







## Current limits of the topic

The approach of ectopic ACTH syndrome is complex and it still represents a matter of discussion. The current twists of the topic may involve the difficulty of differentiation from Cushing disease in some cases requiring bilateral inferior petrosal sinus sampling which is not actually feasible in many centers (49). Also, cabergoline has been suggested as an adjuvant in occult cases (50). ACTH antagonists are still not applicable in every day practice (51).

## CONCLUSIONS

Heterogeneous field of ectopic Cushing syndrome still has several twists in diagnosis and therapy due to various tumours that may cause it and different scenarios of evolution. Nevertheless adequate control of cortisol excess is needed even in case with unidentified primary tumour.

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## REFERENCES

- Young J, Haissaguerre M, Viera-Pinto O, Chabre O, Baudin E, Tabarin A. Management of endocrine disease: Cushing's syndrome due to ectopic ACTH secretion: an expert operational opinion. *Eur J Endocrinol.* 2020;182(4):R29-R58.
- Nakhjavani M, Amirbaigloo A, Rabizadeh S, Rotondo F, Kovacs K, Ghazi AA. Ectopic Cushing's syndrome due to corticotropin releasing hormone. *Pituitary.* 2019; 22(5):561-568.
- Paduraru DN, Albu SE, Carsote M, Valea A. Adrenal Cushing's syndrome in a female with ovarian cancer. *Archives of the Balkan Medical Union.* 2016;51(3):410-412.
- Boers J, Oldenburg-Ligtenberg PC, Stades AM, van Treijen MJ. Possible pitfalls in the workup of ectopic ACTH secretion illustrated by four rare cases. *BMJ Case Rep.* 2019; 12(11):e231067.
- Albu SE, Georgescu CE, Mihalca D, Carsote M, Ghervan C, Valea A. Obesity and hirsutism: how close?. *Archives of Balkan Medical Union.* 2016;51(1):133-136.
- Torpy DJ, Mullen N, Ilias I, Nieman LK. Association of hypertension and hypokalemia with Cushing's syndrome caused by ectopic ACTH secretion: a series of 58 cases. *Ann NY Acad Sci.* 2002; 970:134-44.
- Araujo Castro M, Marazuela Azpiroz M. Two types of ectopic Cushing syndrome or a continuum? Review. *Pituitary.* 2018; 21(5):535-544.
- Valea A, Ghervan C, Carsote M, Albu SE, Georgescu CE. Different surgical options in Cushing's disease. *Journal of Surgical Sciences.* 2016;3(1):39-43.
- Paduraru DN, Nica A, Carsote M, Valea A. Adrenalectomy for Cushing's syndrome: do's and don'ts. *Journal of medicine and life* 2016; 9(4):334-6.
- Hayes AR, Grossman AB. The Ectopic Adrenocorticotrophic Hormone Syndrome: Rarely Easy, Always Challenging. *Endocrinol Metab Clin North Am.* 2018;47(2):409-425.
- Witek P, Witek J, Zieliński G, Podgajny Z, Kamiński G. Ectopic Cushing's syndrome in light of modern diagnostic techniques and treatment options. *Neuro Endocrinol Lett.* 2015;36(3):201-8.
- Javanmard P, Duan D, Geer EB. Mortality in Patients with Endogenous Cushing's Syndrome. *Endocrinol Metab Clin North Am.* 2018;47(2):313-333.
- Carsote M, Valea A, Dumitru N, Terzea D, Petrova E, Albu S, Buruiana A, Ghemigian A. Metastases in daily endocrine practice. *Archives of Balkan Medical Union.* 2016;51(4):476-480.
