·专题讲座·

库欣病临床诊断研究进展

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【摘要】 库欣病亦称垂体促肾上腺皮质激素腺瘤，是一种临床罕见且严重的神经内分泌疾病。其诊断主要基于临床表现、影像学检查和内分泌功能测定。随着影像学技术的发展、实验室检查的精细化和基因组学技术的成熟，库欣病的诊断水平显著提高。本文拟从临床表现、影像学检查、内分泌功能测定、分子标志物检测和基因检测方面对库欣病的定性诊断和定位诊断进展进行综述。

【关键词】 库欣综合征；　垂体肿瘤；　促肾上腺皮质激素；　综述

Advances in clinical diagnosis of Cushing´s disease

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【Abstract】 Cushing´s disease, also known as pituitary adrenocorticotrophin-secreting adenoma, is a rare and serious neuroendocrine disease. At present, the diagnosis of disease is mainly based on the patient´s clinical manifestations, imaging examinations and endocrine-related examinations. With the development of imaging technology, the refinement of laboratory tests and the maturation of genomics technology, the diagnostic level of the Cushing´s disease has improved significantly. This article will review recent research advances on the qualitative and localized diagnosis of Cushing´s disease in clinical manifestations, biochemical detection, imaging diagnostics, molecular markers and genomics detection.

【Key words】 Cushing syndrome; Pituitary neoplasms; Adrenocorticotropic hormone; Review

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库欣病亦称为垂体促肾上腺皮质激素腺瘤，系指促肾上腺皮质激素（ACTH）细胞或垂体促肾上腺皮质激素腺瘤细胞异常增生，使下丘脑-垂体-肾上腺（HPA）轴调节失衡，导致体内皮质醇过度分泌不受负反馈抑制，进而引起的全身代谢紊乱综合征。临床遇到与库欣综合征相似的临床表现时，明确判断病因是提供及时准确治疗的关键。随着实验室检测技术和影像学技术的发展，加之多学科诊疗模式（MDT）的应用，库欣病的诊治水平显著提高。本文拟对近年来库欣病在定性诊断和定位诊断方面的研究进展进行综述，以为临床更好地鉴别诊断库欣病与异位ACTH依赖性库欣综合征提供参考。

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一、定性诊断

库欣病是一种垂体源性病变，约占垂体腺瘤的14%、库欣综合征的70%[1-2]。目前，主要根据临床表现和内分泌功能测定定性诊断库欣病。

1. 临床表现　库欣综合征的典型症状与体征包括面部潮红，满月脸，痤疮，体毛增多，体重增加，体脂重新分布呈向心性肥胖，水牛背，皮肤纤薄并色素沉着、瘀斑，腹部和大腿遍布条形紫纹，真菌感染（好发于手、足、指甲、肛周），精神心理异常（如失眠、焦虑、抑郁、记忆力减退、认知功能障碍），男性性功能障碍，女性月经紊乱甚至停经、呈男性化等；常见并发症包括高血压、糖尿病、高脂血症、关节痛、骨质疏松症、骨折、心功能障碍、凝血功能障碍

