Ectopic ACTH Syndrome

History

- The first report of extra-pituitary ACTH secretion due to malignancy was described in 1928.

- The term of ectopic ACTH secretion (EAS) was proposed by Liddle in 1963; it was based mainly on patients with small cell lung cancer (SCLC).

Lancet 1928; 1022–1023.
Arch Intern Med 1963; 111: 471–475.

Ectopic ACTH Syndrome (EAS)

- A condition of endogenous hypercortisolism sustained by an ACTH-secreting non-pituitary tumor
- In 15% of cases, Cushing's syndrome is associated with nonpituitary tumors secreting ACTH: "the ectopic ACTH syndrome".

Williams Textbook of Endocrinology 14th edition

Ectopic ACTH Syndrome (EAS)

- Overt EAS: followed by a prompt identification of the tumoral source
- Covert EAS: identified during a subsequent evaluation or a prolonged follow-up
- Occult EAS: the tumoral source cannot be identified neither after a meticulous diagnostic work-up nor during an extended follow-up

Williams Textbook of Endocrinology 14th edition

Clinical presentation

- Usually similar to hypercortisolism symptoms due to other causes
- Clinical presentation is often that of a wasting syndrome with weakness and pigmentation.
- Weight loss, myopathy, and glucose intolerance are prominent symptoms and signs.
- Duration of symptoms from onset to presentation is short.

Williams Textbook of Endocrinology 14th edition

Features of EAS and Cushing’s disease

- Discriminating the EAS from Cushing's disease is now especially challenging.
- ACTH-secreting NETs often present with the gradual onset of classical symptoms and signs of Cushing's syndrome, indistinguishable from Cushing's disease.

Rev Endocr Metab Disord (2010) 11:117–126

Features of EAS and Cushing’s disease

- Age of onset: higher in the EAS (38 and 50 yr VS 30–40 yr in Cushing's disease)
- Heterogeneous, and influenced by underlying tumor and the severity of the hypercortisolism.
- Ranged from the abrupt onset to the gradual and slow onset
- May be indistinguishable from the presentation of Cushing's disease, which is typically seen with well-differentiated NET

J Neuroendocrinol. 2022 Aug;34(8):e13137

Tumors associated with EAS

Tumor Type	Approximate Incidence (%)
Small cell lung carcinoma	50
Non-small cell lung carcinoma	5
Lung carcinoids	10
Thymic tumors (including carcinoids)	5
Pancreatic tumors (including carcinoids)	10
Other carcinoids	2
Medullary carcinoma of thyroid	5
Pheochromocytoma and related tumors	3
Rare carcinomas of prostate, breast, ovary, gallbladder, colon	10

