VIII EDIZIONE

NEN PRECEPTORSHIP

LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano

NEN Preceptorship

IEO
Istituto Europeo di Oncologia

HUMANITAS UNIVERSITY

Approccio diagnostico-terapeutico al paziente con NET pancreatico: il ruolo dell'endocrinologo

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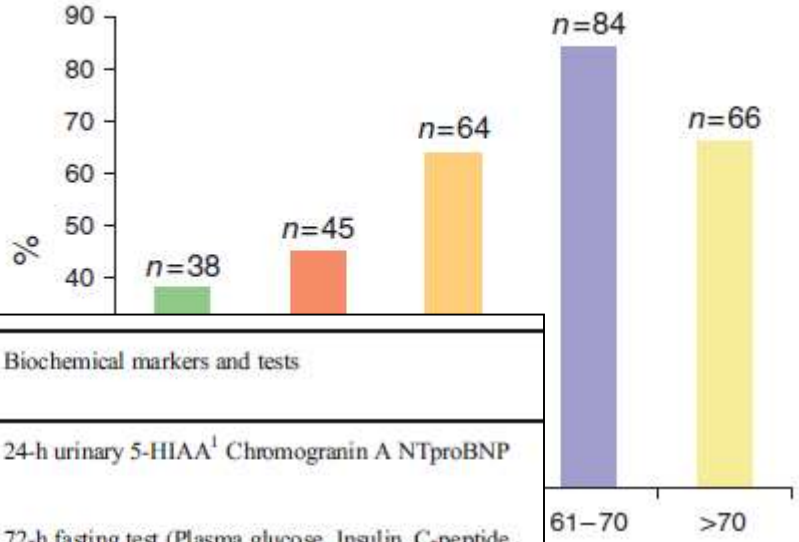
Clinicopathological Features of Pancreatic Endocrine Tumors: A Prospective Multicenter Study in Italy of 297 Sporadic Cases

Mean age 58.6±14.7 anni
F= 51.2 %, M= 48.8%

Alessandro Zerbi, MD[1], Massimo Falconi, MD[2], Guido Rindi, MD[3], Gianfranco Delle Fave, MD[4], Paola Tomassetti, MD[5], Cla
Vanessa Capitanio, MD[1], Letizia Boninsegna, MD[2], Valerio Di Carlo, MD[1] and the members of the AISP-Network Stuc

Am J Gastroenterol 2010; 105:1421–1429;



Non functioning **232 (75.4%)**
Functioning

Clinical syndrome	Main location of primary tumor (rare sites of origin)	Biochemical markers and tests
Carcinoid-Syndrome	jejunum / ileum (pancreas, lung, rectum)	24-h urinary 5-HIAA[1] Chromogranin A NTproBNP
Insulinoma	pancreas	72-h fasting test (Plasma glucose, Insulin, C-peptide, Pro-Insulin, ß-hydroxybutyrate and absence of sulfonylurea and metabolites)
Gastrinoma (Zollinger-Ellison-Syndrome)	duodenum (70%) pancreas (25%); other sites (5%)	Fasting serum gastrin[2], gastric pH Secretin-stimulation Test[3]
Rare functional GEP-NENs		
VIPoma (Werner Morrison Syndrome; WDHA)	pancreas (>90%), adrenal gland and periganglionic (<10%)	Plasma-VIP
Glucagonoma	pancreas	Serum-Glucagon
GHRH secreting NET	pancreas (30%), lung (54%) jejunum (7%) other (13%)	hGH[5], IGF-1, glucose suppression test
Ectopic ACTH syndrome	Pancreas (ileum)	Dexamethasone suppression test, 24-h-urinary cortisol, midnight salivary cortisol
PTHrp secreting NET	pancreas	Serum-Calcium, PTHrp[6] (iPTH[7]), 1,25OH2 Vitamin D3
Calcitonin secreting p-NET[8]	pancreas	Serum-Calcitonin

Name	Biologically active peptide(s) secreted	Incidence (new cases/10^6 population/year)	Tumor location	Malignant %	Associated with MEN-1, %	Main symptoms/signs
A. Most common functional PET syndromes						
Insulinoma	insulin	1–3	pancreas (>99%)	<10	4–5	hypoglycemic symptoms (100%)
Zollinger-Ellison syndrome	gastrin	0.5–2	duodenum (70%); pancreas (25%); other sites (5%)	60–90	20–25	pain (79–100%); diarrhea (30–75%); esophageal symptoms (31–56%)
B. Established rare functional PET syndromes (RFTs)						
VIPoma (Verner-Morrison syndrome, pancreatic cholera, WDHA)	vasoactive intestinal peptide	0.05–0.2	pancreas (90%, adult); other (10%, neural, adrenal, periganglionic)	40–70	6	diarrhea (90–100%); hypokalemic (80–100%); dehydration (83%)
Glucagonoma	glucagon	0.01–0.1	pancreas (100%)	50–80	1–20	rash (67–90%); glucose intolerance (38–87%); weight loss (66–96%)
Somatostatinoma	somatostatin	rare	pancreas (55%); duodenum/jejunum (44%)	>70	45	diabetes mellitus (63–90%); cholelithiases (65–90%); diarrhea (35–90%)