等[3]。但有文献报道，经术后病理证实的垂体促肾上腺皮质激素腺瘤患者中有6%～43%无明显的库欣综合征典型症状与体征，属于静息性垂体促肾上腺皮质激素腺瘤[4]。

2. 内分泌功能测定　排除长期服用过量糖皮质激素和酒精类饮料等外源性因素的影响后，内分泌功能测定有助于定性诊断库欣综合征。(1)血清皮质醇、血浆ACTH和24小时尿游离皮质醇水平升高，应至少重复检测两次，但仍有8%～15%的库欣综合征患者上述生化指标无明显异常[5]。(2)1 mg过夜地塞米松抑制试验(ODST)：午夜23 00–24 00口服地塞米松1 mg，维持8～9小时。血清皮质醇＜50 nmol/L排除库欣综合征的灵敏度为95%，但特异性较低[6]。(3)小剂量地塞米松抑制试验(LDDST)：小剂量(0.50 mg)地塞米松每6小时口服一次，持续48小时。血清皮质醇＜50 nmol/L排除库欣综合征的灵敏度和特异度均接近100%[7]。(4)夜间唾液皮质醇＞5.50 nmol/L诊断库欣综合征的灵敏度为100%、特异度为96%[8-10]。此外，临床亦可根据皮质醇分泌节律异常诊断库欣综合征，人体皮质醇分泌呈现明显的昼夜节律，清晨最高，随后逐渐下降，午夜最低，随后逐渐升高，而库欣综合征患者午夜血清皮质醇谷值消失，但是该方法不作为临床首选检测手段。Wester和van Rossum[11]收集高皮质醇血症患者的头发标本，采用酶联免疫吸附试验(ELISA)和液相色谱-串联质谱(LC-MS/MS)测定其皮质醇水平，该方法不受皮质醇分泌节律、应激反应、激素脉冲式分泌的影响，但目前罕见通过测定头发皮质醇水平诊断库欣综合征的临床研究。

二、定位诊断

根据影像学检查和内分泌功能测定，明确病因，准确定位病灶来源，是及时准确治疗库欣综合征的关键。

1. 影像学检查　(1)CT和MRI：随着影像学技术的发展，CT和MRI已常规用于垂体腺瘤的临床诊断。术前准确定位垂体促肾上腺皮质激素腺瘤的患者，手术治愈率达80%～90%，而术前未准确定位的患者手术治愈率仅50%～70%，因此，术前准确定位垂体腺瘤至关重要[12]。由于80%的垂体促肾上腺皮质激素腺瘤为微腺瘤(直径＜1 cm)，故CT的诊断意义有限，目前分辨力最高的CT对垂体微腺瘤的检出率仅60%，且常需间接改变提示病变，如垂体柄移位、垂体上缘局部膨隆、垂体不对称、鞍底局部下陷、骨质变薄等[13-14]。CT骨窗对经蝶窦入路手术有一定的指导意义，可明确蝶窦气化程度、蝶窦腔间隔，避免手术无法到达鞍区。MRI对软组织的分辨力更高，通过冠状位和矢状位T_1-自旋回波序列(SE)对鞍区进行3 mm的薄层平扫和增强扫描，可定位直径＞6 mm的垂体微腺瘤。对于常规MRI增强扫描难以发现的垂体微腺瘤，动态对比增强MRI可以根据肿瘤与正常垂体的强化时间顺序定位病变。此外，高场强(3.0T和7.0T)MRI较传统1.5T MRI对垂体微腺瘤的敏感性更高。研究显示，注射促肾上腺皮质激素释放激素(CRH)后，垂体血流量明显增加，高场强(3.0T)MRI可获得更高分辨力的图像，从而提高垂体微腺瘤的检出率[15-16]；亦有学者持相反观点，高场强MRI对垂体微腺瘤的敏感性并不优于传统1.5T MRI[17]。故常规MRI扫描阴性的垂体微腺瘤可经高场强MRI检出并明确定位[18-19]。稳态扰相梯度回波采集(SPGR)序列通过更具优势的软组织显示能力、更薄的层厚、更快速的图像获取，被国外学者推荐用于库欣病的诊断[20-21]。此外，术中MRI的应用为术中准确定位垂体腺瘤提供了依据[22]。(2)PET：PET显像对库欣综合征的病因诊断尤为重要，对异位ACTH依赖性库欣综合征有一定的定位诊断价值。例如，正常垂体组织^{18}F-脱氧葡萄糖(^{18}F-FDG)呈低代谢，垂体微腺瘤则放射性摄取能力均匀增高。国内学者回顾比较MRI和PET对垂体微腺瘤的检出率，^{18}F-FDG PET检出率为85.7%，MRI检出率为71.4%，二者结合定位垂体微腺瘤的准确率为100%[23]。亦有国外学者认为，对于MRI扫描阴性的垂体微腺瘤，^{18}F-FDG PET诊断价值并不显著[24-25]。

