Oncology and Chronic Disease

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The impact of childhood cancer therapy on fertility and reproduction of young adults is still the number one topic in pediatric oncology and endocrinology as shown by the number of published papers in the literature. Last year, we selected two guidelines recommending long-term follow-up of male and female survivors with regard to fertility [1, 2]. These guidelines are evidence-based recommendations and they are still valid. In order to assess the late effects of childhood cancer therapy on the endocrine system, it is necessary to define and evaluate the endocrine disorder, analyze the cancer therapy, address risk factors, and counsel the patient on therapeutic options. In this context, the research on fertility preservation for pre- and postpubertal patients is becoming increasingly important.

The number of papers published on the topic 'chronic disease and endocrinology' has remained relatively constant in recent years. We analyzed this topic again from two aspects: (1) from the perspective of affected patients e.g. analyzing growth and pubertal development, and (2) from the perspective of side effects on the endocrine system in relation to the respective therapeutic regimens.

Late effects of tumor therapy Confirmation of previous results

Ovarian function after allogeneic hematopoietic stem cell transplantation in childhood and adolescence

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Background: The study aimed to evaluate long-term ovarian function after allogeneic hematopoietic stem cell transplantation (HSCT) in childhood and adolescence.

Methods: Predictive factors for ovarian function were evaluated among 92 adult or pubertal female survivors transplanted at Huddinge and Helsinki University Hospital during 1978–2000, at a mean age of 9 ± 4.3 years (range 1–19). At the time of the study a mean ($\pm$ SD) of 13 ± 5.5 years (range 6–27) had elapsed since the HSCT and the mean age of the participants was 22 ± 6.3 years (range 9–41).

Results: Spontaneous puberty based on breast development occurred in 40 and menarche in 30 of the 70 girls who were prepubertal at transplantation. Six out of 20 girls who received HSCT after initiation of pubertal development recovered their ovarian function. Younger age at HSCT, conditioning without total body irradiation (TBI), and a non-leukemia diagnosis predicted spontaneous menarche. The incidence of menarche was higher after fractionated versus single fraction TBI ($p < 0.05$), cyclophosphamide (Cy) versus busulfan (Bu)-based conditioning ($p < 0.05$), and among leukemia patients transplanted at first remission versus later remissions ($p < 0.01$) and with no cranial irradiation (cranial radiotherapy, CRT) versus given CRT (14–24 Gy) ($p < 0.01$). The majority of recipients conditioned with only Cy versus TBI ($p < 0.001$) or versus Bu-based regimens ($p < 0.01$) showed preserved ovarian function and required no estrogen replacement at their latest follow-up visit at a mean age of 23 ± 6.3 years (range 15–41). Ten women became pregnant.

Conclusions: Patients conditioned with TBI or Bu-based regimens are at high risk of ovarian failure. Intensive anti-leukemia therapy before HSCT including CRT especially among relapsed patients may further decrease the possibility of spontaneous menarche.

It has been shown that infertility is a major late effect in patients receiving hematopoietic stem cell transplantation (HSCT) in childhood and adolescence. In this paper, the authors identified predictive factors such as younger age, prepubertal stage, conditioning without total body irradiation, etc. for ovarian function in a large cohort of female cancer survivors after HSCT. Thus, with the knowledge of these factors, it might be possible to change the conditioning regimen before HSCT. However, apart from gonadal dysfunction, other abnormalities of endocrine function such as impaired linear growth, adult short stature, primary hypothyroidism and/or reduced bone mineral density are also common after HSCT [3].

Late effects of tumor therapy Broaden existing knowledge

Endocrine complications and components of the metabolic syndrome in survivors of childhood malignant non-brain solid tumors

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Background: Survival of children with cancer has improved substantially over the past decades, but at the cost of late treatment-related sequelae. This study aimed to evaluate endocrine outcome in long-term survivors of childhood non-brain malignant solid tumors (NBMST).

Methods: Medical records were retrospectively reviewed for medical history, clinical, and laboratory data of 139 survivors followed at the endocrine clinic of a tertiary medical center. Frequencies and types of endocrine dysfunction and components of the metabolic syndrome served as the main outcome measures.

Results: Median follow-up time (range) was 9.0 (1.2–29.5) years. 44 (31.7%) patients had at least one of the following endocrine abnormalities: hypogonadism (11.5%), hypothyroidism (9.4%), short stature (9.4%), growth hormone deficiency (8.6%), and components of the metabolic syndrome (15.1%). During follow-up, height SDS decreased significantly ($p = 0.004$), whilst body mass index SDS tended to increase. Logistic regression analysis revealed significant associations with a higher hazard of endocrinopathy for treatment with cranial irradiation ($p = 0.003$), local radiation ($p = 0.042$), or bone marrow transplantation ($p = 0.0001$), and older age at last visit ($p < 0.001$).

Conclusions: Survivors of childhood NBMST show high rates of late endocrine dysfunctions. This highlights that follow-up needs to be optimized at late-effects clinics to identify endocrine problems and enable early and effective intervention.

The authors present a summary of the late endocrine and metabolic sequelae of the treatment of solid tumours located outside the central nervous system. The study clearly demonstrates that there is a great need for structured follow-up of patients treated for such tumours. However, due to the small case number and heterogeneity of tumour entities investigated, the findings for some aspects were not statistically significant. For example, gonadal damage caused by alkylating agents or hypothyroidism after local irradiation was detectable but did not attain statistical significance. Thus, the final interpretation of the results is problematic. However, the study is helpful because, on the one hand, it places other tumours than usual in the focus of endocrine follow-up and, on the other hand, it recommends investigating markers of the metabolic syndrome, which is also of great clinical relevance.

