

J Pediatr 2011;158:1016–1022 e1

Objective: To evaluate the roles of hypothalamic-pituitary and spinal irradiations and chemotherapy in gonadal deficiency after treatment for medulloblastoma or posterior fossa ependymoma by measuring levels of plasma inhibin B and antimüllerian hormone (AMH).

Patients and Methods: A total of 34 boys and 22 girls were classified as having normal levels of plasma follicle-stimulating hormone (FSH; <9 IU/l), or abnormal levels of FSH (>9 IU/l) and luteinizing hormone (LH; <5 or >5 IU/l).

Results: Two boys had partial gonadotropin deficiency, combined with testicular deficiency in 1 boy. Six boys had increased levels of FSH, indicating tubular deficiency, combined with Leydig cell deficiency in 5 boys. The 7 boys with inhibin B levels <100 ng/ml included the 1 with combined deficiencies and the 6 with testicular deficiency. Puberty did not progress in 7 girls; 3 had gonadotropin deficiency, combined with ovarian deficiency in 1, and 4 had increased FSH levels, indicating ovarian deficiency. Inhibin B and AMH levels were low in the girl with combined deficiencies, in the 4 girls with ovarian deficiency, and in 4 girls with normal clinical-biological ovarian function, including 2 who underwent ovarian transposition before irradiation.
Conclusions: The plasma concentrations of inhibin B and AMH are useful means of detecting primary gonad deficiency in patients with no increase in their plasma gonadotropin levels because of radiation-induced gonadotropin deficiency.

In the 2011 issue of the Yearbook of Pediatric Endocrinology, Lena Sahlin and Olle Söder commented on two papers reporting antimüllerian hormone (AMH) levels in healthy female and male patients from birth to adulthood. Additionally, AMH levels were measured in patients with Turner syndrome (TS), showing that low or undetectable AMH levels correlate with ovarian failure in TS patients. They stated that ‘the full potential of AMH measurements most certainly requires more time to develop’. A year later, and two independent groups published AMH data showing the usefulness of AMH measurement as a marker of gonadal damage. Since AMH is produced solely in the granulosa cells of growing ovarian follicles, the AMH serum levels correlate strongly with the number of growing follicles. Inhibin B is also a marker of ovarian reserve. The paper by Mark Brougham et al. shows that the extent of gonadal damage in female cancer survivors is better reflected by measurement of AMH than by inhibin B levels. In boys, inhibin B is produced by Sertoli cells, and its plasma concentration is positively correlated with spermatogenesis and negatively correlated with FSH levels. The paper by Ariane Cuny et al. shows that inhibin B can be used as a marker of gonadal damage in boys after brain tumor therapy.

**AMH and AFC (antral follicle counts) – sensitive measures of ovarian reserve**

**Impact of cancer therapies on ovarian reserve**

Department of Obstetrics/Gynecology, Children's Hospital of Philadelphia, Philadelphia, PA, USA
cgracia@obgyn.upenn.edu
Fertil Steril 2012;97:134–140 e1

**Objective:** To determine whether measures of ovarian reserve differ between females exposed to cancer therapies in a dose-dependent manner as compared with healthy controls of similar age and late reproductive age.

**Design:** Cross-sectional analysis of data from a prospective cohort study.

**Setting:** University medical center.

**Patients:** 71 cancer survivors aged 15–39 years, 67 healthy, similarly aged unexposed subjects, and 69 regularly menstruating women of late reproductive age (40–52 years).

**Intervention(s):** None.

**Main outcome measure(s):** Early follicular-phase hormones (FSH, E₂, inhibin B, antimüllerian hormone (AMH)) and ovarian ultrasound measurements (ovarian volume and antral follicle counts (AFC)) were compared using multivariable linear regression.

**Results:** In adjusted models, FSH, AMH, and AFC differed between exposed vs. unexposed subjects (FSH 11.12 vs. 7.25 mIU/ml, AMH 0.81 vs. 2.85 ng/ml, AFC 14.55 vs. 27.20). In participants with an FSH <10 mIU/ml, survivors had lower levels of AMH and AFC compared with controls. Alkylating agent dose score was associated with increased levels of FSH and decreased levels of AMH. Exposure to pelvic radiation was associated with impairment in FSH, AMH, AFC, and ovarian volume. Antimüllerian hormone was similar in women previously exposed to high-dose cancer therapy and 40- to 42-year-old controls.

**Conclusions:** Measures of ovarian reserve are impaired in a dose-dependent manner among cancer survivors compared with unexposed females of similar age. Reproductive hormone levels in menstruating survivors exposed to high-dose therapy are similar to those in late-reproductive-age women. The predictive value of measures for pregnancy and menopause must be studied.

It has been shown the risk of ovarian failure to be dependent on the dose of alkylating agents and pelvic radiotherapy. The paper by Mark Brougham et al. (see p. 119) correlated the risk of gonado-
toxicity with the used therapeutic regimen and found that AMH levels recovered only in the low-/medium-risk groups after completion of treatment, and not in the high-risk group. Clarisa Gracia et al. studied female cancer survivors together with a control group of healthy, similarly aged unexposed subjects. They found that ovarian reserve was significantly impaired in cancer survivors. Even cancer survivors with regular menstrual cycles or those with normal FSH levels had significantly lower levels of AMH and AFC compared with controls supporting subclinical follicular depletion. Cancer survivors with greater exposure to alkylators, pelvic radiotherapy, or bone marrow transplantation with total body irradiation had the most impaired ovarian reserve. The authors showed that ovarian reserve is impaired in a dose-dependent fashion in subjects exposed to cancer therapies. Current methods of ovarian follicle preservation need to be entertained more seriously before a girl is subject to these devastating therapies.