2. 内分泌功能测定　由于约40%的库欣病MRI扫描呈阴性，且亦有10%的正常人MRI可见垂体异常表现，因此，明确病灶来源更依赖于内分泌功能测定[26]。(1)CRH兴奋试验：主要用于鉴别诊断库欣病与异位ACTH依赖性库欣综合征，其灵敏度达85%～90%，尤其对女性患者更为敏感，但是针对该试验的阳性结果判断尚无统一标准[27-29]。因CRH价格昂贵，目前国内普遍采用去氨加压素兴奋试验作为代替，该试验对库欣病的诊断灵敏度为86%、特异度为55.6%[30]。该试验仅适合于ACTH依赖性库欣综合征的诊断，而对库欣病与异位ACTH依赖性库欣综合征的定位诊断意义则有限[31]。(2)大剂量地塞米松抑制试验(HDDST)：大剂量(2 mg)地塞

米松每6小时口服一次，持续48小时。约90%的库欣病患者24小时尿游离皮质醇下降>50%，而仅不足50%的异位ACTH依赖性库欣综合征患者有此表现。尿游离皮质醇下降>90%对库欣病的诊断特异度达100%[32]。(3)双侧岩下窦采血(BIPSS)联合CRH兴奋试验：是一种有创性检查方法，被认为是鉴别诊断库欣病与异位ACTH依赖性库欣综合征的"金标准"。对于临床高度怀疑库欣病但MRI扫描呈阴性的患者，可考虑行BIPSS联合CRH兴奋试验。同时，采集患者双侧岩下窦和外周静脉血，测定血浆ACTH，计算岩下窦/外周血ACTH比值(IPS/P)和双侧岩下窦ACTH比值(IPS/IPS)，若IPS/P≥2且经CRH刺激后IPS/P≥3，即可诊断为垂体源性库欣病；IPS/IPS≥1.4是定位垂体微腺瘤侧别的标准，如果IPS/IPS<1.4，则认为肿瘤居中。该方法结合术中实际情况，定位垂体腺瘤侧别的准确率可达到72.5%[33-36]。北京协和医院比较去氨加压素兴奋试验与BIPSS联合CRH兴奋试验诊断库欣病和异位ACTH依赖性库欣综合征的准确性，共纳入226例库欣病患者和24例异位ACTH依赖性库欣综合征患者，通过受试者工作特征(ROC)曲线将去氨加压素兴奋试验诊断两种疾病的诊断标准值(cutoff值)设定为1.4和2.8，BIPSS诊断两种疾病的灵敏度分别为94.7%和97.8%、特异度均为100%，而且，当垂体腺瘤直径>6 mm时，CRH兴奋试验并非必须[37]。

三、其他诊断方法

除上述定性诊断和定位诊断方法外，还包括潜在的分子标志物检测和基因检测等。例如，血浆前阿黑皮素原(POMC)前体作为一种肿瘤标志物在肿瘤细胞中呈高表达，可以用于鉴别诊断库欣病与异位ACTH依赖性库欣综合征，但是目前尚处于基础研究阶段[38]；新近研究发现的热点突变基因*USP8*，与其他类型垂体腺瘤相比，特异性表达于垂体促肾上腺皮质激素腺瘤细胞，有可能成为库欣病诊治的新靶点[39-40]。

四、展望

库欣综合征病因复杂，应结合临床表现、影像学检查和内分泌功能测定综合诊断。尽管目前对于库欣病的定性诊断和定位诊断仍存争议，但是随着血液游离DNA、微小RNA(miRNA)、长链非编码RNA(lncRNA)、外泌体等分子检测技术以及全基因组、转录组、外显子组、代谢组、蛋白质组等多组学技术的发展和成熟，新的研究方法有望为库欣病的诊断带来新的思路。

利益冲突 无

参 考 文 献

[1] Asa SL, Ezzat S. The pathogenesis of pituitary tumors[J]. Ann Rev Pathol, 2009, 4:97-126.

