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UTILITY OF CHROMOGRANIN A (CgA) TO SCREEN FOR FAMILIAL PHEOCHROMOCYTOMA. H.J. Heinze, F.B. Diamond, A.W. Root. Section of Pediatric Endocrinology, Department of Pediatrics, University of South Florida College of Medicine, Tampa, FL 33612, USA.

CgA is a 49 kilodalton peptide produced by a variety of endocrine and neuroendocrine tissues and secreted with tissue-specific hormones. We present a family with apparent isolated familial pheochromocytoma in which CgA has served as a useful marker for the identification of affected asymptomatic family members. There was a family history of sudden death in a maternal uncle with subsequent identification of a pheochromocytoma on autopsy. The index case presented with a history of hypertension during a surgical procedure. Elevated urinary catecholamines in this child were associated with bilateral periadrenal masses on MRI. A left periadrenal pheochromocytoma was removed at the time of surgery. Postoperatively, CgA was 30.8 ng/mL (NL < 50 ng/mL) associated with normal urinary catecholamines. Screening in 8 of 13 family members revealed elevation of CgA (> 50 ng/mL) in 5 (63%). Subsequent evaluation in selected family members revealed the presence of a retinal hemangioblastoma in the mother of the index case; elevation of CgA (130 ng/mL) in the maternal grandmother who is hypertensive with elevated urinary catecholamines; elevation of CgA (184 ng/mL) and urinary catecholamines in a maternal cousin; elevation of CgA (487 ng/mL) and urinary catecholamines associated with hypertension and bilateral extra-adrenal pheochromocytomas in another maternal cousin. All subjects were asymptomatic prior to their identification by the screening methods employed here. Other than the retinal hemangioblastoma no other associated solid or vascular tumors have been identified during screening. This family demonstrates the benefit of CgA as a screening tool in identifying family members who are at risk for pheochromocytoma.

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ACTH-INDEPENDENT UNILATERAL MULTINODULAR ADRENOCORTICAL HYPERPLASIA (UMAH) IN INFANCY: A DISTINCT ENTITY? W. Rabl, H. Hahn, T.M. Strom, H.-J. Leifheit, F. Hopner[1], H. Prantl[2], H. Stalla[3], J.A.Carney[4]. Kinderklinik der TU, [1]Kinderchirurgie and [2]Pathologisches Institut Krankenhaus Schwabing, [3]MPI für Psychiatrie, München, Germany, and [4]Mayo Clinic, Rochester, Minn., USA.

ACTH-independent Cushing's syndrome is either due to an adrenal tumor or to bilateral primary pigmented nodular adrenocortical dysplasia (PPNAD). The first category requires unilateral, and the latter bilateral adrenalectomy. We are reporting a 5 m old girl with ACTH-independent UMAH, clinically and histologically distinct from PPNAD, who was cured by unilateral adrenalectomy. Our patient developed obesity, a moon face, and growth arrest within the first 2 m of life. There were no other features suggestive of the "Carney complex". At 4 m of age, serum cortisol at 8, 12, 21, and 24 h was 76.8, 73.1, 115, and 84.4 µg/dl, non-suppressible by dexamethasone (2 and 8 mg/1.7 m²), and ACTH was undetectable (before and after CRF). Ultrasound and NMR showed a multinodular enlarged right and a normal left adrenal. A right-sided adrenalectomy and a biopsy of the left adrenal revealed both diffuse and nodular cortical hyperplasia without intermodular atrophy and with preservation of the fetal cortex in the right adrenal, and normal macro- and microscopic morphology in the contralateral gland, both features being clearly distinct from classical PPNAD. Surgery resulted in clinical and biochemical cure, and 5 m later, the hypothalamo-pituitary-adrenal axis was still partially suppressed, necessitating low-dose hydrocortisone replacement. On the basis of the unilateral process documented both morphologically and biochemically, and the specific histology of the diseased adrenal, we suggest that 1) UMAH in infancy is a separate entity distinct from PPNAD, and 2) the treatment of choice consists of unilateral adrenalectomy.

1) Carney JA et al. Endocrinologist 1992, 2, 6-21. 2) Geßler P et al. Klin Pädiatr 1991, 203, 462-466. 3) Larsen JL et al. Am J Med 1986, 80, 976-984. 4) Shenoy BV et al. Am J Surg Pathol 1984, 8, 335-344.