Carcinoid syndrome 19% of patients diagnosed with NETs (Lancet Oncol. 2017 Apr;18(4):525-534)

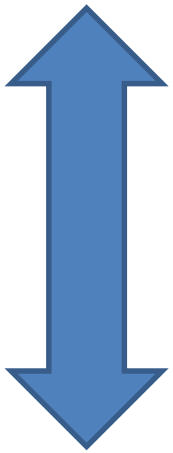
Ectopic ACTH syndrome 1% to 5% in patients with SCLC; 3% in patients with thoracic or gastroenteropancreatic carcinoids

High impact on both morbility and mortality

Ectopic GHRH secretion
98 cases so far reported

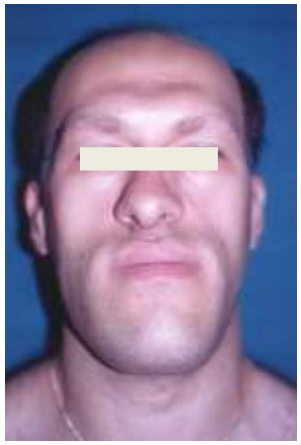
Quale ?

Panel ormonale



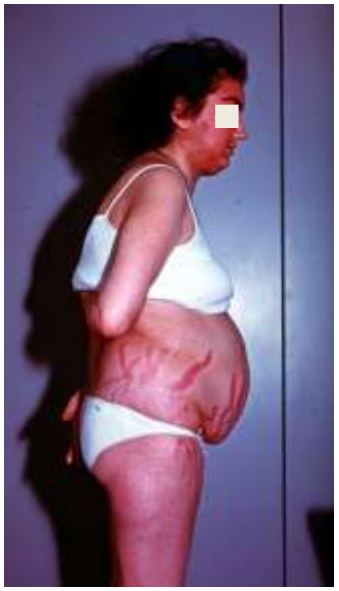
Quando ?

Quadro clinico



IGF-1
GH post OGTT

Ectopic GH secretion (acromegaly)



ACTH/cortisol
Cortisol post Dexa

Ectopic ACTH secretion (Cushing's syndrome)

Carcinoid syndrome

flushing, diarrhea, unspecific abdominal pain, broncho constriction tricuspid and pulmonic valve regurgitation

24-h urinary 5-HIAA1

Insulinoma

Symptoms of hypoglycemia and rapid improvement after application of glucose (Whipples' triad)

Glycemia, Insulin, C peptide
72-h fasting test

Gastrinoma

severe peptic ulcer disease, gastroesophageal reflux, diarrhea

Gastrin
Secretin stimulation test

False positives/false negatives

Carcinoid syndrome

24-h urinary 5-HIAA1

False positives:
plums, pineapples, bananas, eggplants, tomatoes, avocados and walnuts
phenacetin, reserpine, cisplatin, fluorouracil, and melphalan

False negatives:
monoamine oxidase inhibitors, tricyclic antidepressants, chlorpromazine, heparin,isoniazid, levodopa and methyldopa

Sensitivity 70%, Specificity 100% [HPLC]

- Not to be used for screening purposes
- To be evaluated in the presence of symptomatic NEN
- Useful in monitoring response to therapy/evolution of the disease

Gastrinoma

Gastrin diagnostic if 10 times higher than normal levels (40% of patients)

Exclude: PPI, chronic athopic gastritis

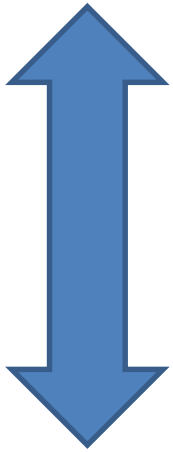
Secretin test: >120 pg/ml
(sensitivity 94%, specificity 100%)