- Lodish MB, Keil MF, Stratakis CA. Cushing's Syndrome in Pediatrics: An Update. *Endocrinol Metab Clin North Am.* 2018; 47(2):451-462.
- Carsote M, Ghemigian A, Terzea D, Gheorghisan-Galateanu AA, Valea A. Cystic adrenal lesions: focus on pediatric population (a review). *Clujul Medical.* 2017; 90(1):5-12.
- Guilmette J, Nosé V. Paraneoplastic syndromes and other systemic disorders associated with neuroendocrine neoplasms. *Semin Diagn Pathol.* 2019;36(4):229-239.
- Poiana C, Carsote M, Trifanescu R, Terzea D, Croitoru A. Case study of Appendiceal Carcinoid during Pregnancy. *J Med Life.* 2012;15(5(3):325-32.
- Valea A, Morar A, Dumitru DP, Carsote M, Ghemigian A, Dumitrache C. Infertility as the onset of Cushing's disease: is pasireotide a treatment option? *Ars Medica Tomitana.* 2015;21(3):128-31.
- Radu L, Carsote M, Gheorghisan-Galateanu AA, Preda SA, Calborean V, Stanescu R, Gheorman V, Albulescu DM. Blood Parathyryn and Mineral Metabolism Dynamics A clinical analyze. *Rev Chim.* (Bucharest). 2018;69(10):2754-8.
- Debono M, Newell-Price JD. Cushing's Syndrome: Where and How to Find It. *Front Horm Res.* 2016;46:15-27.
- Poiana C, Carsote M, Baloescu R, Stanescu B, Petrescu R, Corneci C, Hortopan D, Chirita C, Ioachim D, Terzea D. The adrenalectomy in rare endocrine tumors - two cases report. *Journal of Surgery* (Jurnalul de Chirurgie Iasi). 2010;6(1):47-53.
- Ghemigian A, Cocolos A, Neagu P, Petrova E, Dumitru N, Albu SE, Carsote M. Cushing's disease – same condition, different scenarios. *Archives of the Balkan Medical Union.* 2018;53(1):135-139.
- Zilio M, Barbot M, Ceccato F, et al. Diagnosis and complications of Cushing's disease: gender-related differences. *Clin Endocrinol. (Oxf).* 2014;80:403-410.
- Valassi E, Franz H, Brue T, Feelders RA, Netea-Maier R, Tsagarakis S, Webb SM, Yaneva M, Reincke M, Droste M, Komerudus I, Maiter D, Kastelan D, Chanson P, Pfeifer M, Strasburger CJ, Tóth M, Chabre O, Tabarin A, Krsek M, Fajardo C, Bolanowski M, Santos A, Wass JAH, Trainer PJ; ERCUSYN Study Group. Diagnostic tests for Cushing's syndrome differ from published guidelines: data from ERCUSYN. *Eur J Endocrinol.* 2017;176(5):613-624.
- Wagner-Bartak NA, Baiomy A, Habra MA, Mukhi SV, Morani AC, Korivi BR, Waguespack SG, Elsayes KM. Cushing Syndrome: Diagnostic Workup and Imaging Features, With Clinical and Pathologic Correlation. *AJR Am J Roentgenol.* 2017; 209(1):19-32.
- Goyal A, Gupta U, Kandasamy D, Khadgawat R. Severe Hypercortisolism with Hypokalemic Alkalosis Mimicking Ectopic Cushing Syndrome in a Patient with Cushing Disease Due to Pituitary Microadenoma. *Indian J Endocrinol Metab.* 2018; 22(6):860-863.
- Linling Fan, Yuan Zhuang, Yi Wang, Xinhua Liu, Dan Liu, Boni Xiang, Min He, Zhaoyun Zhang, Yiming Li, Yongfei Wang, Xiaoming Zhu, Hongying Ye. Association of hypokalemia with cortisol and ACTH levels in Cushing's disease. *Ann NY Acad Sci.* 2019;1-7.
- Carsote M, Paun S, Neamtu MC, Avramescu ET, Iosif C, Terzea D, Constantinoiu S, Danculescu Miulescu R, Neamtu OM, Poiana C. The immunohistochemistry aspects in two cases of neurofibromatosis-