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ADRENAL SPECIFIC NUCLEAR TRANSCRIPTION FACTOR (TF) BINDING REGION IN 21-HYDROXYLASE DEFICIENCY. S.F.Siegel, W.A.Rudert, P.A.Lee, M.Trucco. Children's Hospital of Pittsburgh, University of Pittsburgh, Pgh., PA 15213, USA.

Both salt-losing and non-salt-losing 21-hydroxylase deficiency have been associated with a deleterious conversion event at nucleotide 655 (A or C in CYP21) to the CYP21P sequence (G) which modifies mRNA splicing leading to an elongated translation product with altered enzyme activity (PNAS 1988; 85:7486). To determine if the DNA binding region for a cAMP-dependent adrenal specific nuclear TF (JBC 1991; 266:11199) could account for this phenotypic heterogeneity, we determined the sequence of this functionally conserved region (-134 to -122) in 3 patients (2 salt-losing; 1 non-salt-losing) with this mutation. An 849-bp region of CYP21 was amplified by PCR utilizing a biotinylated primer. Sequencing was performed (Sequenase[R]) following Dynabead[R] magnetic avidin-biotin separation. The presence of other reported mutations was assessed by hybridization of specific oligonucleotide probes.

Patient 1 (46,XY) presented at 3 weeks of age with glucocorticoid & mineralocorticoid deficiencies. Patient 2 (46,XX), assigned to a male sex of rearing at birth, presented at 4 years of age with premature virilization. Patient 3 (46,XX) presented at birth with ambiguous genitalia and elevated plasma renin activity. Patients 1 & 3 have G at position 655 on both CYP21 alleles while patient 2 inherited a deletion for this region from his mother & G from his father. No sequence alterations were detected in these 3 patients from -160 to -80 of the 5' noncoding region of CYP21. Patients 1 & 2 have the normal CYP21 sequence for codons 172, 236, 237, 239, 306, 318, and 356 (analysis is incomplete for patient 3).

Differences in regulation through TFs could be postulated as an etiology of phenotypic heterogeneity. However, in these 3 patients, the sequence where the adrenal specific binding protein interacts with DNA is conserved. The basis for the phenotypic heterogeneity may be due to as yet undefined alterations in the coding or promoter regions of CYP21.

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PRESENCE OF THE SRY GENE IN DISORDERS OF SEXUAL DIFFERENTIATION. M.Kocova, S.F.Siegel, W.A.Rudert, M.Trucco. Children's Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, PA 15213, USA.

Identification of Y chromosomal material is important in individuals with disorders of sexual differentiation because 1) an increased risk for gonadal neoplasms exists and 2) insight into the process of sexual differentiation may be augmented. To better understand the role of SRY in disorders of sexual differentiation, tissues from 4 individuals were assessed by SRY specific PCR and Southern blotting with an SRY probe.

Patient	1	2	3	4
Diagnosis	Turner's	TH	MGD	Turner's
Ambig genit	-	-	+	-
Uterus	+	+	+	+
Rt Gonad	NA	ot	os	NA
Lt Gonad	NA	streak	testis	NA
PBL Karyotype	45XO	46XY	45X/46XXq-	isochrosome Xq
PBL SRY-PCR	±	+	+	-
PBL Southern	+	++	+	-

Key: TH=true hermaphroditism, MGD=mixed gonadal dysgenesis, ot=ovotestis, os=ovarian stroma, NA=not available, PBL=peripheral blood leukocyte

The sensitivity of this probe which can easily detect 1:10,000 cells indicates that mosaicism for the SRY portion of the Y chromosome has occurred in patients 1 & 3. For patients with Turner's syndrome, additional investigation of such patients is needed to determine the frequency of this mosaicism. For patient 3, the finding of SRY gene correlates with the observed testicular differentiation and virilization. For patient 2, further evaluation of the function of SRY and additional genes involved in sexual differentiation is necessary.

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MULLERIAN INHIBITING SUBSTANCE (MIS) IN THE EVALUATION OF CHILDREN WITH NONPALPABLE GONADS. MM Lee, ML Gustafson, *BL Silverman, L Asmundson, PK Donahoe and D.T. MacLaughlin. Ped Endocrine Unit and Ped Surgical Research Lab, Mass General Hosp, Boston, MA 02144, and *Div of Ped Endocrinology, Children's Memorial Hosp, Chicago, IL 60614.

