392

DETECTION OF ECUADOREAN LARON SYNDROME GENE CARRIERS BY MOLECULAR GENETIC ANALYSIS OF GUTHRIE CARD BLOOD SAMPLES.
M.A. Berg,[1] J. Guevara-Aguirre,[2] A.L. Rosenbloom,[3] and U. Francke.[1]
(1)Howard Hughes Medical Institute and Depts. of Genetics and Pediatrics, Stanford University, Stanford, CA, (2)Institute of Endocrinology, Metabolism, and Reproduction, Quito, Ecuador and (3)Dept. of Pediatrics, University of Florida Health Science Center, Gainesville, FL

Laron syndrome's high incidence in several southern Ecuadorean villages is due to a high frequency of asymptomatic heterozygous gene carriers who are at risk of having affected offspring. As a single growth hormone receptor (GHR) gene mutation, E180splice, accounts for over 97% of Ecuadorean Laron syndrome (LS) alleles, we have developed a rapid and reliable method to detect this mutation: finger-prick blood spots are collected onto Guthrie filter paper and used directly as DNA templates for PCR amplification of a GHR gene fragment which includes codon 180. The amplification products are applied to nylon membrane and hybridized serially with digoxigenin-labelled oligonucleotide probes complementary to the normal and mutant alleles. Probe hybridization is detected using a chemiluminescence nucleic acid detection kit. We have analyzed blood spot samples from 96 individuals. In 16 affected individuals, homozygosity for the E180splice mutation was confirmed. In 19 parents of affected individuals, heterozygosity was confirmed. Of 61 unaffected individuals at risk to be carriers, 34 were found to carry the E180splice mutation. Accurate determination of carrier status among Ecuadorean individuals at-risk is possible using this method. The testing is simplified by using Guthrie filter blood samples which are easy to obtain, store, mail, and use directly in PCR reactions, eliminating the need for DNA extraction. Detection of the normal and mutant alleles by chemiluminescence eliminates the need for radioisotope use.

393

FINAL HEIGHT AND DISPROPORTION AFTER CRANIAL RADIOTHERAPY FOR LEUKAEMIA
H.A.Davies,* M.Didi,† E.Didcock,# AL Ogilvy-Stuart,† S.M.Shalet,† J.K.H.Wales,* D.A. Walker.#
*University Dept. of Paediatrics, The Children's Hospital, Sheffield.U.K.
†The Christie Hospital, Manchester, U.K.
#University Dept. of Child Health, University Hospital, Nottingham, U.K.

Final height and skeletal proportions were studied in 142 children treated for ALL with cranial irradiation and combination chemotherapy but not spinal irradiation. Cranial irradiation consisted of 21-25 Gy in 60% and 18 Gy in 40% of the cohort. Significant reduction in height standard deviation score (HtSDS) was seen in both dose groups and was greater in girls than boys and greater with the higher doses of radiotherapy. Mean change in HtSDS for girls and boys in the higher dose group was -1.55 and -0.87 respectively and in the 1800 group -1.11 and -0.75. One hundred and seven (75%) of the group had relatively shorter backs than legs, this disproportion being significant (sitting HtSDS-Leg Length (LL) SDS more than ± 2) in 23 (16%). Mean sitting HtSDS for girls and boys in the higher dose group was -1.75 and -1.14 respectively and mean LL SDS -0.81 and -0.24. In the 1800 group mean sitting HtSDS for girls and boys respectively was -1.49 and -1.26 with mean LL SDS of -0.17 and -0.07. In conclusion, cranial irradiation with 18 Gy as well as higher irradiation doses may cause significant standing height SDS loss and disproportion with a relatively short back even if the radiation fields have not included the spine.

394

GROWTH AND ENDOCRINE ABNORMALITIES IN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS.
N. Hashimoto, F. Bessho, Y. Miki, J. Kagawa, S. Nagafuchi, S. Egi and S. Kamoshita.
Department of Pediatrics, University of Tokyo, Tokyo 113, Japan

It is known that patients with Langerhans Cell Histiocytosis (LCH) are accompanied by a variety of hypothalamic-pituitary dysfunction (HPD). To test the hypothesis that the endocrine abnormalities associated with LCH are related to the final height, we studied 45 patients with LCH. Twenty patients (5 boys and 15 girls) had been followed until they reached the final height. Observed clinical manifestations due to HPD were: diabetes insipidus in 11 patients, growth hormone deficiency in 6 patients, precocious puberty in 3 patients, ACTH deficiency in 6 patients and TSH deficiency in 2 patients. The mean SD score of body height of patients was not different from normal control at the onset of LCH. However, the mean SD score of the final height of the patients with LCH was significntly lower than normal control (-1.80±1.81; mean±SD). The mean SD score of the final height of the patients with HPD (n=13) was significantly lower than the patients without HPD (n=7) (-2.50±1.60 vs -0.59±1.38; mean±SD, P<0.05). We conclude that the endocrine abnormalities associated with LCH are related to the final height.

395

BLOOD COAGULATION PARAMETERS IN TURNER SYNDROME BEFORE AND DURING GH AND/OR ESTROGEN THERAPY.
L. Mazzanti, R. Bergamaschi, C. Tognoni*, D. Iascinari, C. Magnani, A.M. Perri, A. Vancini, I. Scarano, S. Cocchieri*, L. Cacciari. 1st Pediatric Clinic, *Dep. Angiology and Blood Coagulation, University of Bologna, Italy.

