149

L. Petersen*, K. Kock*, B. Brock Jacobsen.
Departments of Gynecology, Histopathology and Paediatrics, Odense University Hospital, Odense, Denmark.

GERM CELL NEOPLASMS IN TWO PATIENTS WITH 46,XY KARYOTYPE AND INTERSEXUAL CONDITION.

The risk of malignancy in dysgenetic gonads of patients with a Y chromosomal component seems to be significant. The age at onset of malignancy is unknown. Two cases with germ cell neoplasms are presented, both with normal S-alpha-fetoprotein levels.
Case I: A 46,XY true hermaphrodite with ambiguous external genitalia, persistent Mullerian structures, a cryptorcide testis on the left and an ovary on the right side. At the age of 1o years a laparotomy was performed. The plasma levels of testosterone was 5.4 nmol/l, dihydrotestosterone 1.o nmol/l, oestradiol < 4o pmol/l, LH 1o U/l, and FSH 28 U/l. The bilateral gonadectomy revealed gonadoblastoma and dysgerminoma in the ovary, and an epithelial atypia in the testis.
Case II: A 46,XY mixed gonadal dysgenesis with hypospadia and a labio-scrotal fold, persistent Mullerian structures, and a testicular gonad on one side and no gonadal tissue on the other. At the age of 13 years plasma level of FSH was 4 U/l, LH 33 U/l, oestradiol < 4o pmol/l, testosterone failed, but the urinary excretion of 17-KS was low for age (o.6o mg/24 h). At the subsequent gonadectomy a teratocarcinoma was revealed in the testis.
Conclusion: Germ cell neoplasms appear before the age of 1o years in 46,XY gonadal dysgenesis reinforcing the importance of an early gonadectomy.

150

A. Cassio*, A. D'Errico*, A. Balsamo*, M. Tacconi*, M.G. Pascucci*, S. Tonioli*, F. Zappulla*, A.M. Mancini*, E. Cacciari.
Departments of Pediatrics and Pathology, S.Orsola - Malpighi Hospital, University of Bologna, Italy.

GONADAL HISTOLOGY IN TWENTY SUBJECTS WITH MALE PSEUDO - HERMAFRODITISM.

Gonadal histology was investigated by means of conventional microscopy in 11 Complete Adrogen Insensitivity Syndrome (CAIS), in 5 Incomplete Adrogen Insensitivity Syndrome (IAIS) and in 4 5α-reductase deficiency (5α-R-D) cases. Testicular tissue was removed as a prophylactic measure in all patients.
Age range was 1.8 - 18.6 yrs; 12 were prepubertals and 8 pubertals.
In the CAIS group 1 patient (18.6 yrs, pubertal) showed a "carcinoma in situ" pattern of the germ cells, 3 (1.8 Yrs; 9.8 yrs, prepubertal; 14.8 yrs, pubertal) had severe dysplasia, 5 patients showed a mild or moderate dysplasia and 2 had a normal pattern. In the IAIS group, 2 (5.8 yrs; 11.25 yrs, prepubertal) showed a "carcinoma in situ" pattern, 1 (10.5 yrs, prepubertal) had a severe dysplasia. 2 showed mild dysplasia. In 5α R-D we found 1 patient (13 yrs, pubertal stage) with severe, 2 with mild and 1 with no displasia.
It should be noted that: 1) Pseudohermaphroditisms with different pathogenesis all show frequent histological alterations. The reason for these abnormalities has yet to be fully examined. However, the abnormal position of the testes is the factor common to these disorders. 2) No correlation was found between the age at gonadectomy and the gravity of cellular abnormality.

151

BJ.Otten*, JC.Rijken*, GBA.Stoelinga*, THJ.Benraad*
Department of Paediatrics and Experimental and Chemical Endocrinology, Radboud University Hospital, Nijmegen, The Netherlands. (Introd. by JL.Van den Brande).

DIAGNOSIS OF 21-HYDROXYLASE DEFICIENCY (21-HD) BY DETERMINATION OF SALIVARY STEROIDS.

In 10 native 21-HD patients, 5 newborns and 5 older patients (aged 1-10 yr), salivary 17-OH progesterone (17-OHP) and androstenedione (A-dione) concentrations were measured, along with plasma concentrations. Prepubertal upper reference limits were for 17-OHP ≤ 4 yr: 16 ng/dl, 4-10 yr: 7 ng/dl and for A-dione all ages ≤ 10 yr: 7 ng/dl. In the 21 HD-patients salivary 17-OHP values varied from 56 to 1782 ng/dl and A-dione values from 4 to 720 ng/dl.
Newborns had considerable higher levels than older patients. Correlation coefficients for salivary versus plasma concentrations were 0.957 (17-OHP) and 0.863 (A-dione). Newborns did not show a diurnal variation, while in the older patients 1800 h. values averaged 23% (17-OHP) and 39% (A-dione) of the 0900 h. values, correlation coefficients for saliva versus plasma concentrations being 0.689 (17-OHP) and 0.990 (A-dione). After dexamethasone suppression salivary concentrations paralleled plasma values (r = 0.916 for 17-OHP and r = 0.858 for A-dione). The mean salivary concentrations decreased to 9.2% (17-OHP) and 14.0% (A-dione) of the initial values, in most patients reaching the normal range.
It is concluded that salivary steroid determination is a suitable and reliable index for the diagnosis of 21-hydroxylase deficiency.