[2] Nieman LK, Ilias I. Evaluation and treatment of Cushing's syndrome[J]. Am J Med, 2005, 118:1340-1346.

[3] Lonser RR, Nieman L, Oldfield EH. Cushing's disease: pathobiology, diagnosis, and management [J]. J Neurosurg, 2017, 126:404-417.

[4] Lopez JA, Kleinschmidt - Demasters Bk Bk, Sze CI, Woodmansee WW, Lillehei KO. Silent corticotroph adenomas: further clinical and pathological observations[J]. Hum Pathol, 2004, 35:1137-1147.

[5] Castro MD, Moreira AC. Screening and diagnosis of Cushing's syndrome [J]. Arq Bras Endocrinol Metabol, 2007, 51:1191 - 1198.

[6] Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A, Boscaro M. Diagnosis and complications of Cushing's syndrome: a consensus statement[J]. J Clin Endocrinol Metab, 2003, 88: 5593-5602.

[7] Newell - Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states[J]. Endocr Rev, 1998, 19:647-672.

[8] Carroll T, Raff H, Findling JW. Late-night salivary cortisol for the diagnosis of Cushing syndrome: a meta-analysis[J]. Endocr Pract, 2009, 15:335-342.

[9] Nunes ML, Vattaut S, Corcuff JB, Rault A, Loiseau H, Gatta B, Valli N, Letenneur L, Tabarin A. Late-night salivary cortisol for diagnosis of overt and subclinical Cushing's syndrome in hospitalized and ambulatory patients [J]. J Clin Endocrinol Metab, 2009, 94:456-462.

[10] Yaneva M, Mosnier-Pudar H, Dugué MA, Grabar S, Fulla Y, Bertagna X. Midnight salivary cortisol for the initial diagnosis of Cushing's syndrome of various causes[J]. J Clin Endocrinol Metab, 2004, 89:3345-3351.

[11] Wester VL, van Rossum EF. Clinical applications of cortisol measurements in hair[J]. Eur J Endocrinol, 2015, 173:M1-10.

[12] Leães CG, Pereira-Lima JF, Lenhardt R, Silveira VM, Ferreira NP, Oliveira MC. Spoiled gradient recalled acquisition in the steady state for magnetic resonance imaging diagnosis of Cushing disease[J]. Arq Neuropsiquiatr, 2009, 67:127-129.

[13] Zada G. Diagnosis and multimodality management of Cushing's disease: a practical review[J]. Int J Endocrinol, 2013:ID893781.

[14] Invitti C, Pecori Giraldi F, de Martin M, Cavagnini F; Study Group of the Italian Society of Endocrinology on the Pathophysiology of the Hypothalamic-Pituitary-Adrenal Axis. Diagnosis and management of Cushing's syndrome: results of an Italian multicentre study[J]. J Clin Endocrinol Metab, 1999, 84:440-448.

[15] Ludecke DK, Flitsch J, Knappe UJ, Saeger W. Cushing's disease: a surgical view[J]. J Neurooncol, 2001, 54:151-166.

[16] Portocarrero - Ortiz L, Bonifacio - Delgadillo D, Sotomayor - González A, Garcia - Marquez A, Lopez - Serna R. A modified protocol using half - dose gadolinium in dynamic 3 - Tesla magnetic resonance imaging for detection of ACTH - secreting pituitary tumors[J]. Pituitary, 2010, 13:230-235.