Williams Textbook of Endocrinology 14th edition

Diagnostic approach

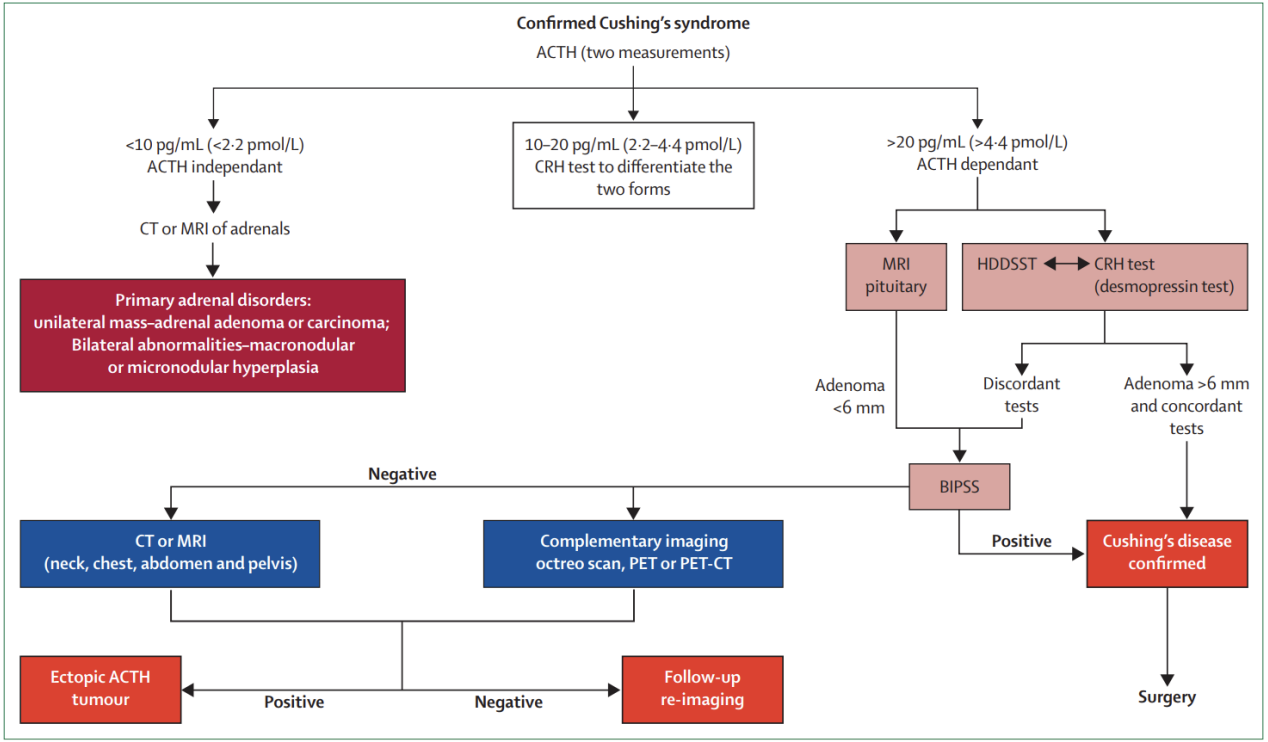
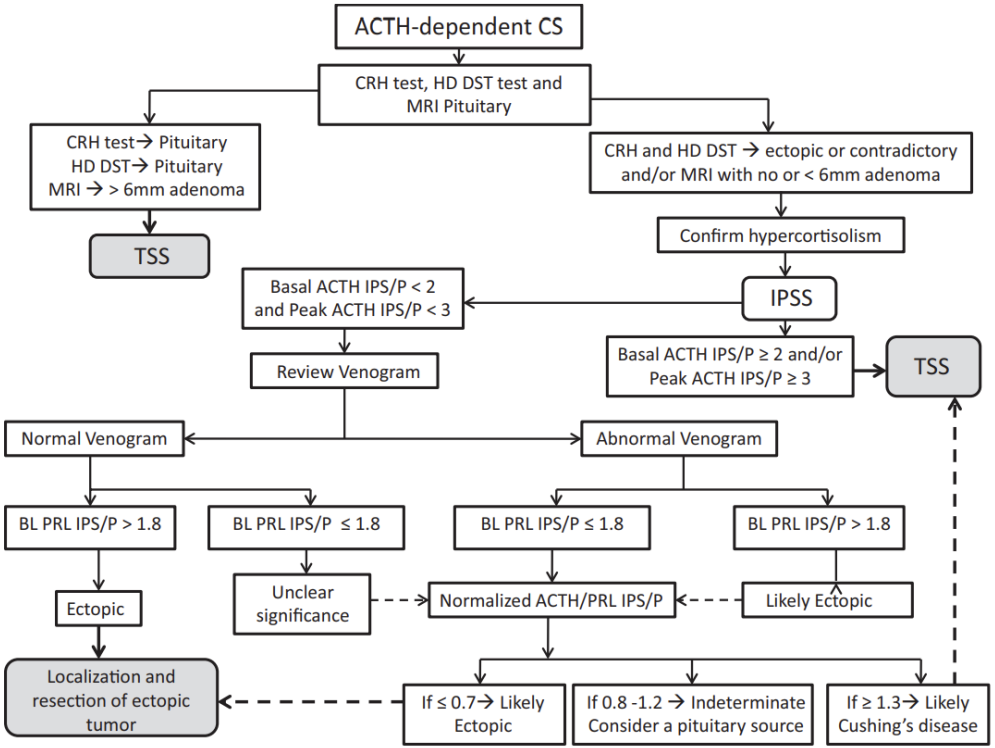


***Figure 3*: Clinical decision-making flow chart for the differential diagnosis of confirmed Cushing's syndrome of different causes**
Modified from reference 170 by permission of The Endocrine Society Press. ACTH=adrenocorticotropic hormone. CRH=corticotropin-releasing hormone. HDDSST=high dose dexamethasone suppression test. BIPSS=bilateral inferior petrosal sinus sampling.