Estrogens influence blood coagulation and fibrinolysis, though there are few data about GH therapy. Coagulation parameters were studied in 66 turner patients, 6.91 to 25.5 yrs of age (B.A. 6 - 15.37) submitted to different treatments and in 20 age-matched controls. Karyotypes were 45,X (42.1%), X mosaicism (37.5%) and X-structural abnormalities (20.4%). Ipato-Quick (HQ%), activated partial thromboplastin time (aPTT sec), Protein C (Prot C %), Protein S (Prot S %), Fibrinogen (mg/dl), Antithrombin III (AT III%) and platelet system and fibrynolitic tests were evaluated. Below 11 yrs B.A., 8 girls were pre-therapy and 26 received hGH (10/kg/week-daily) (GH group); equal to or above 11 yrs B.A., 21 patients were treated with hGH plus ethynilestradiol (EE) (100ng/kg/day) (GH plus EE group) and 8 with EE plus medroxyprogesterone (P) in cycles (EE-P group). In turner girls AT III% was significantly higher than controls ($p<0.01$) before and during each treatment. These results have already been found in menopausal women vs premenopausal. EE plus GH group showed an increase of HQ% values and Prot C% activity vs controls ($p<0.01$) and the GH alone group ($p<0.05$). EE-P group showed an increase of the same parameters vs controls ($p<0.05$). In conclusion GH therapy does not seem to determine any modifications in coagulation parameters. If therapy increases the synthesis of both inhibiting and activating liver-dependent coagulation factors, but not pathologically. In turner girls estrogen therapy does not seem to represent a risk factor.

Fetal, Neonatal, Pregnancy

396

PERSISTENT HYPERINSULINEMIC HYPOGLYCEMIA OF INFANCY (PHHI): PARTIAL AND COMPLETE CLINICAL REMISSION AFTER LONG-TERM OCTREOTIDE TREATMENT.
H. Landau & B. Glaser, M.D. Departments of Pediatrics, Endocrinol & Metabol, Hadassah University Hospital, Jerusalem, Israel.

Moderate to severe PHHI usually requires near-total pancreatectomy to avoid hypoglycemia induced brain damage. We treated 13 such patients with octreotide over the last 6 y. Seven subsequently underwent partial pancreatectomy: 2 had inadequate response due to sepsis, 1 failed to respond to combined octreotide/glucagon/diazoxide and 4 because their family situation did not permit chronic octreotide treatment. Data on the remaining 6 pts on chronic octreotide treatment without pancreatectomy are reported here. Frequent feedings with high glucose intake (11-13 mg/kg/min) and raw cornstarch at night were required in all patients, whereas 2 also required gastrostomy due to poor feeding. Octreotide was started immediately in 5 of 6 patients since previous experience indicates that diazoxide is rarely effective in severe disease. Octreotide was given in 3-4 daily sc injections in 3 patients, and continuous sc infusion (Medix insulin infuser) in 3. All patients had acute GI symptoms (vomiting, abdominal distention, steatorrhea) and weight loss after beginning the drug. This responded partially to oral pancreatic enzyme treatment, and remitted after 2-4 weeks. Asymptomatic gallstones were discovered at routine ultrasound in 1 patient after 1 y of treatment. Growth rate decreased in all during the first 2-6 months, but normalized subsequently as did body weight. All patients have normal psychomotor development for age, however 2 are <1 year old. Every 6-12 months an attempt was made to stop octreotide treatment or switch to diazoxide. Five patients stopped octreotide after 8.5 m to 5.5 y; 1 switched to diazoxide (3y), 2 required per-cutaneous gastrostomy , and 1 (5.5 y old) required no further treatment. The remaining 2 (age 4M-1.5y) are still treated with octreotide. **We conclude** that with octreotide treatment pancreatectomy can be avoided in some patients. However, efficacy is partial, and close follow-up with repeated blood glucose determinations, frequent feedings, gastrostomy and hospital admissions during acute illnesses may still be necessary. Most can eventually stop octreotide and enter complete or partial remission.

397

LONGITUDINAL STUDY OF BLOOD SPOT FSH CONCENTRATIONS IN NORMAL GIRLS AND TURNER SYNDROME DURING EARLY POSTNATAL LIFE.
C. Heinrichs, P. Bourdoux, C. Saussez, H.L. Vis and J.P. Bourguignon.
Department of Pediatrics and Pediatric Laboratory, Children's Hospital Reine Fabiola, University of Brussels, and Medgenix, Belgium.

In different animal species, ovariectomy does not result in increased gonadotropin secretion in the fetus. In contrast, agonadal subjects show elevated FSH secretion during infancy. Neonatal blood FSH levels were studied in 9 fullterm girls with Turner syndrome compared with phenotypically normal fullterm girls born the same week. We used blood spots collected at the time of mass screening, 1 to 29 months prior to this study. FSH was measured using a highly specific immunoradiometric assay. On day 5-6 after birth, FSH was usually undetectable (< 1 mIU/ml) or low (1-3 mIU/ml) in normal girls. Among the 9 GD patients, 5 had FSH < 3 mIU/ml and 4 showed slighlty elevated levels ranging 4.3-10.9 mIU/ml. These differences in FSH secretion were not related to differences in karyotype. Among 5 patients studied longitudinally, 3 showed increase in FSH levels to 14.9-15.9 mIU/ml during the second week of life. However, this increase was comparable to that seen in 13 normal girls sampled on a second occasion 2-3 weeks after birth. One Turner patient had still low FSH (2.5 mIU/ml) on day 23 and showed some increase to 8.5 mIU/ml on day 30. These data indicate that, in Turner patients, perinatal changes in FSH secretion are similar to normal girls though there is no feedback control by gonadal hormones. Then, FSH assay cannot be used as a perinatal screening method for Turner syndrome in girls.

Supported by a grant from the Belgian Study Group for Pediatric Endocrinology.