Pubertal development and fertility in survivors of childhood acute myeloid leukemia treated with chemotherapy only: a NOPHO-AML study

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Pediatr Blood Cancer 2013;60:1988–1995

Background: More than 60% of children with acute myeloid leukemia (AML) become long-term survivors. Most are cured using chemotherapy without hematopoietic stem cell transplantation (HSCT). The authors report on pubertal development and compare self-reported parenthood among AML survivors and their siblings.

Methods: 137 children treated for AML according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO)-AML-84, -88, and -93 trials, who were alive in June 2007, were included in the study. Patients with relapse or treated with HSCT were excluded. AML survivors participated in a physical and biochemical examination (n = 102) and completed a questionnaire (n = 101). One of their siblings completed an identical questionnaire (n = 84).

Results: At a median follow-up of 11 years (range 5–25) after diagnosis of AML, the survivors (median age 16 years, range 5–36) were either prepubertal or had entered puberty normally. Serum levels of FSH, LH, testosterone, estradiol, sex hormone binding globulin (SHBG), inhibin A and B, and testicular volumes were within normal ranges. Anti-müllerian hormone (AMH) levels were decreased in 5 of 40 postpubertal females. Mean reported age at menarche was 13.1 (range 11–17) years. Among survivors 15 years of age or older, 31% of females reported pregnancies and 9% of males reported pregnancies in their partners – rates comparable with the frequency reported by their siblings.

Conclusions: Most AML survivors treated with chemotherapy had normal pubertal development and fertility, however AMH levels were decreased in 13% of postpubertal females. Longer follow-up is necessary to evaluate possible risk of premature ovarian failure.

Acute myeloid leukemia (AML) represents 20% of the acute leukemia cases in children and adolescents. The outcome of the NOPHO-AML studies (Nordic Society of Pediatric Hematology and Oncology) is among the best in the world (5-year survival rate of 65%). Many of the late effects reported in AML survivors were probably caused by cranial irradiation and hematopoietic stem cell transplantation (HSCT). In this study, only those AML survivors were included who were treated with chemotherapy alone. With this strategy, the number of survivors remained high without negative impact on pubertal development and fertility. These results are promising for AML survivors.

New hope

Ovarian reserve – the value of AMH

Anti-müllerian hormone as a measure of reproductive function in female childhood cancer survivors

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Objective: The utility of measuring anti-müllerian hormone (AMH) in childhood cancer survivors to assess ovarian reserve, pubertal status, and fertility potential was evaluated in a cross-sectional study performed by an academic medical center.

Methods: 53 female childhood cancer survivors, median age 13.9 years (range 9–25) were recruited at least 1 year from completion of cancer therapy. Main outcome measures were: serum AMH, luteiniz

ing hormone (LH), follicle-stimulating hormone (FSH), and estradiol measurements, pubertal/menstrual history and Tanner staging, with risk of gonadotoxicity classified as low or high based on chemotherapy agent and pelvic/abdominal radiation.

Results: 31 of the 53 patients (58%) in the cohort had diminished ovarian reserve (DOR) detected by an AMH value <1 ng/ml. DOR was detected by a FSH value of >12 IU/ml in 17 patients (32%). The patients exposed to high-risk chemotherapy or pelvic radiation were at statistically significantly higher risk for DOR as measured by their AMH level. The AMH level was also significantly lower in the patients who had delayed puberty.

Conclusions: Using the serum gonadotropin level to screen childhood cancer survivors for ovarian failure is a suboptimal method. The AMH value identified the patients at risk for delayed puberty and those who could benefit from fertility preservation counseling, which makes AMH perhaps the optimal screening tool for assessing ovarian reserve in this population.

In childhood cancer survivors (CCS), serum anti-müllerian hormone (AMH) is used to assess ovarian reserve. In this study, diminished ovarian reserve (DOR) detected by an AMH value <1 ng/ml was found in 58% of female CCS. The authors suggest that AMH is a more sensitive measure than FSH for detecting DOR in childhood cancer survivors. The results are in line with other published reports [4, 5]. In young females with different cancers, Brougham et al. [5] found a steady decline in serum AMH levels during the course of repeated chemotherapy. In girls with low or medium risk of premature ovarian failure (POF), AMH recovered to pretreatment concentrations, whereas in girls with a high risk of POF, serum AMH levels were undetectable at the end of treatment. However, female childhood cancer survivors are asking for pregnancy and not for DOR. In contrast to the authors' conclusions, the value of AMH was recently questioned in the literature because it has been shown that a low AMH level was not predictive of reduced fertility. Low AMH levels were found in 44% of 45 female childhood cancer survivors, but nearly all (93%) had successful pregnancies [6].

New hope Ovarian reserve – the role of obesity

Decreased ovarian function is associated with obesity in very long-term female survivors of childhood cancer

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Eur J Endocrinol 2013;168:905–912

Background: Obesity and gonadal dysfunction are known major side effects of treatment in adult childhood cancer survivors (CCS). In the general population, obesity has a negative influence on female fertility. The authors aimed to evaluate whether obesity and serum insulin are associated with decreased ovarian reserve markers in CCS.

