Journal of Internal Medicine 2004; 255: 696–730

Abstracts for the Ninth International Workshop on Multiple Endocrine Neoplasia (MEN2004)

Edited by: Constantine A. Stratatis and Stephen J. Marx, Bethesda, MD, USA

Plenary Oral Abstract Title	Presenter/Author	Number
Endocrine neoplasia syndromes: from phenotype to genotype and back	Allen Spiegel (NIDDK, Bethesda, MD, USA)	1
Molecular genetics of pituitary tumors	Shlomo Melmed (Los Angeles, CA, USA)	2
FGF signaling in endocrine tumorigenesis	Shereen Ezzat (Toronto, Canada)	3
Epigenetic mechanisms of tumorigenesis	William Farrell (Stoke-on-Trent, UK)	4
Familial isolated pituitary adenomas	Albert Beckers (Liege, Belgium)	5
Prevention of medullary thyroid carcinoma	Samuel Wells Jr (Durham, NC, USA)	6
Consortia experiences – can we cure MCT?	Henning Dralle (Halle/Salle, Germany)	7
Therapeutic approaches for medullary thyroid carcinoma	Robert Gagel (Houston, TX, USA)	8
Signaling in thyroid tumorigenesis and progression	Matt Ringel, (Columbus, OH, USA)	9
PTEN – One gene, many syndromes	Charis Eng (Columbus, OH, USA)	10
New concepts in clinical, densitometric, and biochemical features of primary hyperparathyroidism	John Bilezikian (New York, NY, USA)	11
Minimally invasive parathyroid surgery in the setting of MEN1 or MEN2a	Robert Udelsman, (New Haven, CT, USA)	12
Genetics of parathyroid tumors	Bin Teh (Grand Rapids, MI, USA)	13
HRPT2 gene expression in hyperparathyroidism-jaw tumor syndrome and parathyroid cancer	Catharina Larsson (Stockholm, Sweden)	14
Partnering and functioning of the MEN1 tumor suppressor gene	Sunita Agarwal (NIDDK, Bethesda, MD, USA)	15
Patterns and consequences of chromosomal aneuploidy in cancer cells	Thomas Reid (NHGRI, Bethesda, MD, USA)	16
Molecular targeting of kidney cancer gene pathways	Marston Linehan (NCI, Bethesda, MD, USA)	17
Hypoxia inducible factors and tumor pathways	Patrick Maxwell (London, UK)	18
Genetics of paragangliomas and pheochromocytoma	Anne-Paule Gimenez-Roqueplo (Paris, France)	19
Current approaches to the biochemical diagnosis, localization and treatment of a pheochromocytoma in patients with MEN2	Karel Pacak (NICHD, Bethesda, MD, USA)	20
Cellular communication and oncogenesis in the adrenal	Stefan Bornstein (Dusseldorf, Germany)	21
Adrenocortical tumors in multiple tumor syndromes: from germ line to somatic diseases	Jerome Bertherat (Paris, France)	22
Mouse models of the Carney complex: Tools for dissecting the roles of Prkar1a in tumorigenesis	Lawrence S. Kirschner, (Columbus, OH, USA)	23
Congenital hyperinsulinism: clinicopathological correlations with molecular data	Jean-Christophe Fournet (Montreal, Canada)	24
The Role of Lkb1 in Pancreatic Development and Cancer	Nabeel El-Bardeesy (Boston, MA, USA)	25
Loss of function mutations in RET	Aravinda Chakravarti (Baltimore, MD, USA)	26
Tumor models in Drosophila: application to MEN1	Allen Bale (New Haven, CO, USA)	27
Genetic testing in a CLIA-certified clinical diagnostic laboratory	Sherri Bale (Gaithersburg, MD, USA)	28
Counseling in multiple endocrine neoplasia (MEN) syndromes	CJM Lips (Utrecht, The Netherlands)	29

several genes involved in growth regulatory pathways, including RB1, DAPK and GADD45g and is associated with gene silencing. To identify novel genes subject to this epigenetic change we used methylation-sensitive arbitrarily primed PCR (MsAP-PCR). We isolated several sequences that showed differential methylation in pituitary tumours relative to normal pituitary. For one of these novel sequences, isolated from chromosome 22, we found that the majority of pituitary adenomas, irrespective of subtype, failed to express the transcript as determined by qRT-PCR. We next performed function studies through transfection analysis in the AtT20 cell lines. Enforced expression of the cDNA encoding this novel gene had no discernible effects on proliferation or cell viability, however, cells expressing this construct showed a threefold increase in apoptosis, as determined by acridine orange staining and TUNEL labelling, compared to those harbouring an empty vector control. Apoptosis was preceded by an increase in active caspases and was reversible in the presence of z-VAD-fmk. The pituitary tumour derivation and role in apoptosis of this gene led us to assign it the acronym PTAG. The ability of cells, showing reduced expression of PTAG, to evade or show a blunted apoptotic response may underlie oncogenic transformation in both the pituitary and other tumour types.