The inability of hCG stimulation testing to consistently identify testicular tissue prompted us to examine whether MIS, a sexually dimorphic hormone, would be useful in evaluating children with nonpalpable gonads. We measured MIS by ELISA in 7 46XY children and 3 chromosomal mosaics.

			T ng/dl		MIS ng/ml		
Age	Karyotype	Genit	pre CG	post CG	pre CG	post CG	Gonads
3yr	46XY	Male	<10	<10	2.2	40.6	nl grossly
12mo	46XY	Male	2.8	406	8.9	11.3	nl grossly
6yr	46XY	Ambig	<10	17.7	10.8	12.8	nl grossly
19mo	46XY	Ambig	<10	<10	<0.5	<0.5	none
5wk	46XY	Ambig	349	405	3.2	2.2	dysgenetic
1wk	46XY9qH+	Ambig	74		13.5		pending
11mo	46XY	Female	low		<0.5		streak
3mo	45XO/46XY /47XYY	Ambig	65	128	11.8	19.7	dysg/streak
2wk	46XX/46XY	Ambig	230		7		ovotestes
3wk	45XO/46XY	Ambig	108		5.5		dysg/streak

MIS, normally >10ng/ml (boys) and <1.5ng/ml (girls) in this age range, was measurable in 7 pts with dysgenetic or grossly nl testes but undetectable in 2 pts with streak/absent gonads. MIS was useful in deciding on exploration of abdominal gonads for removal of dysgenetic testes or for orchiopexy. Thus, random MIS values were more discriminatory for testicular tissue than basal testosterone levels and were specific for testicular tissue in 2 pts with nondefinitive hCG stim tests.

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ALTERED SENSITIVITY TO LOW DOSE DEX IN A SUBSET OF PATIENTS WITH PREMATURE ADRENARCHE (PA) S E Oberfield, T Amer, D Tyson, D Soranno, R David and L S Levine, Depts. of Peds.St.Lukes/ Roosevelt New York 10025 and New York Univ Med Cent New York 10016

The regulatory mechanisms of adrenarche and PA, including the existence of a non-ACTH androgen stimulating factor, are controversial. We sought to evaluate the suppressibility of the HPA axis in PA in 24 children (age 1.5-8.75 yrs, 4M/20F) in whom the dx of PA was confirmed by ACTH testing. We measured cortisol and androgen at 8AM after a single PM low dose of DEX 0.3mg/m2 given between 11PM-MN (Hindmarsh and Brook, Clin Endo 1985.) 2 Groups of PA were defined by their response to DEX. GROUP I:(n=12) cortisol(f) <5ug/dl, GROUP II:(n=12)F ≥ 5ug/dl (p=.01)

					△ HORMONE
MEAN +/-SD	GROUP	Baseline	Post-ACTH	Post-DEX	TIME
F ug\dl	I	8.8±6	28±6	1.8±0.9	-7.0
	II	11.9±8	30±7	10.4±6.4	-1.5
Testo ng\dl	I	8.5±4	10.7±4	5.1±3	-3.4
	II	6.4±3	10.4±6	5.7±2	-0.7
DHEA ng\dl	I	219±166	430±229	94±70	-125.1 *
	II	131±76	250±121	156±103	24.6
△4A ng\dl	I	45±29	86±39	20±13	-24.9 *
	II	34±17	59±22	34±21	0.3
17-OHP ng\dl	I	32±26	214±197	12±18	-20.0
	II	47±64	233±276	21±21	-26.5
△5-17P ng\dl	I	118±135	840±295	13±17	-104.6 *
	II	110±148	633±221	95±129	-15.4

The mean age was 88 vs 84 months for I vs II and the mean CA/BA was 1.2 vs 0.99, I vs II. Although the mean responses to ACTH and DEX of T, DHEA, △4A, 17OHP and △517P did not differ, the rate of increase in response to ACTH and decrease to DEX of △517P, DHEA and △4A were sig. greater in group I vs group II.(*=p<.002) These results suggest a greater sensitivity to changes in ACTH secretion in I vs II These findings further suggest the possibility of different regulatory mechanisms resulting in PA: an ACTH and a non-ACTH factor.