Methods: Using a retrospective single-center cohort design, data of 191 female survivors of childhood cancer were analyzed. Median follow-up time was 18.8 (2,348.8) years. Outcome measures were serum anti-müllerian hormone (AMH) and total follicle count (FC). Potential risk factors were: BMI; body composition measures, determined by dual-energy X-ray absorptiometry (total fat percentage, lean body mass, and visceral fat percentage), and fasting insulin.

Results: Lower serum AMH was found in obese subjects (β (%) -49 , $p = 0.007$) and in subjects with fasting insulin in the highest tertile (β (%) -43 , $p = 0.039$). Total fat percentage tends to be associated with serum AMH (β (%) -2.1 , $p = 0.06$). Survivors in the highest tertile of insulin had significantly lower FC than survivors in the lowest tertile (β -6.3 , $p = 0.013$). BMI and other measures of body composition were not associated with FC. Correlation between serum AMH and antral follicle count (AFC) was $\rho = 0.32$ ($p = 0.08$).

Conclusions: Obesity and insulin resistance are associated with gonadal damage, as reflected by decreased AMH and reduced FC in adult survivors of childhood cancer. In contrast to its highly predictive value for AFC in the healthy female population, serum AMH does not seem to correlate as well with AFC in CCS.

The authors used serum anti-müllerian hormone (AMH) to assess ovarian reserve in childhood cancer survivors (CCS). The prevalence of obesity is high after cancer therapy. It is the merit of the authors that they analyzed this problem in a large number of female CCS. It is known that the ovaries are susceptible to chemotherapy-induced and irradiation-induced damage. The authors show that obesity and insulin resistance also contribute to gonadal damage. After adjusting the analysis for confounders (e.g. age at diagnosis, treatment with irradiation), obesity and high fasting insulin levels remained significantly associated with low serum AMH levels. In agreement with the previous paper by Lunsford et al. (see above), the value of low AMH levels to define diminished ovarian reserve was highlighted.

Reviews

Ovarian transposition in prepubescent and adolescent girls with cancer

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Lancet Oncol 2013;14:e601–e608

Background: With the decrease of mortality from childhood cancer over the past decades, almost 80% of pediatric cancer patients have become long-term survivors. Hence impaired female fertility has increasingly gained importance as a late sequela of abdominal and pelvic radiotherapy for certain childhood cancers. Ovarian transposition before radiotherapy was the first procedure proposed as a measure to prevent radiation-induced ovarian damage and preserve ovarian function. However, the long-term results of ovarian transposition are not well studied.

Methods: Reports in English identified through a PubMed literature search covering the 01/1995–03/2013 period were reviewed and supplemented with a review of the authors' own files. Final selection of reports for inclusion was based on recent date of publication and relevance to the broad scope of the review.

Results: In total, 74 pertinent references were identified, evaluated and discussed in terms of radiotherapy and ovarian function, indications for ovarian transposition in childhood cancers, technical aspects of pelvic radiotherapy in children, technical aspects of ovarian transposition, and results of ovarian transposition. Ovarian transposition is indicated for tumors requiring pelvic radiation doses of 42.0–58.4 Gy, i.e. doses higher than those that induce loss of ovarian function (4–20 Gy). Ovarian transposition is usually performed after neoadjuvant chemotherapy and is completed by laparoscopic surgery, or by laparotomy in case of concomitant resection of the abdominal tumor. Depending on the type of tumor, the ovaries are moved and placed in the paracolic gutters when the radiation field reaches the midline (for medulloblastoma or urogenital rhabdomyosarcoma), contralaterally to the tumor (for pelvic sarcomas), or in line with the iliac crests (for Hodgkin's lymphoma). However, in 10–14% of cases the procedure can fail to protect the ovaries. Although few long-term results in adults are available, a small number of long-term follow-up studies have reported normal hormonal function and pregnancies. The success rate of ovarian transposition appears to be 60–83%.

Conclusions: In view of the continued development of fertility preservation techniques, ovarian transposition should be discussed at a multidisciplinary meeting at the time of cancer diagnosis and treatment planning. Moreover, laboratory markers such as inhibin B and anti-müllerian hormone today enable accurate assessment of ovarian function in cancer survivors. Hence, long-term ovarian function should now be studied prospectively in all children who undergo ovarian transposition. Long-term follow-up data need to be collected in the context of an international multicenter study.

The strength of this review article is that it summarizes and evaluates 74 well-selected publications on the subject of ovarian transposition and related areas. The authors discuss various therapeutic options, their indications, and technical aspects of the surgical procedures, which are usually pre-

ceded by neoadjuvant chemotherapy. The article also addresses surgical complications as well as the maintenance of ovarian function. Importantly, it illustrates the necessity of, and calls for, the establishment of multidisciplinary international databases to document the effectiveness of these rarely performed procedures and the fertility and hormone levels in women who survived childhood malignancies. This article provides an excellent basis for the education of patients currently undergoing treatment.

Update on endocrine and metabolic therapy-related late effects observed in survivors of childhood neoplasia

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Background: Data on prevalence and risk associations are increasingly available from large cohorts of childhood cancer survivors. New directions in research include novel risk-prediction strategies and the study of genetic predisposition. The aim of this review was to provide a summary of the most recent research pertaining to the endocrine and metabolic complications observed in childhood cancer survivors.

Findings and Conclusions: Endocrine complications are observed in more than 50% of adult childhood cancer survivors. Some continue to develop decades following cancer treatment exposures. The present review provides a summary of the most recent outcomes research pertaining to growth, thyroid, gonadal-reproductive, bone and body composition with emphasis on new directions and challenges in each area.