Puzzling result
Testicular size is a better predictor of fertility

Semen quality and fertility in adult long-term survivors of childhood acute lymphoblastic leukemia
Jahnukainen K, Heikkinen R, Henriksson M, Cooper TG, Puukko-Viertomies LR, Makitie O
Division of Hematology-Oncology and Stem Cell Transplantation, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland
kirs.jahnukainen@ki.se

Objective: To assess testicular function and its determinants in adult survivors of childhood acute lymphoblastic leukemia (ALL) at a median time of 20 years after ALL therapy.

Design: Prospective investigation.

Setting: University hospital.

Patient(s): 51 male long-term survivors and 56 age-matched controls (median age of survivors at ALL diagnosis was 5 years, range 1–15 years, and at the study 29 years, range 26–38 years).

Intervention(s): None.

Main outcome measure(s): Testicular size (mean value of both testicular volumes), serum hormone concentrations, semen quality, and number of children fathered correlated with ALL therapy.

Result(s): Survivors treated with 0–10 g/m² of cyclophosphamide had sperm quality and fertility rates comparable with those of controls, but the serum-free testosterone in the survivors treated with cyclophosphamide was lower than in controls (median 213 pmol/l, range 189–260 vs. 296 pmol/l, range 242–338, respectively). Cranial irradiation without cyclophosphamide did not affect semen quality, fertility, or testosterone levels. None of the survivors of a high cumulative dose of cyclophosphamide (>20 g/m²) and testicular irradiation (10–24 Gy) had fathered a child. Testicular size was shown to be better than serum inhibin B in predicting nonazoospermic semen samples or fertility.

Conclusion(s): Treatment of childhood ALL with 0–10 g/m² of cyclophosphamide and cranial irradiation does not affect fertility or semen quality but may impair long-term Leydig cell function.

Nice to hear good news: long-term survivors of ALL therapy who had been treated with cyclophosphamide in a dose of <10 g/m² had sperm quality and fertility rates comparable with those of controls, whereas the serum-free testosterone levels were lower. The result that testicular size is a better predictor of normal semen quality or fertility than serum inhibin B is surprising and not confirmed in the literature. We have some concerns with regard to measurement of the testicular size with a ruler (longitudinal and transverse axis in centimeters). In the literature, there is consensus that inhibin B is the best plasma marker of spermatogenesis, but those of us who do not have access to the new assays may resort to clinical evaluation using a Prader orchiometer. According to the study of subfertile men, the inhibin B concentrations allow accurate differentiation between competent and impaired spermatogenesis [1]. Nevertheless, the study is important and shows that long-term surveillance of the testicular function should be implemented for childhood ALL survivors.
Risk factors for obesity in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study

Department of Epidemiology and Cancer Control, St Jude Children’s Research Hospital, Memphis, TN, USA
daniel.green@stjude.org

Objective: Survivors of childhood cancer are at increased risk for obesity, the etiology of which is not well understood and is likely to be multifactorial.

Methods: The study analyzed demographic, lifestyle, treatment, and intrapersonal factors and self-reported use of pharmaceuticals for their potential contribution to obesity (body mass index ≥ 30 kg/m²) in 9,284 adult participants aged >18 years in the CCSS. Multivariable regression models were used to identify independent predictors of obesity. Interrelationships were determined by means of structural equation modeling (SEM).

Results: Independent risk factors for obesity included cancer diagnosed at age 5–9 years (relative risk (RR) 1.12; 95% confidence interval (CI) 1.01–1.24; p = 0.03), abnormal Short Form-36 physical function (RR 1.19; 95% CI 1.06–1.33; p < 0.001), hypothalamic/pituitary radiation doses of 20–30 Gy (RR 1.17; 95% CI 1.05–1.30; p = 0.01), and the use of the antidepressant paroxetine (RR 1.29; 95% CI 1.08–1.54; p = 0.01). Risk of obesity was reduced by meeting guidelines for vigorous physical activity issued by the US Centers for Disease Control and Prevention (RR 0.90; 95% CI 0.82–0.97; p = 0.01) and by a medium amount of anxiety (RR 0.86; 95% CI 0.75–0.99; p = 0.04). The hierarchical impact of the direct predictors, moderators, and mediators of obesity was described by the results of SEM (n = 8,244; comparative fit index = 0.999; Tucker Lewis index = 0.999; root mean square error of approximation = 0.014; weighted root mean square residual = 0.749).

Conclusions: Treatment, lifestyle, and intrapersonal factors, as well as the use of specific antidepressants, may be factors contributing to obesity among survivors of childhood cancer. Multifaceted intervention, including alternative drug and other treatments for depression and anxiety, may be required to reduce the risk of obesity in these patients.

The study by Green et al. reports hitherto unknown risk factors for later obesity in survivors of childhood cancer. In particular, it provides evidence that in these patients obesity is associated with a sedentary lifestyle, and the use of antidepressants. In this context, self-reported cancer-related anxiety and cancer-related pain are important confounders next to ‘poor physical activity’. The use of an antidepressant (paroxetine) contributed to the development of obesity, as did low social status (less education), older age at survey, cranial irradiation and low family income.

Distinct impact of imatinib on growth at prepubertal and pubertal ages of children with chronic myeloid leukemia

Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan
J Pediatr 2011;159:676–681

Objective: Imatinib side effects are generally mild to moderate but the drug’s long-term effects remain unknown. Effects on growth are a major concern when treating children and growth deceleration after
imatinib has been reported. This study aimed to determine the extent of imatinib-related growth impairment in children with chronic myeloid leukemia (CML).

**Methods:** Clinical records of 48 chronic-phase CML children who received first-line treatment with imatinib during 2001–2006 were analyzed retrospectively. Cumulative change in height was assessed using the height standard deviation score (SDS) and converted height data from age- and sex-adjusted Japanese norms.