Not to be used for screening purposes

AIOM 2018

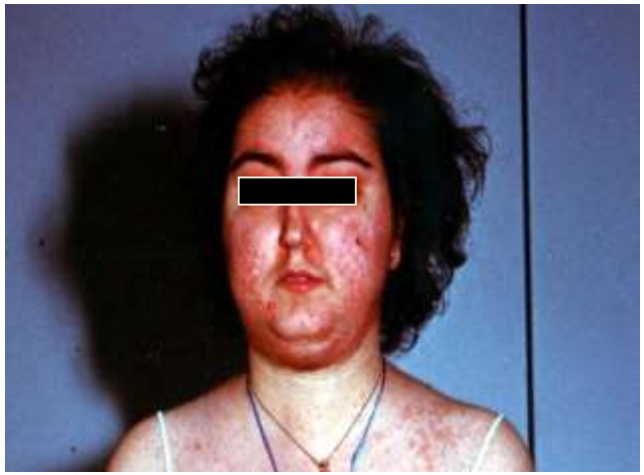
Quale ?

Panel ormonale



Perchè ?

L'identificazione e il trattamento delle sindromi ormonali impatta significativamente su morbilità e mortalità nei pazienti con NET



Coagulopathies

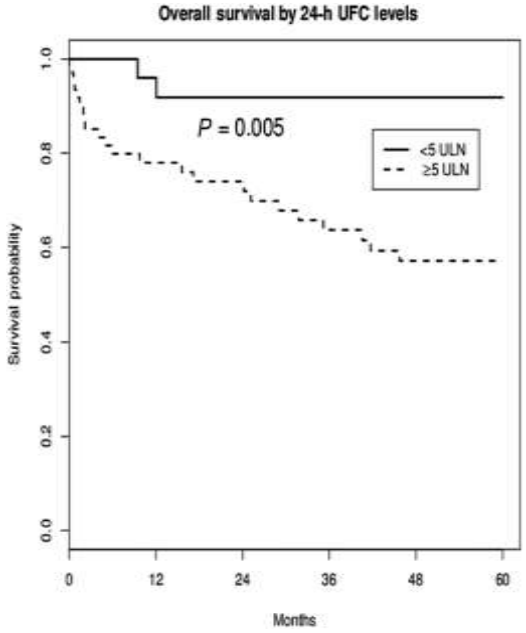
Diabetes

Infections

Hypokaliemia

EAS appears to shorten survival in patients with unresectable carcinoid tumors

Kamp K et al . Eur J Endocrinol 2016;174(3):271–80



Severity of hypercortisolism at diagnosis also appears to have a negative impact on prognosis

Davi et al, 2017 Eur J Endocrinol 453-461

In most series, ACTH-secreting thymic carcinoids, pancreatic carcinoids, and MTCs tend to present with more aggressive disease and distant metastases, and consequently have poorer overall survival

Isidori et al 2009 JCEM; Ilias et al. 2005 JCEM; Davi et al 2017 EJE

Follow-up

«personalized» treatment

counseling

Genetic testing

Costs?

Patients to be screneed?

Predictors?

When ?

Which gene ?

Incidence of PAN NET

PAN-NET

MEN1 40-80%

Gastrinoma (40%), NF (20-50%), insulinoma (10%)
Primary hyperparathyroidism, pituitary adenomas

multiple micro/macroadenomas

VHL 10-17%

Mainly NF (>90%)
Phaeochromocytoma, CNS haemangioblastomas, Renal Cell Carcinoma

Multiple cysts, solid tumors (10%)

NF1 >10%

neurofibromas, café-au-lait spots, Lisch nodules, freckles, and optic glioma

Multiple Endocrine Neoplasia type 1

1–18% (among patients with primary hyperparathyroidism)
16–38% (among patients with gastrinomas)
Less than 3% (among patients with pituitary tumours)

The disorder affects all age groups with no differences between male and female

Age at diagnosis is significantly lower in MEN1+ pts

Clinical and biochemical manifestations of the disorder in more than 98% of patients by the fifth decade

Primary hyperparathyroidism has a 100 % of penetrance by age 50 years

pNET in MEN1+ patients are more frequently multicentric neoplasia

Thakker 2010, Best Clinical Practice Endocrinology and Metabolism

When to suspect a MEN1…
…and to perform a genetic screening

Member(s) of a family with and identified MEN1 mutation

Member(s) of a family with familial pituitary adenoma and/or primary hyperPTH

Pr
m

da successive valutazioni (4). L'analisi mutazionale del gene *MEN1* deve essere effettuata in: 1) un probando con diagnosi clinica di MEN1 (almeno due delle tre manifestazione classiche di MEN1 (iperparatiroidismo primario, adenoma ipofisario, NET duodeno-pancreatico); 2) familiari di primo grado asintomatici di soggetti portatori di una mutazione nota del gene *MEN1*; 3) familiari di primo grado di un portatore di mutazione del gene *MEN1*, con diagnosi di MEN1 familiare; 4) pazienti con sospetto di MEN1 o MEN1 atipica (soggetti con iperparatiroidismo primario che insorge prima dell'età di 30 anni; soggetti con coinvolgimento paratiroideo multiplo e NET duodeno-pancreatici, singoli o multipli, che insorgono a qualunque età; soggetti con due o più tumori MEN1-correlati che non rientrano nella classica triade paratiroidi, ipofisi, duodeno-pancreas) (4) (**livello di evidenza 4**). L'analisi mutazionale del gene *MEN1* nei