This excellent review summarizes the current knowledge on endocrine late effects after childhood cancer. The importance of continued monitoring and follow-up of individuals at risk and the need for continuing research efforts to improve risk prediction models, develop patient-centered screening strategies, and understand modifiable risk factors were emphasized by the authors.

Back to the future

Hospital contacts for endocrine disorders in Adult Life after Childhood Cancer in Scandinavia (ALiCCS): a population-based cohort study

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Background: The pattern of endocrine disorders in long-term survivors of childhood cancer has not been investigated comprehensively. The objective of this study was to assess the lifetime risk of these disorders in survivors of childhood cancer in the five Nordic countries – Denmark, Finland, Iceland, Norway, and Sweden.

Methods: The Nordic countries' national cancer registries were used to identify 31,723 1-year survivors of childhood cancer reported to the registries since registration began in the 1940s and 1950s. A comparison cohort of individuals matched by age, sex, and country was selected from the participating countries' national population registries. Study participants were linked to the national hospital registries, and observed numbers of first-time hospital contacts for endocrine disorders in childhood cancer survivors were compared with the expected numbers derived from the comparison cohort. Absolute excess risks attributable to status as a childhood cancer survivor and standardized hospitalization rate ratios (SHRRs) were calculated.

Results: Of the childhood cancer survivors included in the analysis, 3,292 had contact with a hospital for an endocrine disorder, yielding a SHRR (95% CI) of 4.8 (4.6–5.0). The highest risks were observed in survivors of leukaemia (SHRR 7.3 (6.7–7.9)), CNS tumours (6.6 (6.2–7.0)), and Hodgkin's lymphoma (6.2 (5.6–7.0)). The absolute excess risk for endocrine disorders was approx. 1,000 per 100,000 person-years before the age of 20 years, and 400 per 100,000 person-years during the remaining lifetime. Children diagnosed with cancer at age 5–9 years had the highest cumulative risk for endocrine disorders, and at the age of 60 years the cumulative risk reached 43%. Diagnoses of pituitary hypofunction (SHRR 88.0), hypothyroidism (9.9), and testicular (42.5) and ovarian dysfunction (4.7) together accounted for 61% (655/1078) of all excess disease-induced and treatment-induced endocrine disorders in survivors of childhood cancer.

Conclusions: A cumulative risk for endocrine disorders at age 60 years of >40% in childhood cancer survivors emphasizes the importance of minimizing damage-inducing treatment, intensifying secondary prevention, and targeting survivor follow-up throughout life. Since most long-term childhood cancer survivors are not followed in a specialized late-effect clinic, they present a growing challenge to both physicians in primary care and medical specialists working outside the late-effect area.

This study analyzes data from the Nordic countries' tumour registries with regard to late endocrine effects in adults treated for cancer during childhood. The outstanding feature of the study is that it analyses long-term follow-up data covering a period of 50–60 years. The study demonstrates the need for continued long-term follow-up, especially because late endocrine sequelae of childhood cancer treatment peaked at age 60 years. The publication concludes, firstly, that damage induced by primary therapy needs to be minimized as it leads to the late sequelae in the long term and, secondly, that secondary prevention and a structured long-term follow-up are of great importance. Another strength of the study is that the authors coded the observed endocrine disorders according to the International Classification of Diseases, Injuries and Causes of Death, 10th revision (ICD-10), assigning them to lower-level and higher-level functions and other organ-specific disorders. Moreover, they stratified the study population by primary disease and age at diagnosis. Thus, this study provides an excellent tool for targeted consultation in both pediatric oncology and pediatric endocrinology settings. Moreover, it emphasizes the need for a structured transition from pediatric to adult care.

Back to the future Important for clinical practice

Primary ovarian insufficiency in children after treatment with ¹³¹I-metaiodobenzylguanidine for neuroblastoma: report of the first two cases

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J Clin Endocrinol Metab 2014;99:E112–E116

Background: Primary ovarian insufficiency (POI) is a well-known late sequela in survivors of childhood cancer treated with alkylating agents or radiation that also involved the ovaries. Gonadal failure in pediatric neuroblastoma (NBL) patients exposed to ¹³¹I-metaiodobenzylguanidine (¹³¹I-MIBG) has only been reported in conjunction with chemotherapy. In these patients, the cytotoxic therapy was assumed to have caused the gonadal failure. The authors describe the first two cases of POI after ¹³¹I-MIBG-only treatment for NBL.

Methods and Results: During follow-up, 2 girls aged 12 and 11 years who had been treated for NBL during early childhood presented with elevated gonadotropins (FSH levels of 105 and 161 U/L, respectively), indicative of POI. Both girls had a normal female 46,XX karyotype. There was no other cause of ovar

ian failure except their history of treatment for NBL. The first patient had been diagnosed with stage III intraspinal NBL in the sacral region at the age of 17 months. Treatment had consisted in five courses of ^{131}I -MIBG and local resection. The second patient had been diagnosed with an abdominal (intraspinal) NBL at 8 months of age. Treatment had consisted in acute (neuro)surgery for decompression of the intraspinal tumor that was causing neurological symptoms, followed by two courses of ^{131}I -MIBG.

Treatment: Estrogen supplementation was initiated, and patients and parents were counseled regarding fertility options.

Conclusion: These 2 patients suggest that exposure to ^{131}I -MIBG may cause damage to the female gonads. The reported observations warrant further prospective studies to confirm the potential causative role of ^{131}I -MIBG in POI. Clinicians caring for survivors of childhood cancer should be aware of the risk of POI after ^{131}I -MIBG treatment and provide fertility counseling.

