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A.Larsson, T.Cursted*, U.von Döbeln*, J.Gustafsson*, L.Hagenfeldt*, E.Svensson*
Dept of Pediatrics, University Hospital, Uppsala, Dept of Clinical Chemistry, Karolinska Hospital, Stockholm, PKU Section, Dept of Bacteriology, National Bacteriological Laboratory, Stockholm, and Dept of Pediatrics, Karolinska Hospital and S:t Göran's Children's Hospital, Stockholm, Sweden.

NEONATAL SCREENING FOR CONGENITAL ADRENAL HYPERPLASIA (CAH) USING 17-HYDROXYPROGESTERONE (17-OHP) ASSAYS OF DRIED BLOOD SPOTS

Dried blood on filter paper collected on the 5th day of life was used to screen infants for CAH. A radioimmunoassay for 17-OHP without extraction with organic solvents was developed. The cut-off level was initially set at 100 nmol/l blood based on analyses of stored blood spots from infants who were subsequently found to have CAH.

In a pilot study 22 400 newborns were screened, and 239 (1.1%) were found to have blood 17-OHP above 100 nmol/l. The majority of these high values (84%) were observed in preterm infants. One case of CAH was detected during this study.

Reassay of blood samples from preterm infants with positive tests after extraction with ether yielded considerably lower 17-OHP levels. A considerable part of the 17-OHP was apparently present as glucuronic acid and monosulphuric acid conjugates.

After introducing cut-off levels related to gestational age and changing to a more specific antibody the screening has continued and included another 18 800 infants. The recall rate during this period was 0.08%. No further case of CAH has so far been detected.

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P. Betts*, J. Berry*, P.J. Wood* (Introd. by S.A. Greene*)
Southampton General Hospital, Southampton, England

THE INTERPRETATION OF BLOODSPOT 17α-HYDROXYPROGESTERONE LEVELS IN TERM AND PRETERM NEONATES

Plasma 17α-Hydroxyprogesterone can vary considerably in the first few days of life. Bloodspot 17α-hydroxyprogesterone, plasma cortisol, plasma sodium and urinary 17α-hydroxyprogesterone, cortisol, sodium and creatinine levels were determined in 24 term and 31 preterm infants on the third, eighth and fourteenth day of life. Preterm infants, whether 'well' or 'sick' had significantly raised bloodspot 17α-hydroxyprogesterone levels (up to 158 nmol/l) compared with those found in term sick or well infants (up to 18.8 nmol/l). Urinary 17α-hydroxyprogesterone/creatinine ratios were also higher in preterm infants. Plasma cortisol results showed similar ranges for term and pre-term infants, and bloodspot 17α-hydroxyprogesterone/plasma cortisol ratios for day 3 specimens correlated with the degree of prematurity. These results may be due either to immature enzyme systems in the preterm baby or to an excess of related steroids cross-reacting in the 17α-hydroxyprogesterone assay.

We propose the use of two distinct upper limits of normal of 20 nmol/l (term infants) and up to 200nmol/l (preterm infants) for the interpretation of bloodspot 17α-hydroxyprogesterone levels at the end of the first week of life.

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K.E. Petersen, Dep. of pediatrics, Kolding Hospital, M. Damkjær Nielsen*, Dep. of clinical physiology, Glostrup Hospital, O. Buus*, Medilab., Copenhagen, Denmark, Philippe Couillin*, Unité de recherches de biologie Prénatale, Paris, France.

CONGENITAL ADRENAL HYPERPLASIA (CAH): PRENATAL TREATMENT.

The aim of prenatal treatment of CAH is prevention of virilization of female fetuses with 21 hydroxylase deficiency (21 OH-def.). Two mothers at risk for CAH were followed during pregnancy, according to the plan: treatment as early as possible with decadron 1 mg per day - transabdominal chorion villus biopsy (at week 11) to determine the sex - amniocentesis (at week 17) to establish (HLA types and steroids) if the fetus is affected - continued treatment to birth in affected girls.

Case 1 (JLA) were treated from 9 weeks of pregnancy. The fetus turned out to be a boy, and treatment was stopped. At birth he had no signs of CAH (normal 17 OH-progesterone (17 OHP), androstenedione (Adione), testosterone, cortisol, ACTH, renin).

Case 2 (MMD) was treated and studied according to the plan and the fetus was a girl, amniocentesis was performed and showed raised values for 17 OHP (30 nmol/l), Adione (4 nmol/l). She was HLA-identical to the affected sister (A3B7/A3B47) and the treatment with decadron (discontinued 5 days before the amniocentesis) was continued to birth. The adrenal function of the mother was totally suppressed (urinary cortisol < 20 nmol/24 h), but normal after birth. Study of the girl at day 1 and day 3 showed raised 17 OHP (172-123 nmol/l), Adione (19.5-91.3 nmol/l), renin (530-1824 μGU/ml), ACTH (320 pg/ml) and low aldosterone (16-29 ng/100 ml). The external genitalia showed a definitive lesser virilization (Prader stage 1-2) by comparison with the sister (Prader stage 4).

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Z.Hochberg, A.Benderly*, L.Kahana*, Z.Zadik*
Departments of Pediatrics, Rambam Medical Center, Carmel Hospital and Technion Faculty of Medicine, Haifa, and Kaplan Hospital, Rehovot, Israel.