Y

Patients with multiple pancreatic micro/macrolesions

Patients with at least 2 MEN1-related tumors different from PIT-NET, GEP-NET or PHPT (e.g. adrenal adenomas, meningiomas, carcinoids, Pheo…)

AIOM 2018 LG; JCEM 2016 LG

Genetic analysis and clinical outcome

Characteristics	Group I (n=43) Clinical MEN1 diagnosis	Group II (n=30) Genetic MEN1 diagnosis	Total (n=74)*
Sex			
M/ F (%)	22/21 (51/49)	12/18 (40/60)	35/39 (47/53)
Mean age at diagnosis yrs ± SD (range)†	34±14 (11-64)	30±14 (16-67)	32±13 (10-64)
Median year of diagnosis	1994	2002	1998
Mean age at end follow-up yrs ± SD (range)‡	47±14 (26-77)	36±14 (16-67)	42±15 (16-77)
Median follow-up yrs (IQR;range)§	11 (4.0-17.0; 0-31)	3 (2.0-6.0; 0-13)	5.5 (2.25-12.0; 0-31)
Death			
Death/ alive	10/33	0/30	10/64
Death MEN1 related			
Yes	5		5
No	0		0
Unknown	5		5
Mean age death ± SD (range)	52±16 (26-72)	Not applicable	52±16 (26-72)

…Patients who were diagnosed genetically had a better outcome than those diagnosed clinically…

…malignancy and death only occurred in the clinically diagnosed group…

Pietermann et al. 2008 Clin Endocrinol

MEN1: phenotype/genotype

…No correlation has been observed between genotype and MEN1phenotype. We suggest that the knowledge of structure and location of a specific mutation has not been useful in clinical practice for the follow-up of affected patients and asymptomatic gene carriers…

Wautot et al. , 2002 Hum Mutat

…(100 pazienti) NFPT was more common in the frameshift/nonsense or 1657insC mutation carriers,whereas gastrinoma was more common in the in-frame/missense or 1466del12 mutation carriers...

Vierimaa et al., 2007 EJE

… (1336 mutazioni) comparison of the clinical features in patients and their families with the same mutations reveals an absence of phenotype-genotype correlations….

Lemos & Thakker, 2008 Hum Mutat

MEN1: follow-up

TABLE 2. Suggested biochemical and radiological screening in individuals at high risk of developing MEN1

Tumor	Age to begin (yr)	Biochemical test (plasma or serum) annually	Imaging test (time interval)
Parathyroid	8	Calcium, PTH	None
Pancreatic NET			
Gastrinoma	20	Gastrin (± gastric pH)	None
Insulinoma	5	Fasting glucose, insulin	None
Other pancreatic NET	<10	Chromogranin-A; pancreatic polypeptide, glucagon, VIP	MRI, CT, or EUS (annually)
Anterior pituitary	5	Prolactin, IGF-I	MRI (every 3 yr)
Adrenal	<10	None unless symptoms or signs of functioning tumor and/or tumor >1 cm are identified on imaging	MRI or CT (annually with pancreatic imaging)
Thymic and bronchial carcinoid	15	None	CT or MRI (every 1–2 yr)

EUS, Endoscopic ultrasound. [Adapted from P. J. Newey and R. V. Thakker: Role of multiple endocrine neoplasia type 1 mutational analysis in clinical practice. *Endocr Pract* 17(Suppl 3):8–17, 2011 (21), with permission. © American Association of Clinical Endocrinologists. And from R. V. Thakker: Multiple endocrine neoplasia type 1 (MEN1). *Translational Endocrinology and Metabolism*, Vol 2. (edited by R. P. Robertson and R. V. Thakker), The Endocrine Society, Chevy Chase, MD, 2011, pp 13–44 (5), with permission.]

Two retrospective analyses of chromogranin A, pancreatic polypeptide, and glucagon to screen for emergence of tumor in MEN1 found that singly or in combination, these tests were not effective in early diagnosis of tumors

de Laat JM J Clin Endocrinol Metab . 2013 ;98:4143; Qiu W Clin Endocrinol (Oxf) 2016 ;85:400

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