This is the first report to describe that treatment of infants with NBL with ^{131}I -MIBG alone may result in primary damage to the ovaries in girls. This aspect should be routinely addressed when discussing the effects of ^{131}I -MIBG with the patient's parents or legal guardians. Moreover, it appears that the anatomical proximity between the ovaries and the bladder, where the radioactive iodine accumulates with the urine, and intraspinal NBLs located in close proximity to the female gonads, where the radioactivity also accumulates, are predominantly responsible for primary gonadal damage. Since the girls investigated in this study had not received any concomitant chemotherapy or extracorporeal radiotherapy, the direct effect of the radiation emitted by the ^{131}I -MIBG on the gonads can safely be concluded to be the only remaining cause of ovarian failure. This publication adds new aspects to the overall assessment of ^{131}I -MIBG therapy, the education of parents regarding the potential adverse effects of such treatment, and the follow-up of NBL patients treated with ^{131}I -MIBG.

Chronic disease Important for clinical practice

Pediatric endocrine surgery: a 20-year experience at the Mayo Clinic

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Background: Surgically managed endocrinopathies are rare in children. Most surgeons have limited experience in this field. The authors report their operative experience with pediatric patients, performed over two decades by high-volume endocrine surgeons. The study was conducted at the Mayo Clinic (a tertiary referral center).

Methods: Patients were <19 years old and underwent an endocrine operation (1993–2012). Their demographics, surgical procedure, diagnoses, morbidity, and mortality were retrospectively reviewed.

Results: A total of 241 primary cases included 177 thyroid procedures, 13 neck dissections, 24 parathyroidectomies, 14 adrenalectomies, 7 paragangliomas, and 6 pancreatic procedures. Average age of patients was 14.2 years. There were 133 total thyroidectomies and 40 hemithyroidectomies. 53 cases underwent a central or lateral neck dissection. A 6-month follow-up was available for 98 total thyroidectomy patients. There were 4 cases of permanent hypoparathyroidism (4%) and no permanent recurrent laryngeal nerve (RLN) paralyses. Sequelae of neck dissections included temporary RLN neurapraxia and Horner's syndrome. Parathyroidectomy was performed on 24 patients: 20 with primary hyperparathyroidism (HPT), 3 with tertiary HPT, and 1 with familial hypocalciuric hypocalcemia. Three patients (16%) had recurrent HPT, all with multiglandular disease. One patient had temporary RLN neurapraxia. The authors performed 7 bilateral and 7 unilateral adrenalectomies; 8 were laparoscopic. Indications included pheochromocytoma, Cushing's syndrome, adrenocortical carcinoma, congenital adrenal hyperplasia, and ganglioneuroma. One death was due to adrenocortical carcinoma. Five paraganglioma patients had succinate dehydrogenase subunit B mutations, and 1 recurred. Six patients with

insulinoma underwent enucleation (n = 5) or distal pancreatectomy (n = 1). A single postoperative abscess was managed nonoperatively.

Conclusions: Pediatric endocrine procedures are uncommon but can be safely performed with complication rates comparable to those of the adult population. It is imperative that these operations be performed by high-volume surgeons.

The data published from the Mayo Clinic show that endocrine sequelae of children requiring endocrine surgery are overall very rare. The paper provides an overview on the spectrum of pediatric endocrine surgery over two decades. We appreciate the statement that pediatric patients are not the same as small adult patients, and that standards must be set. The authors emphasize that these rare operations should be performed by high-volume surgeons. We have problems to define a high-volume surgeon with regard to the fact that only 14 adrenalectomies have been performed in 20 years, i.e. less than one adrenalectomy per year. It might be more important to underline the necessity to operate these children in the setting of an experienced tertiary referral center by surgeons who have expertise in endocrinology and children.

Chronic disease Review

Neoplastic causes of abnormal puberty

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Pediatr Blood Cancer 2014;61:664–671

Background: Neoplasm-related precocious puberty (PP) is a rare presenting feature of childhood cancer. Moreover, evaluation of suspected PP in a child is complex, and cancer is often not considered as a cause of PP. Conducted at a large pediatric cancer center, this study was conducted to characterize the clinicopathologic features of patients presenting with PP, review the relevant literature, and develop a specific diagnostic work-up algorithm.

Methods: Demographic, clinical, endocrine, and neoplasm-related features were extracted from the records of all patients with a neoplasm and concomitant PP treated at St. Jude Children's Research Hospital from January 1975 through October 2011. The data were analyzed descriptively and the available literature was reviewed.

Results: Of 13,615 children and adolescents, 24 (16 males and 8 females, 0.18%) were diagnosed with PP within 60 days of presentation. Primary diagnoses included brain tumor (12), adrenocortical carcinoma (5), hepatoblastoma (4), and others (3). Median age at onset of PP was 8.5 years in patients with brain tumors and 3.1 years in patients with extracranial tumors. Median time (range) from onset of PP to tumor diagnosis was 6 (0–48) months in both sexes. 17 patients had peripheral PP and 7 had central PP.

Conclusions: Neoplasm-related PP is rare and presents as a paraneoplastic syndrome caused by tumor-produced hormones or by alteration of physiologic gonadotropin production. PP can precede diagnosis of malignancy by months or years, and neoplastic causes should be considered early to avoid delay in the diagnosis of cancer. This may be facilitated by using the proposed diagnostic algorithm for PP, which includes malignancy as a potential underlying cause of PP. Treatment of the primary malignancy resolved or diminished PP in surviving patients with an intact hypothalamic-pituitary-gonadal axis.

