

115

TRISOMY 22 MOSAICISM LIMITED TO SKIN FIBROBLASTS IN A MENTALLY RETARDED, DYSMORPHIC GIRL
Hans T. Lund, Dept. Pediat., Randers Central Hospital, and
Lisbeth Tranebjærg, Dept. Med. Genet., The J.F. Kennedy Inst., DK-2600 Glostrup, Denmark.

Full trisomy of chromosome 22 is extremely rarely reported in live-born infants. Mosaic trisomy has been reported in very few patients.

Chromosome analysis of cultured skin fibroblasts from a 12-year-old, mentally retarded, dysmorphic girl showed an additional chromosome 22 in 48% of the investigated cells. Analysis of cultured peripheral lymphocytes, done twice, remained normal. The chromosome constitution was: mos 47,XX,+22/46,XX.

Phenotypically the patient had features characteristic of both Turner's and Down's syndromes. The endocrinologic investigation gave evidence of gonadal hypofunction, even if ovaries were demonstrable by ultrasound.

This patient demonstrates the importance of cytogenetic analysis of cultured fibroblasts when lymphocyte karyotype is normal, and the clinical features are highly suspicious of a chromosomal disorder.

116

MEASUREMENT OF CEREBRAL PHENYLALANINE LEVELS IN VIVO
M Avison, N Herschkowitz, E Novotny, O Petroff,
J Colombo, C Bachman, R Shulman & J Prichard,
Yale University and University of Berne

Cerebral phenylalanine (Phe) concentration was measured in vivo by ¹H NMR spectroscopy in rabbits made hyperphenylalaninemic by a diet containing 5% Phe and 0.4% alpha-methyl Phe. A surface coil and a 4.7 T spectrometer were used with a phase-cycled water-suppressing spin echo sequence optimized at 7.35 ppm. At a total echo delay of 4 msec several resonances were observed at 6.5-8.5 ppm. When brain (Phe) was elevated, subtraction of scaled spectra of control animals from those of test animals left a single broad peak centered at 7.35 ppm, the position of the multiplets arising from aromatic protons of Phe. For determination of brain (Phe), the intensity of this resonance, corrected for T1 and T2 differences, was compared to the creatine-phosphocreatine resonance at 3.03 ppm, which was assumed to represent 10 mM. Brain (Phe) determined by NMR and independently by biochemical analysis in 7 rabbits were in excellent agreement (correlation coefficient 0.96), while blood (Phe) correlated less well (0.80). Brain (Phe) above 0.5-1.0 mM was readily detectable. Similar NMR techniques used with large-bore spectrometers should permit non-invasive direct measurement of elevated brain (Phe) in human patients of any age.

117

DECREASED COLLAGEN SYNTHESIS BY SKIN FIBROBLASTS FROM 31 PATIENTS SUFFERING FROM OSTEOGENESIS IMPERFECTA
R.E. Brenner*, U. Vetter*, W.M. Teller, O. Wörsdörfer*¹
P.K. Müller*²

¹st Dept. of Pediatrics, ¹ 3rd Dept. of Surgery Univ. D-7900 Ulm, ² Dept. Connective Tissue Res., MPI, D-8033 Martinsried, FRG

We studied collagen synthesis, secretion and degradation by skin fibroblasts from 31 patients with osteogenesis imperfecta (OI) (5 cases of OI I, 3 of OI II, 14 of OI III, 9 of OI IV) and 12 age-matched controls (C). Control fibroblasts showed an increase in collagen synthesis between 2 and 9 years of donors' ages. Cells from OI patients did not reveal this increase, indicating a lack of collagen synthesis in early childhood. Secretion of collagen was not altered, whereas the relative amounts of collagen were decreased in OI I and II (C: 17.1 ± 5.4%, OI I: 14.4 ± 5.1%, OI II: 12.1 ± 5.9%). In OI III and IV it was normal (OI III: 17.0 ± 6.4%, OI IV: 17.9 ± 5.7%). Intracellular degradation of collagen was increased in all OI types and highest in the lethal OI II (C: 37 ± 12%, OI I: 54 ± 12%, OI II: 65 ± 21%, OI III: 49 ± 19%, OI IV: 50 ± 10%). Suggestion: In OI the lack of adequate synthesis of extracellular matrix proteins during early childhood may be secondary to other defects, but the decrease of fracture rates after that period suggests that above biochemical disturbance may be one step in the pathophysiologic pathway.