BIPSS
: gold standard test to identify a pituitary VS ectopic source of ACTH
: sensitivity and specificity of roughly 95%

Lancet. 2015 Aug 29;386(9996):913-27

Prolactin in BIPSS



J Clin Endocrinol Metab 2011; 96(12):3687-3694

Searching for an ectopic source

- Thin-cut multislice imaging with chest, abdominal, and pelvic CT scanning
- MRI
- Octreotide scan
- SPECT/CT
- FDG-PET
- Whole-body PET
- Selective angiography

Rev Endocr Metab Disord (2010) 11:117–126

Table 1. Summary of three major retrospective review studies comparing the performance of [^{68}Ga]-DOTATATE imaging in detecting ACTH-secreting tumors

Publication		Isidori, 2015	Wannachalee, 2019	Varlamov, 2019[a]
Number of patients		231	28	69
	Overt	121	–	59
	Covert	67	–	–
	Occult	43	17	10
Sex	Female	50.2% (108/215)	78.60%	–
	Male	49.8% (107/215)	21.40%	–
Age (median, range)		43 (3–82)	50 (18–77)	–
CT	Sensitivity	66.2% (137/207)	–	69.7% (34/60)
	True positive	63.7% (137/215)	–	78.5% (37/51)
	False negative	33.6% (70/215)	–	27.4% (14/51)
	False positive	3.7% (8/215)	–	–
	Covert sensitivity	43.6% (24/55)	–	–
MRI	Sensitivity	51.5% (53/103)	–	–
	True positive	50.5% (53/105)	–	–
	False negative	47.6% (50/105)	–	–
	False positive	1.9% (2/105)	–	–
	Covert sensitivity	44.8% (13/29)	–	–
[^{111}In]- pentetreotide	Sensitivity	48.9% (84/172)	–	–
	True positive	48.3% (84/174)	–	–
	False negative	50.6% (88/174)	–	–
	False positive	1.1% (2/174)	–	–
	Covert Sensitivity	64%% (32/50)	–	–
^{68}Ga SSR PET/CT	Sensitivity	81.8% (18/22)	65% (11/17) occult	70% (42/60)
	True positive	78.3% (18/23)	–	–
	False negative	17.4% (4/23)	–	–
	False positive	4.3% (1/23)	–	–
	Covert Sensitivity	100% (9/9)	–	50% (13/26)

[a]Results are presented as number of lesions, not patients, as in the other two studies; –, no data available.

Histopathological markers

- Positive staining for ACTH in 40–64%

- Definitive proof:

-Required reversal of the clinical picture after resection of the tumor

and/or

-Demonstration of ACTH immunohistochemical staining in the tumor tissue or in metastatic deposits

and/or

-Complete/partial resolution of the hypercortisolemia after tumor removal/debulking

