CHILD WITH EXTENDED DELETION OF MONOCARBOXYLATE TRANSPORTER 8 (MCT8): EIGHT-YEAR FOLLOW-UP AND A TRIAL OF HIGH-DOSE LIOTHYRONINR

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Objective: The monocarboxylate transported 8 (MCT8) has a pivotal role in neuronal T3 uptake. Mutations of this transporter determine a distinct X-linked psychomotor retardation syndrome (Allan-Herndon-Dudley Syndrome, AHDS) that is attributed to low intracellular levels of T3. We describe the cytogenetics analysis of the MCT8 gene in a patient with the syndrome. We also evaluate the clinical and endocrine effects of long-term elthroxine treatment and a trial of high-dose lithyronine. In that trial we attempted to overcome the T3 uptake resistance through alternative transporters.

Methods: The six exons of MCT8 gene were individually amplified by PCR. The length of the deleted region was determined by SNP array, followed by PCR-based mapping to define the exact borders of the deleted segment. The clinical and endocrine data of the patient during 6.5 years of elthroxine treatment and two periods (3 month each) of low- and high-dose of liothyronine were evaluated.

Results: An extended deletion of the MCT8 gene (comprised of 5 out of 6 exons) was detected. MCT8 dysfunction was associated with partial resistance to T3 at the hypothalamus and pituitary level, with normal responsiveness at the peripheral organs (liver and cardiovascular system). Liothyronine administration had no beneficial effect on the neurological status of the patient.

Conclusion: Liothyroine administration had no therapeutic effect in our patient with severe MCT8 dysfunction due to extended deletion of its gene. Yet, this treatment might be considered in early life, especially in patients with residual function of MCT8.

NEWBORN SCREENING FOR CONGENITAL ADRENAL HYPERPLASIA USING CUTOFF BASED ON GESTATIONAL AGE AND BIRTH WEIGHT

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Objective: To evaluate whether congenital adrenal hyperplasia (CAH) patients can be detected by newborn screening before the occurrence of life threatening salt wasting while maintaining overall adequate levels of prevalence, sensitivity and specificity.
DESIGN: In a two year pilot (2008 and 2009), neonatal screening was performed measuring 17a-hydroxy-progesterone (17OHP) using Auto DELFIA Neonatal 17OHP B024 kits (PerkinElmer). Cutoff levels were based on both gestational age and birth weight.

Results: Data obtained from patient archives revealed that nationwide the incidence of 21-hydroxylase deficiency (21OHD) was 1:19,000 live births (1:30,000 for Jews and 1:8,000 for Arabs). The M:F ratio was 1:2.5 suggesting that 21OHD male patients in the general population might have been missed or died early due to a salt-loosing crisis.
In the 2008-2009 period 319,394 newborns were screened and 15 CAH patients were detected, 8 male and 7 female. The 17OHP levels were between 202 and 609 nmol/l. Overall prevalence was 1:21,300; among them 8 were Jews (1:28,000) and 7 were Arabs (1:10,000). Therapy was started at the median age of less than 6 days. Total recall rate was 0.02% (60 cases), there were 4 suspected cases referred to Endocrinology but were false positive. No false negative were reported. Sensitivity was100%, specificity 99.98% and positive predicted value was 20%.

Conclusions: Severe salt wasting can be prevented by neonatal screening. Our screening, based on gestational age in combination with birth weight, reduces false positive results thus reducing the psychological distress of parents whose infants might have a potentially life threatening chronic disease as well as unnecessary load on the medical system.

FINAL HEIGHT OF SUBJECTS WITH NON CLASSICAL 21 HYDROXYLASE DEFICIENCY BY AGE AT INITIATION OF GLUCOCORTICOIDS THERAPY AND GENOTYPE

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Background: Non-classical 21-hydroxylase deficiency (NC21OHD) is a mild form of congenital adrenal hyperplasia (CAH) associated with different degrees of postnatal virilization developing from infancy to adulthood. The genotype might be either homozygous or compound heterozygous for mild mutations or compound heterozygous for one mild and one severe mutation of the gene encoding 21-hydroxylase (*CYP21*). It has shown that subjects with classical form of CAH tend to be shorter than expected from their midparental height. The loss of height in CAH is partially due to effect of sex steroids on epiphyseal closure and partially due to glucocorticoid-induced suppression of growth.

Aims: 1. to determine whether NC21OHD compromises final height. 2. to look for clinical parameters affecting final height in this population.
Methods: Retrospective review of medical records of subjects with NC21OHD who have reached final height for age at diagnosis, age at initiation of therapy, midparental height and *CYP21* genotype. The SD score (SDS) for final height and corrected height SDS (defined as final height – midparental height SDS) were estimated for each subject.