This retrospective study shows the great importance of excluding neoplastic causes in patients with precocious puberty. Although neoplasms are rare causes of precocious puberty, it is essential to perform brain-imaging scans (MRI, or CT in settings where MRI is unavailable) in children – especially boys – with true precocious puberty. In patients with pseudo-precocious puberty, it is essential to exclude tumours as the cause. The study by Wendt et al. emphasizes the importance of close clinical and laboratory follow-up of patients with idiopathic precocious puberty. Notably, the authors present a clear and well-structured diagnostic algorithm for precocious puberty in the form of a flow-

chart that considers testing for tumours at a relatively early point. This flowchart is not quite different from previous published flowcharts but it helps in establishing rare diagnoses and critically evaluating the diagnostic information obtained.

Chronic disease Important for clinical practice

Puberty and plexiform neurofibroma tumor growth in patients with neurofibromatosis type I

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Background: Tumor burden and sex steroid levels during the course of puberty have not been clearly evaluated in pediatric patients with neurofibromatosis type 1 (NF1). A common concern among patients and physicians is whether puberty may lead to accelerated plexiform neurofibroma (PN) growth. While dermal neurofibroma numbers are known to increase during puberty, the impact of puberty on PN is undetermined. This study was conducted to assess the relationship between pubertal progression and change in PN burden over time in pediatric and young adult patients with NF1 and PNs.

Methods: 41 (15 female and 26 male) NF1 patients were evaluated for Tanner stage and hormone levels, including testosterone, progesterone, estradiol, insulin-like growth factor-1, luteinizing hormone, and follicle-stimulating hormone. Tumor volume was measured by automated detection and volume measurement of PNs using magnetic resonance imaging and software developed locally. Analyses accounted for sex, age, race, and chemotherapy. Patients were divided into two groups based on whether they were actively progressing through puberty ($n = 16$) or were peripubertal ($n = 25$). Median follow-up was 17.3 ± 6.7 and 21.7 ± 17.1 months, respectively. Tumor growth rates in the puberty and peripubertal group were analyzed for a subset of patients.

Results: Tumor burden change over time (cm^2/kg per month) showed no statistically significant difference between the pubertal and peripubertal groups (-0.16 ± 0.34 vs. 0.03 ± 1.8 , $p = 0.31$) and in the PN growth rates before and during puberty ($p = 0.90$). Change in relative tumor burden (tumor volume/kg body weight) over time did not correlate with changes in testosterone over time in males or estradiol levels over time in females.

Conclusions: These findings support the conclusion that the hormonal changes of puberty do not accelerate PN growth. Further characterization of the interaction between puberty and tumor growth requires additional long-term follow-up of patients.

In women, cutaneous and plexiform neurofibromas may increase during pregnancy both in number and in size. Evidence from animal studies suggests that sex steroids influence the progression of neurofibromas. The distinguishing feature of this study is that it examined the influence of the stage of puberty on tumour growth in prepubertal and pubertal children. In addition, the study investigated changes in tumour volumes and the underlying testosterone and estradiol levels in boys and girls, respectively. Cutaneous neurofibromas have been demonstrated to exhibit tumour growth during puberty. What sets this study apart from others is that it analyzed the effect of puberty and hormone levels on plexiform neurofibromas (PN). The data do not demonstrate an increase in PN growth rates during puberty. When adulthood is reached, tumour growth rates decrease again in the same patients. Possible limitations of the study are that specific therapies for neurofibromas were not considered. Moreover, both the limited possibilities of correctly measuring estradiol levels in the low concentration range and the fact that estrogen levels fluctuate during the menstrual cycle render it difficult to establish an association between estradiol levels and tumour growth.

Oxandrolone for the treatment of bone marrow failure in Fanconi anemia

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Background: A majority of Fanconi anemia (FA) patients will experience bone marrow failure (BMF) and androgen therapy (most often oxymetholone) may be utilized as a treatment to improve BMF-related cytopenias. However, oxymetholone is associated with toxicities making identification of other agents of interest. In this study we aimed to evaluate the toxicity profile and hematologic response in patients with FA who are treated with low-dose oxandrolone, a synthetic non-fluorinated anabolic steroid, similar to oxymetholone, with known dosing thresholds for virilization.

Methods: A single arm, phase I/II study was designed to treat patients on low-dose oxandrolone. If no toxicity or hematologic response was noted at 16 weeks, a single-dose escalation was offered. Subjects were regularly assessed for toxicity, including determinations of virilization, behavioral changes, and liver and kidney function. At 32 weeks, those who demonstrated hematologic response were allowed to continue study treatment, and those without improvement were deemed non-responsive.

Results: Nine subjects completed the study and were followed for a median of 99 (46–136) weeks. Three (33.3%) subjects developed mild subclinical virilization and continued treatment with a dose reduction. None (0%) had adverse behavioral changes. Two (22.2%) developed elevated liver function tests at 42 and 105 weeks. Seven (77.8%) subjects had a hematologic response.

Conclusion: Oxandrolone appears to be well tolerated, has limited toxicities at the administered doses in FA with patients, and may be an alternative androgen for the treatment of BMF in FA.