- associated abdominal tumors, *Rom Journal Morphol Embryol*. 2012;53(2):401-405.
29. Carsote M, Preda SA, Mitroi M, Camen A, Radu L. Serum Osteocalcin, P1NP, Alkaline Phosphatase, and CrossLaps in Humans: the relationship with body mass index. *Rev Chim*. (Bucharest). 2019;70(5):1615-1618.
  30. Poiana C, Neamtu MC, Avramescu ET, Carsote M, Trifanescu R, Terzea D, Neamtu OM, Ferechide D, Danciulescu Miulescu R. The poor prognosis factors in G2 neuroendocrine tumor. *Rom J Morphol Embryol*. 2013;54(3 Suppl):717-720.
  31. Poiana C, Carsote M, Ardeleanu C, Terzea D, Avramescu ET, Neamtu MC, Danciulescu Miulescu R. The value of the immunohistochemistry in a case of gastric neuroendocrine tumor and thyroid metastasis. *Rom J Morphol Embryol*. 2011; 52(1):187-192.
  32. Grigoryan S, Avram AM, Turcu AF. Functional imaging in ectopic Cushing syndrome. *Curr Opin Endocrinol Diabetes Obes*. 2020;27(3):146-154.
  33. Nica AE, Carsote M, Paduraru DN, Valea A. Bilateral adrenalectomy and Nelson's syndrome. *Archives of Balkan Medical Union*. 2016;51(2):280-283.
  34. Sun X, Lu L, Feng M, Fan Y, Bao X, Dai C, Deng K, Guo D, Yao Y, Zhu H, Wang R. Cushing Syndrome Caused by Ectopic Adrenocorticotropic Hormone-Secreting Pituitary Adenomas: Case Report and Literature Review. *World Neurosurg*. 2020; 142:75-86.
  35. Rubinstein G, Osswald A, Hoster E, Losa M, Elenkova A, Zacharieva S, Machado MC, Hanzu FA, Zopp S, Ritzel K, Riester A, Braun LT, Kreitschmann-Andermahr I, Storr HL, Bansal P, Barahona MJ, Cosaro E, Dogansen SC, Johnston PC, Santos de Oliveira R, Raftopoulos C, Scaroni C, Valassi E, van der Werff SJA, Schopohl J, Beuschlein F, Reincke M. Time to Diagnosis in Cushing's Syndrome: A Meta-Analysis Based on 5367 Patients. *J Clin Endocrinol Metab*. 2020;105(3):dgz136.
  36. Paleń-Tytko JE, Przybylik-Mazurek EM, Rzepka EJ, Pach DM, Sowa-Staszczak AS, Gilis-Januszewska A, Hubalewska-Dydejczyk AB. Ectopic ACTH syndrome of different origin-Diagnostic approach and clinical outcome. Experience of one Clinical Centre. *PLoS One*. 2020;15(11):e0242679.
  37. Wannachalee T, Turcu AF, Bancos I, Habra MA, Avram AM, Chuang HH, Waguespack SG, Auchus RJ. The Clinical Impact of [(68) Ga]-DOTATATE PET/CT for the Diagnosis and Management of Ectopic Adrenocorticotropic Hormone - Secreting Tumours. *Clin Endocrinol (Oxf)*. 2019;91(2):288-294.
  38. Walia R, Gupta R, Bhansali A, Pivonello R, Kumar R, Singh H, Ahuja C, Chhabra R, Singh A, Dhandapani S, Sahoo S, Rana N, Vatsa R, Dutta P, Bhadada SK, Sachdeva N, Mittal BR, Nahar U, Shukla J. Molecular Imaging Targeting Corticotropin Releasing Hormone Receptor for Corticotropinoma: A Changing Paradigm. *J Clin Endocrinol Metab*. 2020:dgaa755.
  39. Micko A, Wolfsberger S, Knosp E, Marik W, Haberler C, Winhofer Y, Luger A, Vila G. Ectopic Cushing's syndrome in a patient with inferior petrosal sinus sampling indicating pituitary-dependent ACTH secretion. *Clin Case Rep*. 2019;8(1):104-107.
  40. Sharma ST. An individualized approach to the evaluation of Cushing syndrome. AACE Adrenal Scientific Committee. *Endocr Pract*. 2017;23(6):726-737.
  41. Zhang HY, Zhao J. Ectopic Cushing syndrome in small cell lung cancer: A case report and literature review. *Thorac Cancer*. 2017;8(2):114-117.
  42. Ma L, Yin L, Hu Q. Therapeutic compounds for Cushing's syndrome: a patent review (2012-2016). *Expert Opin Ther Pat*. 2016;26(11):1307-1323.
  43. Arnaldi G, Tremontino L. Update on Hypercortisolism Therapy. *Front Horm Res*. 2016;46:87-105.
  44. Łebek-Szatańska A, Nowak KM, Zgliczyński W, Baum E, Żyłka A, Papierska L. Low-dose etomidate for the management of severe hypercortisolemia in different clinical scenarios: a case series and review of the literature. *Ther Adv Endocrinol Metab*. 2019;10:2042018819825541.
  45. Carsote M, Ghemigian A, Valea A, Dumitrascu A, Chirita C, Poiana C. Subclinical Cushing's syndrome with bilateral adrenal tumours in a patient with gallbladder multiple stone: therapeutic options. *Ars Medica Tomitana*. 2015;3(21):124-127.
  46. Albu SE, Carsote M, Capatina C, Dumitrascu A, Ghemigian A. Adrenal surgical approach in a woman with synchronous bilateral adrenal tumours. *Journal of Surgical Sciences*. 2015;2(3):132-135.
  47. Petrescu R, Valea A, Terzea D, Dumitrascu A, Albu SE, Carsote M. Laparoscopic right adrenalectomy and cholecistectomy: from endocrine decision to surgical procedure. *Medicine in evolution*. 2016;22(4):473-477.
  48. Stoian VR, Carsote M, Ghemigian A, Valea A. Postoperative contra-lateral incidental imagery finding following laparoscopic surgery for adrenal Cushing's syndrome. *Archives of the Balkan Medical Union*. 2016;51(3):417-420.
  49. Purwar N, Kumar A, Sharma B, Sharma H, Saran S, Garg U, Sahlot R, Mathur SK. Bilateral Inferior Petrosal Sinus Sampling in Corticotropin-Dependent Cushing's Syndrome: A Single Center Experience from Western India. *Indian J Endocrinol Metab*. 2020;24(4):343-348.
  50. Ilie MD, Raverot V, Tronc F, Vasiljevic A, Borson-Chazot F, Raverot G. Cabergoline in severe ectopic or occult Cushing's syndrome. *Eur J Endocrinol*. 2019;181(1):K1-K9.
  51. Clark AJ, Forfar R, Hussain M, Jerman J, McIver E, Taylor D, Chan L. ACTH Antagonists. *Front Endocrinol (Lausanne)*. 2016;7:101.