Results: Final height was available for 104 patients (81 females) diagnosed at mean age of 10.5 (median 8.5, range 0.1-32.1 years). Genotype was available for 86 patients of whom 60 (58%) were homozygous for V281L or compound heterozygous for mild mutations, 17 (16%) were compound heterozygous for one mild and one severe mutation, and 9 (9%) were heterozygous for V281L. The mean final height SDS achieved by NCCAH patients was -0.55 ± 1, and the mean corrected height SDS was -0.16 ± 0.7. No significant correlation or association was found between final height SDS and genotype, gender, or age at diagnosis, although those with one severe mutation tend to be shorter.

Conclusions: Unlike classical CAH NC21OHD does not seem to affect final height significantly irrespective of clinical parameters such as gender, age of diagnosis, genotype or treatment. This result may have application on the management approach of these patients.

CONSTRUCTION OF GENE THERAPY VIRAL VECTORS TARGETING THYROID CARCINOMA CELLS

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Introduction: The successful use of tissue-specific promoters in targeted gene therapy for cancer depends on a high level of cell type specificity. In this study, we defined and characterized a minimal thyroid cancer-specific enhancer which provides maximal, thyroid-specific, transcriptional activity from the Tg promoter in human thyroid papillary (NPA), follicular (MRO,WRO), anaplastic (ARO) carcinoma and primary human goiter cell cultures. This minimal Tg enhancer is intended for use in "safe", gutless recombinant adeno-associated viral (rAAV) vectors.

Methods: CAT was used to measure the Tg enhancer/promoter transcriptional activity. Five gutless rAAV serotypes [2,4,5, 8-9(DJ) and 12] expressing eGFP were prepared. Infection efficiency was measured by calculating the percentage of green fluorescent cells following different time periods.

Results: The full length Tg enhancer (1.4kbp) gave 13 and 2% CAT conversion in follicular and papillary thyroid carcinoma cells, respectively. The minimal Tg enhancer/promoter (-2.8 and -2.2 kbp) construct achieved a level of transcriptional activity: follicular 38%, papillary 28% and anaplastic <1% CAT conversion. On gel shift and supershift analysis, the minimal Tg enhancer fragment was found to bind TTF1 using NPA and MRO nuclear extracts.
rAAV12nlsGFP infected 82.7% of NPA and 92% of WRO cells, peaking at 3 days, rAAV2nlsGFP infected 82.1% of ARO cells, peaking at 6 days after infection. Furthermore, for primary human papillary thyroid cells, rAAV12nlsGFP infected the tumor cells more efficiently than normal thyroid cells from the same patient (n=3). rAAV8-9(DJ)nlsGFP infected 100% of WRO cells, peaking at 3 days. Upon replacement of the CMV enhancer/promoter with the minimal Tg enhancer element into this virus, rAAVDJ-Tg-nlsGFP gave specific infection in WRO cells (26.3%) compared to pre-adipocyte cells (3%).

Conclusions: The minimal Tg enhancer element can serve to drive a Tg promoter-driven suicide gene within an AAV12/2/8-9(DJ) viral coat as a future tool in thyroid cancer gene therapy.

RET PROTO-ONCOGENE MUTATIONS IN ISRAEL-20 YEARS EXPERIENCE

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Introduction: Germ-line mutations in the RET proto-oncogene cause Multiple Endocrine Neoplasia (MEN)-2 syndrome, Familial Medullary Thyroid Carcinoma (MTC) and Hircshprung's disease. Little is known about the incidence of RET mutations in Israel, the ethnic characteristics of its carriers, and their clinical presentation.

Patients and Methods: Analysis of RET-mutations was conducted at the biochemistry laboratory, Tel-Aviv Sourasky Medical Center. All results from 1990-2010, including demographic, clinical and genetic data were reviewed.

Results: A total of 208 RET gene mutations examinations were conducted. Indications for conducting the test included: MTC (33.6%), first degree relatives of mutation carrier (46.6%), combined endocrinopathies (9.6%), pheochromocytoma (3.4%), familial MTC (1.4%), and Primary Hyperparathyroidism (PHT) (14%). Only 2.85% of patients with sporadic MTC were positive. No mutations were found in patients tested due to PHT or pheochromocytoma alone. 36% of family members were carriers. In 7 out of 20 (35%) patients presenting with combined endocrinopathy, no mutation was found. In three of these patients partial sequencing was done. Only 2.88% from the patients examined were from Arabic origin, and no mutations were found in this group. Out of 54 positive samples 8 were sporadic mutations, and 46 belonged to patients from 8 families. In the sporadic cases 6 different mutations in exons 10, 11, 14, 15, 16 were found. The ethnic origin was diverse. Six families carried 4 different mutations compatible with MEN-2A. Two other families carried a mutation compatible with MEN-2B.