**Results:** Height SDS was decreased in 72.9% of children; median maximum reduction in height SDS was 0.61 during imatinib treatment. Patients were followed up for a median (range) of 34 (10–88) months. Growth impairment was predominantly seen in children who started imatinib before pubertal onset compared with those who started treatment after reaching puberty. Growth velocity tended to recover as prepubertal children with growth impairment reached puberty, suggesting that imatinib had little impact on growth during puberty.

**Conclusions:** Growth impairment was a major adverse effect of long-term imatinib treatment in children with CML. The study revealed a distinct inhibitory effect of imatinib on growth in prepubertal and pubertal children with CML. The authors call for awareness of growth deceleration in children, especially in young children, given imatinib before puberty and subjected to prolonged exposure.

Imatinib is a specific inhibitor of several tyrosine kinases (TKs). By occupying the TK-active site it causes a decrease in activity. There are many different TK enzymes present in the body, including the insulin receptor. The authors demonstrated an association between imatinib treatment and growth impairment and postulated a negative effect of imatinib on GH secretion and function. Unfortunately, no IGF-1 data were reported in this study. A further limitation of the study results from short follow-up periods in the majority of cohort patients who showed no late effects on growth. To detect iatrogenically induced GH deficiency resulting from TK inhibitor therapy, the authors recommended careful monitoring of growth velocity, bone metabolic markers, and serum IGF-1. Performing GH stimulation tests before and during treatment with TK inhibitors would provide new insights into the dynamics of growth under such treatment.

**Clinical trial**

**Endocrine outcomes after childhood NHL therapy**

**Endocrine late sequelae in long-term survivors of childhood non-Hodgkin lymphoma**


Department of Pediatric Oncology/Hematology, Erasmus Medical Center-Sophia Children’s Hospital, Rotterdam, The Netherlands

*Ann Oncol* 2012;23:1626–1632

**Objective:** Studies investigating the late endocrine sequelae of treatment in survivors of childhood non-Hodgkin lymphoma (NHL) are scarce. Available studies are often limited by small sample size or combination of NHL survivors with survivors of other malignancies. This study therefore undertook to investigate the long-term endocrine effects of childhood NHL treatment.

**Methods:** Included in this retrospective analysis of single-center data from 84 (males/females 62/22 females) survivors (median (range) age: 21 (9–40) years; time since cessation of therapy: 12 (4–30) years). Study assessments included height, weight, body mass index (BMI), percentage of body fat (% fat), lean body mass (LBM), bone mineral content (BMC), and bone mineral density of total body (BMD(TB)) and lumbar spine (BMD(LS)). Endocrine evaluation included thyroid-stimulating hormone (TSH), free thyroxine (fT4), insulin-like growth factor-1 (IGF-1), inhibin B, and antimüllerian hormone (AMH). Results were compared with Dutch control groups of children and young adults.

**Results:** Survivors had significantly decreased height (mean standard deviation score (SDS): −0.36, p = 0.002), but closer analysis revealed that shorter stature had already been present at diagnosis (mean SDS −0.28, p = 0.023). BMI, % fat, BMC, BMD(TB), and BMD(LS) did not differ significantly from controls. LBM was lower in survivors (mean SDS −0.47, p = 0.008). TSH, fT4 and IGF-1 levels were
normal in all survivors. Low AMH levels were noted in 3 of 20 adult females, and inhibin B levels were decreased in 23/42 adult males.

**Conclusions:** Twelve years after the end of treatment, no NHL survivors of either sex had developed obesity, osteoporosis or thyroid disease. Male survivors may be at risk for infertility.

In long-term childhood NHL survivors, especially males, shorter stature seems to be determined by height at diagnosis rather than treatment-related side effects. This was a retrospective study and therefore IGF-1 levels were analyzed in the absence of data on dynamic stimulations tests. Since NHL, as a rule, is treated by chemotherapy, and occasionally by local irradiation, the study confirmed that treatment-related damage primarily affects the testes and does not cause central deficiencies, i.e. hypothalamic or pituitary damage. In addition, the study showed that long-term childhood NHL survivors appear not to be at risk for endocrine late sequelae such as osteoporosis, obesity, or hypothyroidism. However, males might be especially at risk for gonadal damage possibly related to cumulative doses of cytarabine. This is the first study to demonstrate such a cumulative effect of cytarabine. Usually, alkylating chemotherapeutic agents, e.g. cyclophosphamide, or abdominal irradiation are responsible for gonadal damage. By adjusting for these factors the authors were able to demonstrate the effect of cytarabine.

### Endocrine tumors

**Extremely rare but important for clinical practice**

**Ectopic ACTH syndrome in children and adolescents**


Department of Endocrinology, University Hospital of Bordeaux, Pessac, France

*J Clin Endocrinol Metab* 2011;96:1213–1222

**Objective:** Ectopic ACTH syndrome (EAS) in youngsters has seldom been reported and is poorly known.

**Setting:** We conducted a multicenter retrospective study involving 18 French tertiary hospitals. Cases of EAS presenting Cushing’s syndrome before the age of 20 during the period from 1985 to 2008 were analyzed.

**Patients:** Ten patients aged 14–20 years were identified and compared to 20 age-matched patients with Cushing’s disease diagnosed during the same period.

**Main Outcome Measures:** Etiologies, clinical, biochemical and radiological features, prognosis, and treatment were described.

**Results:** Seven patients had well-differentiated neuroendocrine tumors (5 bronchial carcinoids, 1 mediastinal lymph node, and 1 thymic), 1 had a poorly differentiated thymic carcinoma, 1 had a pleural Ewing’s sarcoma, and 1 had a liver nested stromal epithelial tumor. At presentation, seven tumors were identified with computed tomography scanning and somatostatin receptor scintigraphy, and one with 18F-l-dihydroxyphenylalanine positron emission tomography scan. Two carcinoids were occult and were identified during follow-up. Cushing’s syndrome was more intense in EAS, but the clinical and biological spectrum overlapped with that of Cushing’s disease. No dynamic test achieved 100% accuracy, whereas petrosal sinus sampling provided correct diagnosis in all patients tested. Medical treatment of hypercortisolism was successful in 6 of the 8 patients with whom it was attempted, and bilateral adrenalectomy had to be performed in only 2 cases. Prognosis was good; 9 patients with curative resection of the tumor were alive and cured (median follow-up 6.5 years), whereas 1 patient died.