118

MULTIPLE PEROXISOMAL ENZYME DEFICIENCIES IN RHIZOMELIC CHONDRODYSPLASIA PUNCTATA.
Ruud B.H. Schutgens¹, Ronald J.A. Wanders¹, Hugo S.A. Heymans² (Spon. by H. Przyrembel³) Dept. Pediatrics, Universities of Amsterdam¹, Groningen², Rotterdam³, Netherlands.

Rhizomelic Chondrodysplasia Punctata (RCDP) is a severe, autosomal recessive disorder with specific clinical abnormalities. As ocular features in RCDP resemble those in Zellweger syndrome (ZS), we compared peroxisomal functions in 14 RCDP patients, ZS patients and controls. Some of the results are presented in the Table:

Table	RCDP	ZS	Controls
PLASMA	range	$\bar{x} \pm$ s.d.	$\bar{x} \pm$ s.d.
phytanic acid (mg/l)	15 - 380 (10)	137 ± 60 (12)	9.2 ± 2.2 (27)
FIBROBLASTS			
DIAP-AT* activity (nmoles/2h/mg protein)	0.26-2.43 (11)	0.66±0.50 (19)	7.2 ± 2.1 (58)
(C ₂₆ /C ₂₂) fatty acids	0.02-0.13 (14)	0.57±0.23 (17)	0.07±0.03 (39)
Particle-bound catalase (%)	>65 (11)	≤5 (32)	>65 (58)

*DIAP-AT=acyl-CoA: dihydroxy-acetone phosphate acyltransferase. So, RCDP results from multiple peroxisomal deficiencies. However, in contrast to ZS, peroxisomal β-oxidation and intracellular catalase localisation are normal. Pre- and postnatal diagnosis of RCDP can be based on these findings. No peroxisomal dysfunction was found in Conradi-Hündermann syndrome and in X-linked dominant CDP.

119

3-HYDROXY 3-METHYL-GLUTARYLCO-A LYASE DEFICIENCY
S.W. MOSES* M. AVIRAM*, R. GEIGER**, R. BERGER*** AND
P.C. SMIT*** Depts of Pediatrics, Soroka Med. Cent.* Poria Hosp., Israel** Groningen University, the Netherlands***

An 8 month old Arab boy was investigated for recurrent attacks of hypoglycemia occurring during intercurrent infections, which were associated with metabolic acidosis and on one occasion with transient abnormal liver function tests. Parents are first cousins. A sibling suffered from similar manifestations and succumbed at 2 years. The patient tolerated an 18 hour fast without evidence of hypoglycemia nor did he become ketonemic. His serum carnitine was total 15 and free 1.2 nmol/l. Treatment included oral carnitine, a high CHO low fat and protein diet. After stopping carnitine, the patient went into coma with metabolic acidosis from which he recovered slowly with iv glucose and electrolytes. Gas chromatographic/mass spectrometric analysis of his urinary organic acids revealed abnormal peaks identified as glutaric acid, methylglutaric acid, 3-methylglutaconic acid and 3-OH-3-methylglutaric acid. fibroblast 3-OH-3-methylglutaryl CoA lyase activity was 0.1 (normal 22.1 ± 6.7) nmol/min/mg prot. This is the first patient with HMG CoA lyase deficiency described in Israel. The Authors are indebted to Dr. D. Abellowitz for tissue cultures and Dr. A.J. Wanders for determining fibroblast enzyme activity.

120

α-ADRENOCEPTOR (α-AR) MEDIATED INOTROPIC EFFECT (IE) OF NORADRENALINE (NA) IN HUMAN MYOCARDIUM.

Tor Skomedal, Halfdan Aass, Jan-Ebjørn Osnes, Asbjørn Langslet and Gudmund Semb. University of Oslo, Department of Pharmacology and Ullevål Hospital, Departments of *Pediatrics and **Surgery, Oslo, Norway.

In order to investigate whether NA could elicit IE through activation of α-AR also in human heart, specimens of both atrial (AM) and ventricular muscle (VM) were obtained during open heart surgery and studied *ex vivo* at extensive β-AR blockade. In adult patients, NA elicited an α-adrenergic inotropic effect (α-AIE) both in AM and VM with maximal response (MR) of about 50% compared to control contraction before addition of NA. In VM from two children with subvalvular pulmonary stenosis (SVPS), NA was less potent compared to adult VM, although MR was rather similar. In AM from one child with Down's syndrome (trisomy 21) and heart malformation, NA showed about the same potency as in VM from SVPS-hearts. MR was about 600% compared to control contraction. The basal function of this AM during control period was rather poor possibly explaining the large relative response. Thus NA can elicit an α-AIE in AM and VM from both children and adults. The potency and efficacy may differ depending upon age or pathophysiology or both.