Today, allogeneic hematopoietic stem cell transplantation is the curative therapy of choice in patients with FA, and long-term survival rates in matched related donors are over 80%. However, outcome rates are much lower in unrelated donors and range between 13 and 84%. Therefore, alternative therapies are needed for these patients. Among others, therapy protocols with synthetic androgens mainly using oxymetholone have been developed. This prospective pilot study including 9 patients with Fanconi anemia and bone marrow failure shows that toxicity in terms of virilization, growth acceleration, renal function or behavioral changes were not present or acceptable, whereas significant elevation of liver enzymes led to the discontinuation of oxandrolone therapy. With respect to efficacy, 7 of 9 patients showed a positive hematologic response. Larger studies are needed to get more evidence as to whether oxandrolone therapy is superior to other androgens.

Modifiers of ovarian function in girls and women with classic galactosemia

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Background: Classic galactosemia is a potentially lethal genetic disorder resulting from profound impairment of galactose-1P uridylyltransferase (GALT). More than 80% of girls and women with classic galactosemia experience primary or premature ovarian insufficiency despite neonatal diagnosis and rigorous lifelong dietary galactose restriction. The goal of this study was to test the relationship between

markers of ovarian reserve, cryptic residual GALT activity, and spontaneous pubertal development in girls with classic galactosemia.

Methods: This cross-sectional study, with some longitudinal follow-up in a university research environment, included girls and women with classic galactosemia and unaffected controls, <1 month to 30 years old. Main outcomes were plasma anti-müllerian hormone (AMH) and FSH levels, antral follicle counts ascertained by ultrasound, and ovarian function as indicated by spontaneous versus assisted menarche.

Results: More than 73% of the pre- and postpubertal girls and women with classic galactosemia in this study, ages >3 months to 30 years, demonstrated AMH levels below the 95% CI for AMH among controls of the same age, and both pre- and postpubertal girls and women with classic galactosemia also demonstrated abnormally low antral follicle counts relative to age-matched controls. Predicted residual GALT activity $\geq 0.4\%$ significantly increased the likelihood that a girl with classic galactosemia would demonstrate an AMH level ≥ 0.1 ng/ml.

Conclusions: The majority of girls with classic galactosemia demonstrate evidence of diminished ovarian reserve by 3 months of age, and predicted cryptic residual GALT activity is a modifier of ovarian function in affected girls and women.

Girls and women with classic galactosemia are at risk of premature ovarian failure. The value of the present study is that the authors assessed AMH and FSH levels in 158 affected patients aged <1 month to 30 years. Additional data on antral follicle counts ascertained by ultrasound are given in 14 patients with galactosemia. The authors concluded for clinical practice that serum AMH levels and ultrasound detection of antral follicle count are good parameters to decide about initiating hormone replacement therapy. If both parameters are low, then hormone replacement therapy should be started timely (e.g. at the age of 11 years). If ovaries are visible by ultrasound, and AMH is detectable, then one should wait and see whether spontaneous puberty initiates.

Chronic disease

Reviews: Important for clinical practice and new evidence

Delays in puberty, growth, and accrual of bone mineral density in pediatric Crohn's disease: despite temporal changes in disease severity, the need for monitoring remains

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Long-term inflammation and glucocorticoid therapy impair skeletal modeling during growth in childhood Crohn disease

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Background: Glucocorticoids and inflammation inhibit bone formation, however the impact on skeletal modeling is unknown. This study aimed to examine changes in bone mineral density (BMD) and cortical structure after Crohn disease (CD) diagnosis and identify associations with growth, glucocorticoids, and disease activity.

Methods: The authors performed a prospective cohort study among 76 CD participants, aged 5–21 years. Tibia quantitative computed tomography trabecular BMD and cortical dimensions were obtained at diagnosis and 6 and 12 and a median of 42 months later; 51 completed the final visit. Sex, race, and age-specific z-scores were generated for outcomes based on more than 650 reference participants, and

cortical dimension z-scores were further adjusted for tibia length. Generalized estimating equations were used to model changes in z-scores.

Results: Disease activity improved over the study interval ($p < 0.001$). Trabecular BMD z-scores improved over the first 6 months; increases were associated with improved disease activity ($p < 0.001$), younger age ($p = 0.005$), and increases in vitamin D levels ($p = 0.02$). Greater increases in tibia length were associated with greater increases in cortical area z-scores ($p < 0.001$). Greater glucocorticoid doses and disease activity were significantly associated with failure to accrue cortical area and were more pronounced with greater linear growth (interaction $p < 0.05$). Mean ($\pm$ SD) trabecular BMD (-1.0 ± 1.21) and cortical area (-0.57 ± 1.10) z-scores at the final visit were significantly reduced.

Conclusions: CD was associated with persistent deficits in trabecular BMD, although younger participants demonstrated a greater potential for recovery. In addition, greater linear growth was associated with a greater recovery of cortical dimensions, especially among participants with less glucocorticoid exposure and inflammation. These data suggest that younger age and concurrent growth provide a window of opportunity for skeletal recovery.

The excellent review by de Boer and Denson summarizes current knowledge on endocrine comorbidities of Crohn's disease. There is a detailed discussion of all studies focusing on puberty, growth, and bone health. The paper by Tsampalieros et al. presents data on bone mineral density, vitamin D levels, and growth in 76 patients aged 5–21 with Crohn's disease. The low BMD is mostly due to delayed puberty, and will recover when puberty ensues. It was also shown that less glucocorticoid exposure was associated with a greater recovery of bone cortical area and better linear growth. The detailed data derived from pQCT measurement showed impaired trabecular and cortical modelling.