**Conclusions:** EAS in youngsters displays many similarities to that described in adults. The diagnostic and therapeutic algorithms recommended in adults can be used in this population.

This paper summarizes the experiences of different tertiary hospitals in France with ectopic ACTH syndrome (EAS) in 10 patients aged 10–20 years. Endogenous Cushing syndrome is rare in children, but as one can see – not unheard of. Etiologically, cortisol-producing adrenocortical tumors are more common in children than ACTH-producing pituitary tumors whereas ectopic ACTH production is extraordinarily rare. There are some case reports in the literature on infants with neuroblastomas or...
other neuroendocrine tumors, and adolescents with carcinoids. The most important messages of the paper are: (1) clinical overlap with Cushing’s disease, and (2) diagnostic and therapeutic algorithms recommended in adults can be used in this population. Since most patients with EAS had neuroendocrine tumors, it is necessary to consider MEN1 syndrome, as is the case with any childhood pituitary adenoma.

**Sporadic and genetic forms of pediatric somatotropinoma: a retrospective analysis of seven cases and a review of the literature**

Fédération d’Endocrinologie du Pole Est, Groupement Hospitalier Lyon Est, Bron, France  
cecile.noziieres@chu-lyon.fr  
Orphanet J Rare Dis 2011;6:67

**Objective:** Somatotropinoma is extremely rare in childhood. This pituitary adenoma is characterized by excessive growth hormone (GH) production. In some cases, involvement of genetic defects has been demonstrated, including multiple endocrine neoplasia type 1 (MEN1), Carney complex, McCune-Albright syndrome, and aryl hydrocarbon receptor-interacting protein (AIP). The study reports on 7 pediatric patients, placing a particular focus on the differences between genetic and sporadic forms of somatotropinoma.

**Methods:** The study retrospectively analyzed the clinical data of children aged <18 years who presented to a French regional pediatric endocrinology network during 1992–2008. First-line treatment consisted in somatostatin (SMS) analogs or transsphenoidal surgery. Endocrine control was defined as insulin-like growth factor-1 (IGF-1) levels within the age-appropriate normal range at 6 months after initiation of therapy in conjunction with a decrease in tumor volume.

**Results:** Included were 7 patients (6 males, 1 female) aged 5–17 years. Four patients had an identified genetic mutation (McCune-Albright syndrome (1 patient), MEN1 (1) and AIP (2)) whereas the other 3 had a sporadic form of somatotropinoma. Accelerated growth rate was reported as the first clinical sign in 4 patients. Macroadenoma was diagnosed in 5 patients, invasion being noted in 4 of these patients, 1 with a sporadic form and 3 with genetic forms of somatotropinoma. Six patients received SMS analogs; normalization of IGF-1 occurred in 1 patient with sporadic intrasellar macroadenoma. All patients with an identified genetic mutation required several different types of treatment (1 patient received 4 types, 2 patients had 3 types, and 1 patient had 2 types), whereas 2 of the 3 sporadic somatotropinoma patients needed only one type of therapy.

**Conclusions:** This is the first series that analyzes the therapeutic response of somatotropinoma in pediatric patients with identified genetic defects. In children, genetic forms of somatotropinoma are more invasive than the sporadic forms. Furthermore, SMS analogs appear to be less effective against genetic forms than against sporadic forms of somatotropinoma. In both adults and children, conventional treatment of somatotropinoma consists in transsphenoidal surgery. In cases of intracavernous extension or incomplete surgery, SMS analog treatment may be administered preoperatively and/or postoperatively to suppress GH release. The study shows that SMS analogs are effective without surgery and can normalize IGF-1 levels and reduce tumor size. The observational nature of the study and the small sample size however weaken the authors’ conclusions concerning the influence of genetic forms of somatotropinoma on the effect of SMS analogs.
Management of medullary thyroid carcinoma and MEN2 syndromes in childhood
Waguespack SG, Rich TA, Perrier ND, Jimenez C, Cote GJ
The Department of Endocrine Neoplasia and Hormonal Disorders, Houston, TX, USA
swagues@mdanderson.org
Nat Rev Endocrinol 2011;7:596–607

Objective: Medullary thyroid carcinoma (MTC) and the multiple endocrine neoplasia (MEN) type 2 syndromes are rare but important endocrine diseases that are increasingly managed by pediatric providers. MTC is generally associated with a favorable prognosis when diagnosed during childhood, where it frequently occurs secondary to activating mutations in the RET proto-oncogene and arises from preexisting C-cell hyperplasia.

Results: MEN2A accounts for 90–95% of childhood MTC cases and is most commonly due to mutations in codon 634 of RET. MEN2B is associated with the most aggressive clinical presentation of MTC and is almost always due to the Met918Thr mutation of RET. Surgery is the primary treatment and only chance of cure, although the advent of targeted therapies seems to be improving progression-free survival in advanced cases. Since the discovery of the role of RET in MEN2A, considerable advances in the management of this syndrome have occurred, and most of the children with MEN2A who have undergone early thyroidectomy will now lead full, productive lives. Strong genotype-phenotype correlations have facilitated the development of guidelines for interventions. Contemporary approaches for deciding the appropriate age at which surgery should take place incorporate data from ultrasonography and calcitonin measurements in addition to the results of genotyping.

Conclusions: To optimize care and to facilitate ongoing research, children with MTC and the MEN2 syndromes are optimally treated at tertiary centers with multidisciplinary expertise.