[17] Erickson D, Erickson B, Watson R, Patton A, Atkinson J, Meyer F, Nippoldt T, Carpenter P, Natt N, Vella A, Thapa P. 3

Tesla magnetic resonance imaging with and without corticotropin releasing hormone stimulation for the detection of microadenomas in Cushing's syndrome[J]. Clin Endocrinol (Oxf), 2010, 72:793-799.

[18] Kim LJ, Lekovic GP, White WL, Karis J. Preliminary experience with 3-Tesla MRI and Cushing's disease[J]. Skull Base, 2007, 17:273-277.

[19] de Rotte AA, van der Kolk AG, Rutgers D, Zelissen PM, Visser F, Luijten PR, Hendrikse J. Feasibility of high-resolution pituitary MRI at 7.0 Tesla[J]. Eur Radiol, 2014, 24:2005-2011.

[20] Oldfield EH. Surgical management of Cushing's disease: a personal perspective[J]. Clin Neurosurg, 2011, 58:13-26.

[21] Patronas N, Bulakbasi N, Stratakis CA, Lafferty A, Oldfield EH, Doppman J, Nieman LK. Spoiled gradient recalled acquisition in the steady state technique is superior to conventional postcontrast spin echo technique for magnetic resonance imaging detection of adrenocorticotropin-secreting pituitary tumors[J]. J Clin Endocrinol Metab, 2003, 88:1565-1569.

[22] Tanei T, Nagatani T, Nakahara N, Watanabe T, Nishihata T, Nielsen ML, Takebayashi S, Hirano M, Wakabayashi T. Use of high-field intraoperative magnetic resonance imaging during endoscopic transsphenoidal surgery for functioning pituitary microadenomas and small adenomas located in the intrasellar region[J]. Neurol Med Chir (Tokyo), 2013, 53:501-510.

[23] Li YN, Tao W, Ren ZY, Su CB, Wang RZ, Cheng X, Yang Y, Ma WB. Diagnosis of pituitary microadenoma with ^{18}F-FDG positron emission tomography[J]. Zhongguo Er Bi Yan Hou Tou Jing Wai Ke, 2007, 14:131-133.[李永宁, 陶蔚, 任祖渊, 苏长保, 王任直, 程欣, 杨义, 马文斌. ^{18}F-脱氧葡萄糖正电子发射断层扫描诊断垂体微腺瘤[J]. 中国耳鼻咽喉头颈外科, 2007, 14:131-133.]

[24] Patt HP, Lele V, Lila A, Bandgar T, Shah N. Utility of hCRH-stimulated (18) FFDG PET-CT scan in localisation of pituitary microadenoma in Cushing's disease[J]. J Med Imaging Radiat Oncol, 2014, 58:213.

[25] Hyun SH, Choi JY, Lee KH, Choe YS, Kim BT. Incidental focal ^{18}F-FDG uptake in the pituitary gland: clinical significance and differential diagnostic criteria[J]. J Nucl Med, 2011, 52:547-550.

[26] Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population[J]. Ann Inter Med, 1994, 120:817-820.

[27] Erickson D, Erickson B, Watson R, Patton A, Atkinson J, Meyer F, Nippoldt T, Carpenter P, Natt N, Vella A, Thapa P. 3 Tesla magnetic resonance imaging with and without corticotropin releasing hormone stimulation for the detection of microadenomas in Cushing's syndrome[J]. Clin Endocrinol (Oxf), 2010, 72:793-799.

[28] Nieman LK, Oldfield EH, Wesley R, Chrousos GP, Loriaux DL, Cutler GB Jr. A simplified morning ovine corticotropin-releasing hormone stimulation test for the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome[J]. J Clin Endocrinol Metab, 1993, 77:1308-1312.

[29] Newell-Price J, Morris DG, Drake WM, Korbonits M, Monson JP, Besser GM, Grossman AB. Optimal response criteria for the human CRH test in the differential diagnosis of ACTH-dependent Cushing's syndrome[J]. J Clin Endocrinol Metab, 2002, 87:1640-1645.