Rev Endocr Metab Disord (2010) 11:117–126

Treatment

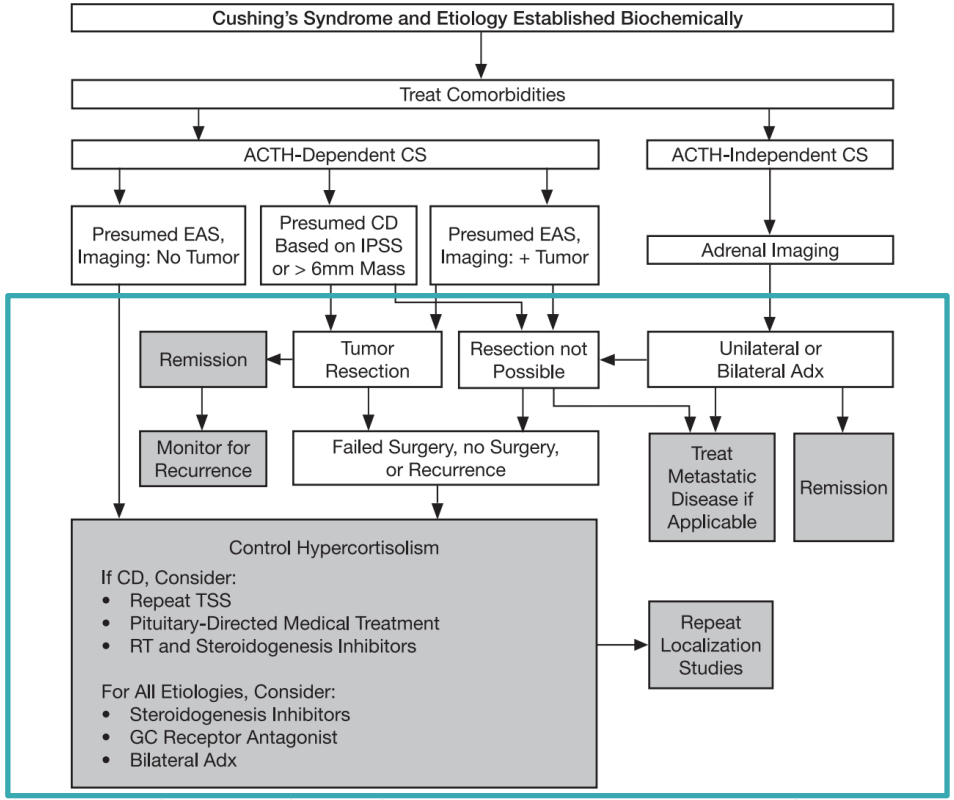


Figure 1. An algorithm for the treatment of CS. Derived from Nieman LK, Biller BM, Finding, JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93:1526–1540. (17)

J Clin Endocrinol Metab, August 2015, 100(8):2807–2831

Treatment

- Complete excision of the ACTH-secreting tumor
- Steroidogenesis inhibitors in patients with occult or metastatic EAS
- Bilateral adrenalectomy
- The intensity of hypercortisolism, the general condition of the patient and associated comorbidities

Rev Endocr Metab Disord (2010) 11:117–126
Lancet. 2015 Aug 29;386(9996):913-27

Prognosis

- Influenced by tumor histology and by the severity of hypercortisolemia
- Small cell lung carcinoma and thymic carcinoids seem to have the worst prognosis.
- Bronchial carcinoid tumors have a better outcome.

Rev Endocr Metab Disord (2010) 11:117–126

Prognosis

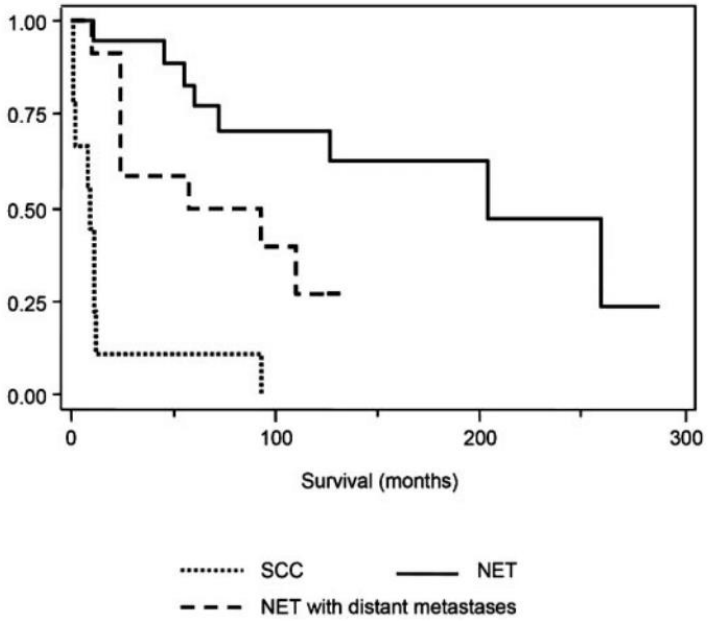


FIG. 2. Kaplan-Meier survival estimates, according to the histology and stage of the tumor.

- Patients with SCC had the worst prognosis.
- Bronchial carcinoid tumors, often showed prolonged survival.
- Patients with an occult source of ACTH but adequate control of hypercortisolemia also had a good prognosis.

J Clin Endocrinol Metab, February 2006, 91(2):371–377

Cyclic Cushing's syndrome

- Cushing's disease was the underlying cause in 54%, ectopic secretion of ACTH in 26%, and primary adrenal CS in 11%
- In comparison, the corresponding prevalences of patients with CS in general are 68, 12, and 20% respectively.
- Thus, it appears that occurrence of ectopic ACTH syndrome is more frequent in patients with cyclic CS.

All reported cases since 1960-2007→ 65 reported cases

Eur J Endocrinol. 2007 157:R245-254.

Cyclic Cushing's syndrome

Table 1 Cases with cyclic Cushing's syndrome reported in the literature.