Conclusions: A variety of sporadic and familial mutations in the RET proto-oncogene in the Jewish population in Israel was found among different ethnicities. No Arab carriers were found in this cohort. A low incidence of positive tests was found in patients with sporadic MTC. The genotype-phenotype correlation found is similar to that described in the literature. The diversity of the mutations found in different exons underscores the importance of complete sequencing of the gene.

HEMITHYROIDECTOMY FOR PAPILLARY THYROID CARCINOMA –WHEN LESS IS SOMETIMES MORE

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Introduction: Although total thyroidectomy is standard treatment for papillary thyroid carcinoma (PTC), hemithyroidectomy may be sufficient for small, low-risk, intrathyroidal tumors. There are no clear guidelines for the long term follow-up of hemithyroidectomy.

Objective: To evaluate follow-up regimen and outcome in patients with suspected intrathyroidal PTC treated with hemithyroidectomy or total thyroidectomy at a single institute.

Patients and methods: The study sample consisted of 161 patients with PTC treated at a tertiary medical center in 2001-2010: 60 consecutive patients after hemithyroidectomy, and 101 patients after total thyroidectomy. Only patients without visible neck metastases preoperatively were included. Clinical data were collected from the medical files. Number of patient visits to the endocrine clinic, laboratory thyroid tests, neck ultrasound, and fine needle aspirations (FNAs) during follow-up were documented as well. Independent t-test was used to evaluate between-group differences, and Pearson correlation was used to evaluate the relationship between characteristics in the hemithyroidectomy group.

Results: Tumor size was significantly greater in the total-thyroidectomy group (16.9mms) than the hemithyroidectomy group (7.25mms). There was no significant difference between the groups in the rate of permanent surgical complications. In the hemithyroidectomy group, 37 patients (61.6%) had known bilateral thyroid nodules preoperatively; this finding was positively correlated with the performance of repeated FNAs during follow-up. The hemithyroidectomy patients visited the endocrine clinic less frequently than the total thyroidectomy patients, but they were referred more often to neck ultrasound and FNAs . Significantly more patients in the hemithyroidectomy group were re-operated for suspicious recurrent/persistent disease.

Conclusions: Hemithyroidectomy for PTC is associated with a significant laboratory, imaging and cytological test burden, frequently even more than total thyroidectomy for more advanced disease. It provides no clear benefit to the patient. Clinicians should consider these factors when planning initial treatment for PTC, especially in patients with known bilateral thyroid nodules preoperatively.

PARATHYROID HORMONE SELECTIVE VENOUS SAMPLING FOR PREOPERATIVE EVALUATION OF PRIMARY HYPERPARATHYROIDISM

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Background: Minimally Invasive parathyroidectomy (MIP) is preferably used for the treatment of primary hyperparathyroidism (PHPTH) caused by a single adenoma. When the sestamibi scan and cervical ultrasound localization are negative, the classical 4-gland exploration is usually recommended. In the present investigation we evaluated the use of preoperative PTH selective venous sampling (PTH-SVS) for localization of an adenoma in patients with negative or questionable sestamibi scintigraphy.

Methods: PTH-SVS was performed in patients with proven HPTH and a negative preoperative sestamibi scan, and in patients with persistent or recurrent HPTH. When a significant PTH gradient was detected preoperatively MIP was chosen.

Results: PTH-SVS was performed in 115 patients. In 33 patients with persistent o recurrent PHPT a significant gradient was detected in 24 patients, and 13 patients were cured by reoperation. In 82 patients with a negative sestamibi scan before the first operation, a significant gradient was detected in 66 patients, and successful MIP performed in 41 patients. In 6 of the patients with a significant preoperative PTH gradient, but negative bilateral neck exploration, the side of thyroid lobectomy was chosen according to the PTH gradient, and resulted in cure of all 6 patients.

Conclusions: The preoperative use of PTH-SVS in PHPTH with a negative or questionable sestamibi scan resulted in successful MIP in 50.0% of the patients. We recommend the use of PTH-SVS for preoperative localization in patients with PHPT and a negative or questionable sestamibi scan.