MINERALOCORTICOID REPLACEMENT IN 11β-HYDROXYLASE DEFICIENCY (11-OHD)

Marginal salt loss and hyperreninemia were previously reported in patients with 11-OHD on glucocorticoid replacement (JCEM 58:384, 1984). To evaluate the need for mineralocorticoid therapy, 7 patients with 11-OHD, 5-14 years of age, were subjected to 3 consecutive schedules of treatment: 1) 1 mg/day dexamethasone (DEX) for 4 days, 2) 17 mg/m^2/day hydrocortisone acetate (HC) for 4 days, and 3) HC and 0.1-0.2 mg/day 9α-fluorohydrocortisone (9αF) for 10 days. Results (mean±SD) were compared to multiple determinations before the protocol (PRE):

	PRE	DEX	HC	HC + 9αF
FE (Na^+)	0.72±0.11	0.91±0.08	0.55±0.08	0.27±0.03
PRA (ng/ml/hr)	11±3.2	10.4±2.9	6.2±2.1	1.5±0.6
S-Aldos (ng/dl)	4.5±11.0	5.0±1.1	7.8±2.5	3.5±2.0
ACTH (pg/ml)	130±62	20±18	183±33	42±16
11-Deoxycortisol (μg/dl)	2.8±3.6	0.3±0.03	6.2±2.1	1.5±0.6

The latter combination suppressed PRA, produced better control of the pituitary-adrenal axis and enabled the use of a physiologic dose of HC. PRA needs to be monitored in 11-OHD patients; when it is elevated, mineralocorticoid replacement is indicated.

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M.C. RAUX-DEMAY*, T. PIERRET*, F. GIRARD, Lab. Expl. Fonctionnelles - Hôpital Trousseau, Paris, France.

CONGENITAL VIRILIZING ADRENAL HYPERPLASIA (CVAH) DUE TO 21 HYDROXYLASE DEFICIENCY, RESULTS OF THERAPY WITH CYPROTERONE ACETATE (CA).

Results obtained from ten prepubertal patients (6 girls, 4 boys) suffering of CVAH were compared over 12-41 months periods before and over 14-52 months periods during CA therapy (63 ± 21 (SD)mg/m^2/day). At the beginning of treatment with CA, growth parameters were as follow : chronological (Ch) ages 5 to 10 years, heights (H) 102.5 ± 9.2% of normal H for Ch ages, bone (B) ages 6 to 92 (mean 49) months over Ch ages. CA induced decreases in growth velocity (6.9 ± .66 (SEM) to 4.3 ± .54 cm/year, $p < .01$), in bone maturation (2.4 ± .76 to .35 ± .11 years/Ch year $p < .05$) and in B/H ages ratios (1.42 ± .09 to 1.23 ± .06, $p < .05$). In spite of reduced cortisol therapy from 15.4 ± 1.23, before, to 12.24 ± .72 mg/m^2/day, during CA treatment, ($p < .05$), 17 hydroxyprogesterone (17OHP) and testosterone (T) plasma levels decreased from 62 ± 9.8 to 22.7 ± 7 ($p < .01$) and from .42 ± .07 to .17 ± .03 ($p < .05$) respectively. When compared to normal values for B ages, most plasma DHA values were normal before (9/10) and during (7/10), most Δ_4 androstenedione (Δ_4A) values were elevated before (9/10) and normal (9/10) during CA treatment, while Δ_4A/T ratios increased significantly from 3.7 ± .32 to 6.4 ± .86 ($p < .01$). In conclusion, CA appears to be of interest in the treatment of prepubertal patients with CVAH. The antiandrogenic effect is demonstrated by the improvement of bone maturation, the inhibition of ACTH production by the decreases in 17OHP levels. In addition there is evidence of a decrease in the conversion rates of adrenal androgens to testosterone.

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J.DiMartino-Nardi*, E.Stoner*, A.O'Connell*, M.I.New, Dept Pediatrics, New York Hosp-Cornell Med Ctr, New York NY 10021 USA

THE EFFECT OF TREATMENT ON FINAL HEIGHT IN CLASSICAL CONGENITAL ADRENAL HYPERPLASIA (CAH).

One of the goals of glucocorticoid therapy in classical CAH is to suppress excess androgen production to prevent premature epiphyseal closure and resultant short stature. This retrospective study was conducted to determine if the final height (FH) of 45 adult patients (pts) with CAH was influenced by the clinical variant (salt-wasting (SW) vs simple virilizing (SV)), age diagnosis was made and treatment initiated, and the degree of hormonal control. Good or poor hormonal control were determined from levels of 24 hr urinary 17-KS, serum Δ4-androstenedione (Δ4-A) and 17-OHP. The patient was assigned to the category of good control if more than 50% of daily urinary 17-KS or serum Δ4-A were normal for age (mean±2SD) or if 50% of the serum 17-OHP levels were < 1000 ng/dl. All others were assigned to the poor control category; 3 pts had insufficient data for assignment. Final height was compared to the mid-parental height (MPH), to the normal population, and to 5 never treated pts with SVCAH. The mean final Ht for all male patients was 163.2 cm and for all female patients was 153.3 cm. Conclusion: The adult height of 3 never treated females was not different from any treated females, whether in good or poor control, SW or SV, or treated early or late. Among the treated males, height was not different whether they were in good or poor control, SW or SV, or treated early or late. Although the 2 never treated males are shorter than treated males, the small number of pts precludes statistical analysis. The mean final heights of all pts were significantly less than the mean heights of males and females in the normal population.