[30] Suda T, Kageyama K, Nigawara T, Sakihara S. Evaluation of diagnostic tests for ACTH-dependent Cushing's syndrome[J]. Endoc J, 2009, 56:469-476.

[31] Salgado LR, Fragoso MC, Knoepfelmacher M, Machado MC, Domenice S, Pereira MA, de Mendonca BB. Ectopic ACTH syndrome: our experience with 25 cases[J]. Eur J Endocrinol, 2006, 155:725-733.

[32] Paul M, Nils P. Classification and pathophysiology of Cushing's Syndrome[M]//Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. Williams textbook of endocrinology. 12th ed. Philadelphia: Elsevier Saunders, 2011: 479-545.

[33] Wind JJ, Lonser RR, Nieman LK, DeVroom HL, Chang R, Oldfield EH. The lateralization accuracy of inferior petrosal sinus sampling in 501 patients with Cushing's disease[J]. J Clin Endocrinol Metab, 2013, 98:2285-2293.

[34] Potts MB, Shah JK, Molinaro AM, Blevins LS, Tyrrell JB, Kunwar S, Dowd CF, Hetts SW, Aghi MK. Cavernous and inferior petrosal sinus sampling and dynamic magnetic resonance imaging in the preoperative evaluation of Cushing's disease[J]. J Neurooncol, 2014, 116:593-600.

[35] Oldfield EH. Surgical management of Cushing's disease: a personal perspective[J]. Clin Neurosurg, 2011, 58:13-26.

[36] Feng M, Liu Z, Liu X, Zhang X, Bao X, Yao Y, Deng K, Xing B, Lian W, Zhu H, Lu L, Wang R. Tumour lateralization in Cushing's disease by inferior petrosal sinus sampling with desmopressin[J]. Clin Endocrinol (Oxf), 2018, 88:251-257.

[37] Chen S, Chen K, Wang S, Zhu H, Lu L, Zhang X, Tong A, Pan H, Wang R, Lu Z. The optimal cutoff of BIPSS in differential diagnosis of ACTH-dependent Cushing's syndrome: Is stimulation necessary[J]? J Clin Endocrinol Metab, 2019. [Epub ahead of print]

[38] Page-Wilson G, Freda PU, Jacobs TP, Khandji AG, Bruce JN, Foo ST, Meece K, White A, Wardlaw SL. Clinical utility of plasma POMC and AgRP measurements in the differential diagnosis of ACTH-dependent Cushing's syndrome[J]. J Clin Endocrinol Metab, 2014, 99:E1838-1845.

[39] Ma ZY, Song ZJ, Chen JH, Wang YF, Li SQ, Zhou LF, Mao Y, Li YM, Hu RG, Zhang ZY, Ye HY, Shen M, Shou XF, Li ZQ, Peng H, Wang QZ, Zhou DZ, Qin XL, Ji J, Zheng J, Chen H, Wang Y, Geng DY, Tang WJ, Fu CW, Shi ZF, Zhang YC, Ye Z, He WQ, Zhang QL, Tang QS, Xie R, Shen JW, Wen ZJ, Zhou J, Wang T, Huang S, Qiu HJ, Qiao ND, Zhang Y, Pan L, Bao WM, Liu YC, Huang CX, Shi YY, Zhao Y. Recurrent gain-of-function USP8 mutations in Cushing's disease[J]. Cell Res, 2015, 25:306-317.

[40] Reincke M, Sbiera S, Hayakawa A, Theodoropoulou M, Osswald A, Beuschlein F, Meitinger T, Mizuno-Yamasaki E, Kawaguchi K, Saeki Y, Tanaka K, Wieland T, Graf E, Saeger W, Ronchi CL, Allolio B, Buchfelder M, Strom TM, Fassnacht M, Komada M. Mutations in the deubiquitinase gene USP8 cause Cushing's disease[J]. Nat Genet, 2015, 47:31-38.

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