O5

Familial isolated pituitary adenomas

A. BECKERS *et al.*

Endocrinology – University Hospital Liège, Liège, Belgium

Familial pituitary adenomas have been characterized in the settings of multiple endocrine neoplasia type 1 (MEN1) and Carney complex (CNC). Furthermore, isolated familial somatotropinomas have been reported. Interestingly, we have observed other pituitary phenotypes not linked to these previous syndromes, suggesting a new entity: familial isolated pituitary adenomas (FIPAs). To get further clinical and genetic insight of FIPAs, a retrospective European multicentre study was undertaken. A hundred and forty cases (56 males and 84 females) have been identified in 64 families, including prolactinomas (40%), GH-omas (34%), clinically non-secreting adenomas (16%), ACTH-omas (5.7%) and gonadotrophinomas (4.3%). FIPAs represented less than 2% of all pituitary adenomas followed in the centre involved in the study. There were 54 families with two patients, 8 with three, and two with four affected members. A direct familial relationship (siblings and/or parents/offsprings) was the most frequently encountered (75%), and, where at least two generations were present, the mean age at diagnosis was significantly lower in the second generation compared to the first one (50.3 ± 15 vs 29.7 ± 10.6, $P < 0.001$). The main bioclinical features of FIPAs were also compared to a control series of sporadic pituitary adenomas.

The mean age at diagnosis was 38, ± 16 years. During follow-up (10, ± 8 years) no MEN-1 nor CNC-associated features was observed. From a genetic point of view, sequencing of the MEN-1 gene in at least one affected patient in each family allowed to exclude a pituitary-restricted form of MEN-1 in all FIPAs subgroups, and sequencing of the PKARIA gene for Carney complex was also normal in all tested kindreds ($n = 14$).

We suggest, on the basis of clinical, epidemiological and genetic data, that FIPAs represent a new entity. Further molecular studies should help to clarify FIPAs? | etiology, plan relative familial screening and provide new insights into the pathogenesis of pituitary adenomas.

O6

Prevention of medullary thyroid carcinoma

S. WELLS JR.,[*,†] W. G. DILLEY,[†] M. DEBENEDETTI,[†] F. J. QUAYLE,[†] & J. F. MOLEY[†]

[*]Departments of Surgery, The Duke University Medical Center, Durham, NC; [†]The Washington University School of Medicine, St. Louis, MO

Formerly, multiple endocrine neoplasia (MEN) type 2a or familial medullary thyroid carcinoma (FMTC) were detected by clinical examination or biochemical testing. Currently, direct DNA analysis for mutations in the RET protooncogene is the preferred method of diagnosis. Regardless, affected patients are candidates for total thyroidectomy (TT), since virtually all will develop MTC.

In screening new kindreds with MEN 2a or FMTC, one finds disease in family members of various ages. We sought to compare clinical outcomes in patients whose MTC was diagnosed either below 25 years of age or above 50 years of age.

Our clinic, as part of a molecular screening program, performed TTs on 61 patients with MEN 2a (57) or FMTC (4). All patients were under 24 years of age and had no physical evidence of MTC. Our clinic also performed TTs on 39 patients over 50 years of age (36 with MEN 2a and 3 with FMTC), who were identified during screening of kindreds with hereditary MTC. The MTC was diagnosed either by direct DNA analysis ($n = 2$), elevated plasma CT levels ($n = 29$) or a nodule in the neck ($n = 8$). In the immediate postoperative period stimulated plasma CT values were either undetectable or within the normal range in all 61 patients under 25 years of age. Postoperative testing was performed immediately postoperatively in 30 of the 39 patients over 50 years of age and CT values were undetectable or within the normal range in 15 patients (50%) but elevated above the normal range in 15 patients (50%).

Currently, TT appears to be preventative or curative therapy for patients with MEN 2a and FMTC. The therapy is most often preventative when performed in young patients, whose only detectable abnormality is a mutation in the RET protocooncogene.

O7

Consortia experiences – can we cure MTC?

H. DRALLE, J. UKKAT, M. BRAUCKHOFF, O. GIMM & A. MACHENS

Department of Surgery (Chairman: Prof. Dr. Med. Henning Dralle), University of Halle, Medical Faculty, Halle, Denmark

Medullary thyroid carcinoma (MTC) is a rare tumour characterized by the occurrence of two different variants, sporadic and hereditary, and the development of early lymphangic and haematogenous metastases. Although patients with occult metastasis and persistent hypercalcitonemia may have a favourable long-term course [1], distant metastases and locoregional lymph node metastases (LNMs) are proven risk factors of local recurrence and impaired survival [2,3]. The aim of this study was to identify risk factors of postoperative persistent hypercalcitoninemia in sporadic and hereditary MTC based on single centre as well as multicentric studies.

Pre- and postoperative calcitonin levels and extent of disease: Preoperative calcitonin levels have shown to be correlated as well with the T-category, as with N- and M-categories [4–6]. Also postoperative calcitonin levels paralleled with the extent of disease. In patients with 10 or more LNM biochemical are could not be achieved. Remarkably, calcitonin normalization occurred only in about 70% of pT1, and nodal-negative patients, respectively