Cause		Number of cases (n=65)	References
Pituitary ACTH		35 (54%)	(9, 10, 11[a], 13, 14, 23, 24, 25–44[a])
Ectopic ACTH	Overall	17 (26%)	(5 12 15 45–49 51–58 66)
	Thymic carcinoid	6	(15, 47, 48, 53, 54, 66)
	Bronchial carcinoid	4	(5, 45, 46, 55)
	Pancreatic carcinoid	1	(51)
	Renal carcinoid	1	(12)
	Gastric carcinoid	1	(58)
	Epithelial thymoma	1	(56)
	Phaeochromocytoma	1	(57)
	Occult	2	(49, 52)
Adrenal	Overall	7 (11%)	(7, 10, 20[a], 21, 59–61)
	Adenoma	3	(10, 60[a], 61)
	Pigmented nodular adrenocortical disease	3	(20, 21, 59)
	Hyperplasia	1	(7)
Unclassified	Overall	6 (9%)	(50 62–66)

[a]Reference reporting more than 1 patient with cyclic Cushing' syndrome.

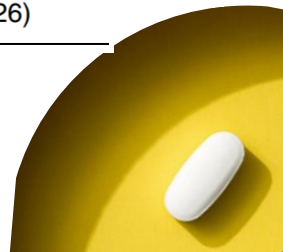
Carcinoids are the most frequently reported cause of patients with cyclic ectopic ACTH secretion

Eur J Endocrinol. 2007 157:R245-254.

Cyclic Cushing's syndrome

Table 2 Clinical characteristics of patients with cyclic Cushing's syndrome. Data retrieved from 65 case reports.

	Overall[a] (*n*=65)	**Pituitary** (*n*=35)	**Ectopic ACTH** (*n*=17)	**Adrenal** (*n*=7)
Female sex, *n* (%)	47 (72)	25 (71)	13 (76)	4 (57)
Age at diagnosis, median (range), years	41 (0–72)	41 (4–71)	43 (12–72)	21 (0–46)
Cushing features[b], *n* (%)	61 (94)	32 (91)	17 (100)	6 (86)
Additional disorders, *n* (%)				
Diabetes mellitus or glucose intolerance	25 (38)	12 (34)	8 (47)	1 (14)
Mood disorders	15 (23)	6 (17)	3 (18)	2 (29)
Acne	7 (11)	3 (9)	2 (12)	0 (0)
Hirsutism	15 (23)	9 (26)	4 (24)	0 (0)
Amenorrhoea (% of women)	6 (13)	6 (17)	0 (0)	0 (0)
Cycle length, median (range), days	21 (3–510)	18 (0.5–510)	30 (4–180)	35 (14–60)
Intercyclic phase, median (range), days	30 (1–2160)	20 (1–1642)	35 (1–2160)	120 (60–720)
Survival, % of reported (*n*/*n*)	94 (58/62)	97 (33/34)	80 (12/15)	100 (7/7)
Follow-up, years, median (range)	2.7 (0.08–26)	3 (0.08–13)	2.25 (0.8–11)	7 (1–26)



Eur J Endocrinol. 2007 157:R245-254.

Table 1 Factors associated with low-moderately elevated serum calcitonin levels in non-medullary thyroid carcinoma.

Drugs
PPI
Glucocorticoids
Beta-blockers
Glucagon
Enteroglucagon
Pancreozymin
CGRP inhibitors, used for migraine treatment
Non-thyroid non-tumor diseases
Hypergastrinemia (chronic anthropic gastritis, Zollinger-Ellison syndrome)
Hypercalcemia (including hyperparathyroidism)
Pseudohypoparathyroidism
Chronic renal insufficiency
Pernicious anemia
Hepatic cirrhosis
Pancreatitis
Inflammatory states (including sepsis)
Non-thyroid neoplasms
NENs (including pheochromocytoma, paraganglioma, entero-pancreatic NEN, insulinoma, esophageal NEN, small cell lung carcinoma)
Breast cancer
Methodology
Heterophilic antibodies
Macrocalcitonin

CGRP, calcitonin gene-related peptide; NENs, neuroendocrine neoplasms; PPI, proton pump inhibitors.

Calcitonin in extra-thyroid neuroendocrine neoplasms

Eur J Endocrinol. 2020 Dec;183(6):R197-R215.

Calcitonin in extra-thyroid neuroendocrine neoplasms

- Pancreatic, laryngeal and lung NENs are most frequently associated with hypercalcitoninemia.
- The interpretation of increased serum calcitonin is still a gray area in endocrinology given the many confounding factors
- A careful diagnostic evaluation of all patients presenting with hypercalcitoninemia is therefore essential for an accurate early diagnosis identifying the thyroidal or extra-thyroidal origin of the secretion.

Eur J Endocrinol. 2020 Dec;183(6):R197-R215.


Thank You