Chronic disease Important for clinical practice

Long-term linear growth and puberty in pediatric liver transplant recipients

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Background: This study aimed to explore linear growth, puberty, and predictors of linear growth impairment among pubertal liver transplant recipients.

Methods: The authors reviewed data collected prospectively through the Studies of Pediatric Liver Transplantation Registry. 31 variables were tested as risk factors for linear growth impairment, and factors significant at $p < 0.1$ were included in a logistic regression model. Risk factor analysis was limited to 512 patients who had complete demographic and medical data.

Results: 892 patients surviving their first liver transplant by >1 year, with ≥ 1 height recorded, and who were between 8 and 18 years old between the years 2005 and 2009 were included. Median follow-up was 70.2 ± 38.6 months, mean age was 12.9 ± 3.3 years, and mean height z-score (zH) was -0.5 ± 1.4 SD. 20% had linear growth impairment at last follow-up. Of 353 subjects with Tanner stage data, 39% of girls and 42% of boys aged 16–18 years were not yet Tanner 5. Growth impairment rates were higher among boys than girls (30 vs. 7%, $p < 0.05$) at Tanner stage 4, and occurred in 8/72 (11%) of Tanner 5 subjects. Among patients with parental height data, zH were lower than calculated mid-parental zH ($p < 0.005$). Independent predictors of growth impairment included linear growth impairment at transplant (OR 11.53, $p \leq 0.0001$), re-transplantation (OR 4.37, $p = 0.001$), non-White race ($p = 0.0026$), and primary diagnosis other than biliary atresia ($p = 0.0105$).

Conclusions: Linear growth impairment and delayed puberty are common in pubertal liver transplant recipients, with pre-transplant growth impairment identified as a potentially modifiable risk factor. Catch-up growth by the end of puberty may be incomplete.

This impressive data of 892 children, aged 8–18 years, who received liver transplantation were collected and retrospectively analyzed on behalf of the Studies of Pediatric Liver Transplantation Research Consortium, USA. The data confirm that persistent growth failure and pubertal delay are common in those children. As risk factors, they identified preexisting metabolic disease, re-transplant, and long-term use of steroids. The role of IGF1 deficiency was not studied.

Chronic disease

PCOS: New guideline for clinical practice and review of ontogeny

Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline

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Objective: The aim of this study was to formulate practice guidelines for the diagnosis and treatment of polycystic ovary syndrome (PCOS).

Methods: An Endocrine Society-appointed task force of experts, a methodologist, and a medical writer developed this evidence-based guideline using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence. The consensus process involved one group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of The Endocrine Society and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines. Two systematic reviews were conducted to summarize supporting evidence.

Results and Conclusions: The authors suggest using the Rotterdam criteria to diagnose PCOS (i.e. presence of two of the following criteria: androgen excess, ovulatory dysfunction, or polycystic ovaries). Establishing a diagnosis of PCOS is problematic in adolescents and menopausal women. Hyperandrogenism is central to the presentation in adolescents, whereas there is no consistent phenotype in postmenopausal women. Evaluation of women with PCOS should exclude alternate androgen-excess disorders and risk factors for endometrial cancer, mood disorders, obstructive sleep apnea, diabetes, and cardiovascular disease. Hormonal contraceptives are the first-line management for menstrual abnormalities and hirsutism/acne in PCOS. Clomiphene is currently the first-line therapy for infertility; metformin is beneficial for metabolic/glycemic abnormalities and for improving menstrual irregularities, but it has limited or no benefit in treating hirsutism, acne, or infertility. Hormonal contraceptives and metformin are the treatment options in adolescents with PCOS. The role of weight loss in improving PCOS status per se is uncertain, but lifestyle intervention is beneficial in overweight/obese patients for other health benefits. Thiazolidinediones have an unfavorable risk-benefit ratio overall, and statins require further study.

Ontogeny of polycystic ovary syndrome and insulin resistance in utero and early childhood

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Polycystic ovary syndrome (PCOS) is a prevalent hyperandrogenic infertility and cardiometabolic disorder that increases a woman's lifetime risk of type 2 diabetes mellitus. It is heritable and intensely familial. Progress towards a cure has been delayed by absence of an etiology. Evidence is mounting, however, for in utero T excess, together with gestational hyperglycemia, contributing to either early differentiation of PCOS or phenotypic amplification of its genotypes. Abnormal endocrine, ovarian,

and hyperinsulinemic traits are detectable as early as 2 months of age in daughters of women with PCOS, with adiposity enhancement of hyperinsulinemia during childhood potentially contributing to hyperandrogenism and LH excess by adolescence. These findings encourage increasing clinical focus on early childhood markers for adiposity and hyperinsulinemia accompanying ovarian and adrenal endocrine abnormalities that precede a diagnosable PCOS phenotype. They raise the possibility for lifestyle or therapeutic intervention before and during pregnancy or during childhood and adolescence alleviating the manifestations of a familial genetic predisposition to PCOS.

The new guideline of The Endocrine Society provides an evidence-based overview on diagnosis, comorbidities, and treatment. The diagnosis in adolescents is based on the presence of clinical and/or biochemical evidence of hyperandrogenism (after exclusion of other pathologies) in the presence of persistent oligomenorrhea. The paper by Abbott and Bacha adds new aspects to PCOS by reviewing the role of genes, insulin resistance, in utero effects of prenatal programming, childhood obesity, and family history of PCOS.

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