This is an excellent overview on the current management of children with medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia (MEN) type 2 – genetic syndromes caused by germline mutations in the RET proto-oncogene. The best strategy is to prevent MTC by early surgical thyroidectomy. The authors make the important note that to understand rare diseases, it is important that such children are managed in networked disease-specific research clinics, so that the knowledge gained from each case is utilized in an optimal manner. Referring patients to such networks requires both organization and good will. An example of that approach is provided in the next abstract.

Clinical trial
Prognostic factors of disease-free survival after thyroidectomy in 170 young patients with a RET germline mutation: a multicenter study of the Groupe Français d’Etude des Tumeurs Endocrines
Centre hospitalier universitaire Angers, Endocrinologie, Faculté de médecine, Université Angers, Angers, France
virohmer@chu-angers.fr
J Clin Endocrinol Metab 2011;96:E509–518

Background: In hereditary medullary thyroid carcinoma (HMTC), prophylactic surgery is the only curative option, which should be properly defined both in time and extent.

Objectives: To identify and characterize prognostic factors associated with disease-free survival (DFS) in children from HMTC families.

Design: We conducted a retrospective analysis of a multicenter cohort of 170 patients below age 21 at surgery. Demographic, clinical, genetic, biological data (basal and pentagastrin-stimulated calcitonin
Oncology and Chronic Disease

(CT and CT/Pg, respectively)), and tumor node metastasis (TNM) status were collected. DFS was assessed based on basal CT levels. Kaplan-Meier curves, Cox regression, and logistic regression models were used to determine factors associated with DFS and TNM staging.

Results: No patients with a preoperative basal CT <31 ng/ml had persistent or recurrent disease. Medullary thyroid carcinoma defined by a diameter \( \geq 10 \) mm (hazard ratio (HR) 6.0, 95% confidence interval (CI) 1.8–19.8) and N1 status (HR 20.8, 95% CI 3.9–109.8) were independently associated with DFS. Class D genotype (odds ratio (OR) 48.6, 95% CI 8.6–274.1), and age >10 (OR 4.6, 95% CI 1.1–19.0) were associated with medullary thyroid carcinoma \( \geq 10 \) mm. No patient with a preoperative basal CT <31 ng/ml had a N1 status. Class D genotype (OR 48.5, 95% CI 10.6–225.1), preoperative basal CT >30 ng/l (OR 43.4, 95% CI 5.2–359.8), and age >10 (OR 5.5, 95% CI 1.4–21.8) were associated with medullary thyroid carcinoma \( \geq 10 \) mm. No patient with a preoperative basal CT <31 ng/ml had a N1 status. Class D genotype (OR 48.6, 95% CI 8.6–274.1), and age >10 (OR 4.6, 95% CI 1.1–19.0) were associated with N1 status.

Conclusions: In HMTC patients, DFS is best predicted by TNM staging and preoperative basal CT level <30 pg/ml. Basal CT, class D genotype, and age constitute key determinants to decide preoperatively timely surgery.

By analyzing a large group of patients with hereditary MTC the authors could identify various important key factors (basal calcitonin, class D genotype, chronological age) which should be considered to determine the optimal time point of surgery.

Endocrine aspects of chronic disease

Early onset of primary hypogonadism revealed by serum antimüllerian hormone determination during infancy and childhood in trisomy 21

Division de Endocrinología, Centro de Investigaciones Endocrinológicas (CEDI-ENDICET), Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina
rgrinspon@cedie.org.ar
Int J Androl 2011;34:e487–498

Background: Primary hypogonadism, or testicular dysfunction, in male patients with an extra sex chromosome or autosome is expected to manifest at puberty owing to meiotic germ-cell failure. Relevant data on patients with trisomy 21, a frequent autosomal aneuploidy, are sparse. This study aimed to assess whether trisomy 21 in males presents with pubertal-onset, germ cell-specific, primary hypogonadism, or whether the condition is established earlier and affects other testicular cell populations.

Methods: The study evaluated 117 boys and young men with trisomy 21 aged 2 months to 20 years by assessing the pituitary-testicular axis for functional status, especially Sertoli cell function. To enable comparison with an appropriate control population, reference levels for serum antimüllerian hormone (AMH) were prospectively established in 421 males of normal karyotype aged 2 days to 52 years by means of a recently developed ultrasensitive assay.

Results: From early infancy, trisomy 21 was associated with lower than normal AMH levels, indicating Sertoli cell dysfunction, regardless of cryptorchidism. In infants with trisomy 21, overall prevalence of AMH below the 3rd percentile was 64.3%. Follicle-stimulating hormone was elevated at age <6 months and after the onset of puberty. Testosterone was within the normal range, but luteinizing hormone was elevated in most patients aged <6 months and after pubertal onset, indicating mild Leydig cell dysfunction.

Conclusions: In trisomy 21, primary hypogonadism involves combined dysfunction of both Sertoli and Leydig cells, which can be observed soon after birth independently of cryptorchidism. The authors expect their findings to trigger the search for new hypotheses explaining the pathophysiology of gonadal dysfunction in autosomal trisomy.

This cross-sectional study in a relatively large cohort of individuals with Down syndrome shows that males with this trisomic disorder develop primary hypogonadism soon after birth and that Sertoli and Leydig cell function are both impaired. The study thus demonstrates that both testosterone pro-
duction and spermatogenesis are impaired from early childhood rather than puberty and are also independent of cryptorchidism. Even though other markers such as inhibin B for Sertoli cells and INSL-3 for Leydig cells are available today, the hormonal constellation of gonadotropins and testosterone provides a basis for a valid statement regarding Leydig cells. Hence AMH can be considered a marker of clinical relevance. The study of a trisomy provides a unique opportunity to understand the role of excess genetic material on specific endocrine mechanisms [2].