152

BJ.Otten*, JC.Rijken*, GBA.Stoelinga*, THJ.Benraad*
Departments of Paediatrics and Experimental and Chemical Endocrinology, Radboud University Hospital, Nijmegen, the Netherlands. (Introd. by JL.Van den Brande).

DIURNAL SALIVARY STEROID PATTERNS AS AN INDEX OF ADEQUACY OF TREATMENT IN 21-HYDROXYLASE DEFICIENCY(21-HD)

18 prepubertal patients treated for 21-HD collected saliva samples 3 times a day for determination of 17-OH progesterone (17-OHP) and Androstenedione (A-dione) at a total of 43 occasions. Adequacy of therapy at the moment of sampling was designated as undertreated (I:n=13), adequately treated (II:n=15), or probably overtreated (III:n=15) according to the growth velocity. The upper reference limit for both salivary 17-OHP and A-dione was 7 ng/dl. Diurnal variation was defined as the highest value divided by the lowest one on the same day.
Results are presented as median values (ng/dl).:

		Morning	Afternoon	Evening	Diurnal Var.
I	17 OHP-A-dione	180 - 18	105 - 13	33 - 6	3.5 - 1.6
II	17 OHP-A-dione	18 - 2.6	6 - 2.8	1.3- 1.9	14.0 - 3.0
III	17 OHP-A-dione	8 - 0.3	0.6 - 0.4	0.5- 0.4	6.4 - 3.0

During undertreatment both steroids were elevated during most of the day. Adequate treatment coincided with high normal A-dione values, but elevated 17-OHP levels, only during a part of the day, resulting in a pronounced diurnal variation. Very low A-dione values and only moderately elevated 17-OHP values with much less diurnal variation pointed to overtreatment. It is concluded that diurnal salivary steroid patterns are a reliable index of adequacy of treatment in 21-HD, even for detection of overtreatment.

153

M.C. Young*, M.W. Thomas*, C.Darke*, R.F. Walker*, D. Riad-Fahmy*, I.A. Hughes.
Departments of Child Health and Tenovus Institute, University of Wales College of Medicine, and Tissue Typing Laboratory, Cardiff, UK.

PLASMA AND SALIVA STEROID RESPONSE TO ACTH AND HLA HAPLOTYPES IN CONGENITAL ADRENAL HYPERPLASIA (CAH).

HLA haplotypes and biochemical phenotypes were determined in the families of 14 patients with CAH (total 49 subjects) to ascertain the genotype (normal, N; heterozygote, HZ; homozygote, HH). HLA-A, B,C and DR frequencies in these and 4 more propositi showed the expected increased frequence of Bw47 (control 0.5%, n=600; CAH 22.2%; $p < 0.01$) and an unexpected increase in Bw22 (controls 6.3% CAH 27.8%; $p < 0.05$). A decreased frequency of B8 and DR3 in CAH was not significant. Plasma/saliva levels of 17OH-progesterone (17P), androstenedione (A) and cortisol (F) determined before and 60 min. after I.M. Synacthen were used for biochemical phenotyping. In discriminating HH subjects, only 17P values were useful. Saliva 17P, a putative index of free steroid, was no more discriminatory than plasma 17P values (HH: pre 2100 ± 170 pmol/l, post 6600 ± 7400; HX: pre < 100, post 610 ± 870; N: pre < 100, post 220 ± 40 (mean ± SD)). Basal saliva 17P at 0900 hr was > 200 pmol/l in 80% of HH but none of HZ and N subjects. Saliva 17P and its response to ACTH is a useful test to screen for and confirm the diagnosis of homozygous CAH, but the test is only complimentary to HLA typing for heterozygote detection.

154

M.C. RAUX DEMAY*, P. SINASSAMY*, F. GIRARD, (Introd. by F. GIRARD). Hôpital TROUSSEAU, PARIS, FRANCE.

SALIVARY (S) AND PLASMA (P) PHARMACOKINETICS (PK) OF PREDNISOLONE (Pol) IN CHILDREN TREATED WITH PREDNISONE (Pon)

In order to improve previous results obtained with studies of PK of Pol in plasma, we set-up a new direct, sensitive Pol assay to compare PK of Pol (the active metabolite of Pon) in S and P. This RIA uses a Cortisol (C) antisera (crossreactions are 46% and 3% with Pol and Pon, respectively), C as standard and ^{125}C as tracer. Parallel displacements of the curves are obtained with both C and Pol. Intra and interassay dispersions are 2.5 and 4.6%, respectively. Each assay uses either 50 (S) or 25 µl (P) in duplicate and the sensitivity threshold is 8 ng/ml. Ten children were studied. All of them were previously treated with Pon (1 to 2 mg/kg/d) and their 0800h C levels were <50 (P) or <8 (S) ng/ml. Ten P and S samples were collected simultaneously before and over 12 hours periods following a unique dose of oral Pon (1mg/kg). Pol peaks occured at similar times in Saliva (77 ± 12 mn) and in Plasma (63 ± 12 mn). S peak values (118 ± 23 ng/ml) were 21 ± 4% (range 3.5 to 44) of those of P peak levels (559 ± 36 ng/ml). Half lifes of Pol were shorter (88 ± 13 mn) and slopes of disappearance (λ) (-9.8×10^{-3}) steeper in S than in P (143 ± 13', $p<.001$ and -5.2×10^{-3}, $p<.02$, respectively). Correlation between S and P λ was significant ($r=.80$, $p<.01$).
In conclusion, S samplings provide a non invasive, accurate method for further studies of PK of Pol. In addition the S studies reflect the PK of unbound fraction of circulating Pol.