Cerebral palsy: important for clinical practice: weight-for-age charts

**Low weight, morbidity, and mortality in children with cerebral palsy: new clinical growth charts**

Brooks J, Day S, Shavelle R, Strauss D
Life Expectancy Project, San Francisco, CA, USA
brooks@lifeexpectancy.org

*p*edia*tics* 2011;128:e299–307

**Objective:** To determine the percentiles of weight for age in cerebral palsy according to gender and Gross Motor Function Classification System (GMFCS) level and to identify weights associated with negative health outcomes.

**Study Design:** This study consists of a total of 102,163 measurements of weight from 25,545 children with cerebral palsy who were clients of the California Department of Developmental Services from 1988 through 2002. Percentiles were estimated using generalized additive models for location, scale, and shape. Numbers of comorbidities were compared using t tests. The effect of low weight on mortality was estimated with proportional hazards regression.

**Results:** Weight-for-age percentiles in children with cerebral palsy varied with gender and GMFCS level. Comorbidities were more common among those with weights below the 20th percentile in GMFCS levels I through IV and level V without feeding tubes (p < 0.01). For GMFCS levels I and II, weights below the 5th percentile were associated with a hazard ratio of 2.2 (95% CI 1.3–3.7). For children in GMFCS levels III through V, weights below the 20th percentile were associated with a mortality hazard ratio of 1.5 (95% CI 1.4–1.7).

**Conclusions:** Children with cerebral palsy who have very low weights have more major medical conditions and are at increased risk of death. The weight-for-age charts presented here may assist in the early detection of nutritional issues or other health risks in these children.

Unlike the longevity effect of low BMI in the general population, in chronic diseases low weight is associated with higher rates of comorbidities and mortality. This is also true for children and adolescents with cerebral palsy. However, it is difficult to define low weight within these patients because they do not follow growth and weight charts that were based on data of healthy children. Thus, Brooks et al. developed weight-for-age charts and, in addition, for each degree of severity of loss of motor function based on the Gross Motor Function Classification System (GMFCS). They could define the 5th percentile for GMFCS levels I and II and the 20th percentile for GMFCS levels III–V (without feeding tube) as cut-off values associated with higher degrees of chronic major medical conditions included, but were not limited to, diabetes mellitus, hypertension, congenital or arteriosclerotic heart disease, upper respiratory infections, etc. The authors showed how important it is to achieve a certain weight level when suffering from a chronic disease. Surprisingly, the authors did not find higher morbidity or mortality rates associated with overweight and obesity. This issue should be addressed in further long-term studies reaching adult ages.
Asthma: new data on dysfunction of the HPA axis

Salivary cortisol levels in prepubertal children using inhaled corticosteroids with or without concurrent intranasal corticosteroids

Heijsman SM, de Vries TW, Wolthuis A, Kamps AW
Department of Paediatrics, Medical Centre Leeuwarden, Leeuwarden, The Netherlands
Pediatr Pulmonol 2011;46:1055–1061

Background: Inhaled corticosteroids (ICS) and intranasal steroids (INS) are frequently coadministered in children with asthma and rhinitis. In contrast to monotherapy with ICS or INS, little is known about the safety of concurrent use of topical steroids on hypothalamic-pituitary-adrenal (HPA) axis function in prepubertal children.

Objective: Comparison of morning salivary cortisol levels in prepubertal children using maintenance treatment with ICS with and without concurrent use of INS to steroid-naive control groups (healthy children, and children with constipation who are under pediatric care).

Study Design: Cross-sectional observational study in prepubertal children (6–12 years) using ICS alone (n = 41) or in combination with INS (n = 22), compared to different control groups with no steroid treatment (18 healthy children, and 28 children with constipation). Morning salivary cortisol levels were determined from saliva samples collected at home.

Results: The morning salivary cortisol levels of the healthy children (8.7 nmol/l; 95% CI 5.9–18.8), and the children with constipation (8.9 nmol/l; 8.0–11.3) were comparable. The salivary cortisol levels of prepubertal children using ICS (median 4.7 nmol/l; 95% CI 4.6–6.9) or a combination of ICS and INS (5.1 nmol/l; 4.2–7.6) were comparable, but significantly reduced compared to both control groups. There was no correlation between salivary cortisol level and age, duration of disease, or cumulative daily dose of topical steroids.

Conclusions: Salivary cortisol levels in prepubertal children using ICS, with or without concurrent use of INS, were comparable. However, salivary cortisol levels were significantly reduced compared to steroid-naive controls, irrespective of the cumulative daily dose of topical steroids.

Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled and nasal corticosteroids: is the early-morning serum adrenocorticotropic hormone (ACTH) a useful screening test?

Paediatric Endocrine Unit, Tygerberg Children’s Hospital, University of Stellenbosch, Cape Town, South Africa
zollner@sun.ac.za

Background: Hypothalamic-pituitary-adrenal axis suppression (HPAS) in asthmatic children treated with inhaled corticosteroids (ICS), with or without nasal steroids (NS), may be more common than previously thought. Only dynamic testing will identify children at risk of adrenal crisis. It is impractical to test all asthmatic children for HPAS with a gold standard adrenal function test, i.e. the metyrapone or insulin tolerance test.

Objective: To determine which clinical or biochemical parameter is the most useful screening test for HPAS in asthmatic children.

Study design: 26 asthmatic children, 5–18 years old, on ICS ± NS, not treated with oral or topical steroids in the preceding year were recruited. Height, weight, height velocity, weight velocity and a change in systolic blood pressure from the recumbent to the standing position (ΔSBP) were recorded. Early-morning urine for urinary-free cortisol (UFC) and urinary cortisol metabolites (UCM) was collected. UFC was analyzed by both a chemiluminescent assay and gas chromatography/mass spectrometry (GC-MS). Morning serum cortisol and adrenocorticotropic hormone (ACTH) levels were measured. The overnight metyrapone test was performed if the fasting morning serum cortisol was >83 nmol/l. HPAS was diagnosed if the ACTH failed to rise >100 pg/ml after metyrapone. Spearman correlation coefficients (r) were calculated between the post-metyrapone ACTH and each variable. A receiver-operating characteristics (ROC) curve was drawn for the most promising test, and the diagnostic performance was calculated.
Results: All clinical and biochemical parameters investigated were weakly and nonsignificantly correlated with the post-metyrapone ACTH, except for the morning serum ACTH (r = 0.68; p < 0.001). The best discrimination between those who have and those who do not have HPAS is a morning serum ACTH level of 11.7 pg/ml. This corresponds to a sensitivity of 0.89 (0.57–0.98), a specificity of 0.77 (0.53–0.90), a positive predictive value of 0.67 (0.39–0.87), a negative predictive value of 0.93 (0.69–0.99), an accuracy of 0.81 (0.61–0.94), a positive likelihood ratio of 3.78 (1.68–9.49) and a negative likelihood ratio of 0.15 (0.03–0.60).

Conclusions: The morning serum ACTH level was found to be the most useful screening test to detect HPAS in this sample of children receiving ICS ± NS. A larger study should be undertaken to refine the diagnostic precision of the morning serum ACTH level.

Suppression of the hypothalamic-pituitary-adrenal axis (HPA) in asthmatic children treated with inhaled corticosteroids (ICS), with or without nasal steroids (INS), is one of the major endocrine concerns among these patients. The debate has been around for many decades. Two recent papers address this issue. Up to 80% of children with asthma also suffer from concomitant allergic rhinitis which requires long-term treatment with a combination of inhaled (ICS) and intranasal corticosteroids (INS). Heijsman et al. studied morning salivary cortisol levels in prepubertal children and could not find an additional suppressive effect of combined glucocorticoid treatment on HPA axis function. However, cortisol levels have been decreased among treated children compared with steroid-naive controls, irrespective of the cumulative daily dose of topical steroids. None of the treated children had growth restrictions based on height SDS; data on height velocities were not provided. The authors speculate about an individual susceptibility for suppression of HPA axis. Relative hypocortisolemia may have other untoward effects such as fatigue, but mostly when a child needs his maximal adrenal capacity in extreme stress.

The second paper by Zöllner et al. focused on the important question how to screen for suppression of HPA axis among children with asthma. They compared morning urinary-free cortisol and serum levels of cortisol and ACTH with post-metyrapone ACTH levels as the gold standard (it is important to keep in mind this neglected test as the ultimate test for HPA axis activity). Only the morning ACTH was significantly correlated with post-metyrapone ACTH. Unfortunately, the better available salivary cortisol levels or 24 h urine measurements have not been performed. In line with the paper of Heijsman et al., further long-term studies addressing the question of diagnosis and clinical relevance based on robust parameters like final heights are necessary. The debate goes on.

Inflammatory bowel disease and vitamin D insufficiency

Treatment of Vitamin D Insufficiency in Children and Adolescents with Inflammatory Bowel Disease: A Randomized Clinical Trial Comparing Three Regimens

Center for Inflammatory Bowel Diseases (H.M.P., S.K.); Clinical Research Center, Design and Analysis Core (P.D.M., H.J., R.F.D.); Clinical and Translational Study Unit (D.D., N.Q.), Children's Hospital Boston, Boston, MA; Northwestern University Feinberg School of Medicine (R.C.L.), Center for Psychosocial Research in Gastrointestinal Diseases, Chicago, IL; Johns Hopkins University (M.V.), Department of Psychiatry, Division of Medical Psychology, Baltimore, MD, USA; Academic Medical Center (S.V.S.), Amsterdam, The Netherlands, and Bone Health Program (C.M.G.), Children's Hospital Boston, Boston, MA, USA
J Clin Endocrinol Metab 2012;97:2134–2142

Background: Vitamin D insufficiency (serum 25-hydroxyvitamin D (25OHD) concentration <20 ng/ml) is prevalent among children with inflammatory bowel disease (IBD), and its treatment has not been studied.

Objective: The aim of this study was to compare the efficacy and safety of three vitamin D repletion regimens.

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J Clin Endocrinol Metab 2012;97:2134–2142

Background: Vitamin D insufficiency (serum 25-hydroxyvitamin D (25OHD) concentration <20 ng/ml) is prevalent among children with inflammatory bowel disease (IBD), and its treatment has not been studied.

Objective: The aim of this study was to compare the efficacy and safety of three vitamin D repletion regimens.
Study Design: We conducted a randomized, controlled clinical trial from November 2007 to June 2010 at the Clinical and Translational Study Unit of Children’s Hospital Boston. The study was not blinded to participants and investigators. Eligibility criteria included diagnosis of IBD, age 5–21, and serum 25OHD concentration <20 ng/ml. 71 patients enrolled, 61 completed the trial, and 2 withdrew due to adverse events.

Intervention: Patients received orally for 6 weeks: vitamin D2, 2,000 IU daily (arm A, control); vitamin D3, 2,000 IU daily (arm B); vitamin D2, 50,000 IU weekly (arm C), and an age-appropriate calcium supplement.

Main Outcome Measure: We measured the change in serum 25OHD concentration (Δ25OHD) (ng/ml). Secondary outcomes included change in serum intact PTH concentration (ΔPTH) (pg/ml) and the adverse event occurrence rate.

Results: After 6 weeks, Δ25OHD ± se was: 9.3 ± 1.8 (arm A); 16.4 ± 2.0 (arm B); 25.4 ± 2.5 (arm C); p (A vs. C) = 0.0004; p (A vs. B) = 0.03. ΔPTH ± se was −5.6 ± 5.5 (arm A); −0.1 ± 4.2 (arm B); −4.4 ± 3.9 (arm C); p = 0.57. No participant experienced hypercalcemia or hyperphosphatemia, and the prevalence of hypercalciuria did not differ among arms at follow-up.

Conclusions: Oral doses of 2,000 IU vitamin D3 daily and 50,000 IU vitamin D2 weekly for 6 weeks are superior to 2,000 IU vitamin D2 daily for 6 weeks in raising serum 25OHD concentration and are well tolerated among children and adolescents with IBD. The change in serum PTH concentration did not differ among arms.

Besides the classical role of vitamin D, new evidence has been reported that vitamin D deficiency might be implicated in a host of other diseases including psoriasis, multiple sclerosis, inflammatory bowel disease, type 1 and 2 diabetes, hypertension, cardiovascular disease, the metabolic syndrome and various cancers. Pappa et al. conducted a randomized control trial (RCT) on different supplementation regimens in IBS patients. They postulate that 50,000 IU of oral vitamin D2 weekly or 2,000 IU of oral vitamin D3 daily for 6 weeks are sufficient to raise serum 25OHD concentration in children and adolescents with IBD and vitamin D insufficiency. The second finding was that PTH seems to play no role in diagnosis and treatment control, since PTH levels were low before initiation of substitution. The authors speculate about a potential involvement of antibodies against the calcium-sensing receptor which directly upregulate its expression driving downward the calcium level needed to stimulate PTH secretion. In agreement with the authors, one major limitation of this study was the lack of a healthy control group. These issues should be addressed in upcoming studies.

The role of growth hormone and insulin-like growth factor-1 in Crohn’s disease: implications for therapeutic use of human growth hormone in pediatric patients

Vortia E, Kay M, Wyllie R
Department of Pediatric Gastroenterology and Nutrition, Children’s Hospital, Cleveland Clinic, Cleveland, OH, USA
Curr Opin Pediatr 2011;23:545–551

Objective: This review evaluates the role of the growth hormone (GH) and insulin-like growth factor (IGF) in influencing linear growth in pediatric Crohn’s disease. It also examines the current evidence concerning the use of recombinant human growth hormone (rhGH) as a potential therapy in achieving optimal growth and inducing mucosal healing for pediatric Crohn’s disease.

Recent Findings: Current treatment strategies for Crohn’s disease including antitumor necrosis factor-α (TNF-α) therapy have been demonstrated to improve growth velocity, but linear growth deficits persist despite optimization of therapy. By complex mechanisms, including the reduction of levels of IGF-1 and induction of systemic and hepatic GH resistance, cytokines such as TNF-α and interleukin-6 (IL-6), commonly elevated in active Crohn’s disease, are important as mediators of linear growth delay. Recent
evidence suggests that rhGH therapy is effective in improving short-term linear growth for a selected group of patients but of limited benefit as a therapy for improving mucosal disease and reducing clinical disease activity.

Summary and Conclusions: Crohn’s disease interacts with the GH-IGF-1 axis in important ways. Recent studies evaluating rhGH use in pediatric Crohn’s disease have demonstrated some efficacy in reversing persistent linear growth delay but limited benefits in terms of improving mucosal disease and clinical disease activity. Larger studies of adequate power are needed to confirm a true benefit in terms of growth, to examine a potential benefit with regard to modification of disease activity, and to evaluate long-term risks.

Growth failure and delayed puberty are particular comorbidities among children with inflammatory bowel disease such as Crohn’s disease. Several studies with different patient numbers ranging between 3 and 37 have been conducted. However, to date there is no convincing evidence that there is a substantial role for rhGH in these patients on linear growth or disease activity. We agree with Vortia et al. that larger studies are needed examining disease activity and robust parameters of linear growth like final heights.

**Review**

**Endocrine diseases after liver transplantation**

Högler W, Baumann U, Kelly D
Department of Endocrinology and Diabetes, Birmingham Children’s Hospital, Birmingham, UK
wolfgang.hogler@bch.nhs.uk

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**Background:** With improved survival of orthotopic liver transplantation (OLT) in children, prevention and treatment of pre- and posttransplant complications have become a major focus of care. End-stage liver failure can cause endocrine complications such as growth failure and hepatic osteodystrophy, and, like other chronic illnesses, also pubertal delay, relative adrenal insufficiency, and the sick euthyroid syndrome.

**Results:** Drug-induced diabetes mellitus post-OLT affects approximately 10% of children. Growth failure is found in 60% of children assessed for OLT. Despite optimization of nutrition, rarely can further stunting of growth before OLT be prevented. Catch-up growth is usually observed after steroid weaning from 18 months post-OLT. Whether growth hormone treatment would benefit the 20% of children who fail to catch up in height requires testing in randomized controlled trials. Hepatic osteodystrophy in children comprises vitamin D deficiency rickets, low bone mass, and fractures caused by malnutrition and malabsorption. Vitamin D deficiency requires aggressive treatment with ergocalciferol (D2) or cholecalciferol (D3). The active vitamin D metabolites alphacalcidol or calcitriol increase gut calcium absorption but do not replace vitamin D stores. Prevalence of fractures is increased both before OLT (10–28% of children) and after OLT (12–38%). Most fractures are vertebral, are associated with low spine bone mineral density, and frequently occur asymptptomatically, but they may also cause chronic pain. Fracture prediction in these children is limited. OLT in children is also associated with a greater risk of developing avascular bone necrosis (4%) and scoliosis (13%–38%).

**Summary:** This article reviews the literature on endocrine and skeletal complications of liver disease and presents preventive screening recommendations and therapeutic strategies.

The number of long-term survivors after childhood liver transplantation is increasing. Thus, questions about long-term outcomes and disease/treatment associated comorbidities have to be asked. The excellent review by Högler et al. summarizes current knowledge on these issues. Short stature, a role for growth-promoting therapies like treatment with rhGH, ‘sick thyroid syndrome’ due to low thyroid hormone transport protein production in liver disease, and transient or persistent...
adrenal insufficiency are among them. As previously commented on rare diseases, this review underlines the need for collecting long-term data in (inter)national registries of patients after liver transplantation.

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