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亚临床库欣研究进展

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摘　要

亚临床库欣综合征是指皮质醇自主分泌轻度增高而无典型库欣综合征临床表现、可以导致多种代谢异常的一种疾病，在临床上较库欣综合征常见；亚临床库欣综合征多见于肾上腺意外瘤的患者。随着当前医学研究、影像学技术的不断进展，亚临床库欣综合征的检出率在不断增加。亚临床库欣综合征可以造成葡萄糖代谢障碍、血脂异常、高血压、骨脆性增高、亚临床动脉粥样硬化、内脏脂肪堆积、感染风险高、肌肉损伤、情绪障碍和高凝状态等，但因无典型临床症状且起病隐匿、病程进展缓慢，在临床工作中容易被忽视。本文就近年来亚临床库欣综合征的研究进展做一综述。

关键词

亚临床库欣综合征，肾上腺意外瘤，临床表现，诊断，预后

Progress in Subclinical Cushing's Syndrome

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Abstract

Subclinical Cushing's Syndrome refers to a mild increase in autonomous secretion of cortisol without the clinical manifestations of typical Cushing's syndrome, and can lead to a variety of metabolic abnormalities, which is more common than Cushing's syndrome; subclinical Cushing's syndrome is most commonly seen in patients with adrenal adenomas. The detection rate of Subclinical Cushing's Syndrome is increasing with the current advances in medical research and imaging technology. Subclinical Cushing's Syndrome can cause impaired glucose metabolism, dyslipidemia, hypertension, increased bone fragility, subclinical atherosclerosis, accumulation of visceral fat, high risk of infection, muscle damage, mood disorders and hypercoagulability, etc. However, it is easy to be neglected in clinical work because of the absence of typical clinical symptoms, insidious onset, and

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slow progression of the disease. In this article, we review the research progress of Subclinical Cushing's Syndrome in recent years.

Keywords

Subclinical Cushing's Syndrome, Adrenal Incidentaloma, Clinical Manifestations, Diagnosis, Prognosis

1. 引言

亚临床库欣综合征(Subclinical Cushing's Syndrome, SCS)是丘脑－垂体－肾上腺轴的改变，其特征是非依赖 ACTH、皮质醇自主分泌轻度增高，不能被 1 毫克地塞米松抑制试验(1 mg-DST)所抑制。Beierwaltes 等[1]早在 1972 年就对 SCS 进行了报道。SCS 又称为“轻度高皮质醇血症”、“亚临床高皮质醇血症”、“库欣综合征前期”和“皮质醇自主分泌”等，可见目前对该疾病的认识并不是十分清楚。这些患者在临床上并无典型库欣综合征(Cushing's syndrome, CS)的症状和体征[2] (例如宽大紫纹、多血质、满月脸、近端肌肉萎缩、皮肤菲薄、瘀斑、近端肌无力、女性月经紊乱等)。由于国际上没有统一的命名、临床表现多样并缺乏相关高质量的循证医学证据，造成诊断、治疗和随访的随意性。2022 年白求恩精神医学会内分泌分会组织国内 35 位专家，结合国内外最新研究与我国临床工作实际，建议目前使用“亚临床库欣综合征”这一称谓[3]。

2. 流行病学

通过对既往国内外的研究进行总结，SCS 较库欣综合征更为常见。SCS 在普通人群检出率为(0.8~2)/1000，60 岁以上的人群中为 0.2%~2.0%，在肾上腺意外中检出率 5%~20% [4]，在垂体肿瘤的检出率为 5% [5]。2014~2022 年我国学者通过对 1173 名社区人群的调查研究显示肾上腺意外瘤患者中 SCS 检出率为 5.54%~8.29% [2] [6]；最近我国一项基于社区人群的调查显示肾上腺意外瘤中 SCS 的占比达 15.6% [7]，是最常见的功能性病变[7]。在影像技术的进步、预防保健意识的提高等多种因素的驱动下，亚临床库欣综合征的检出率在不断增加。

3. 病因

亚临床库欣综合征常见于肾上腺意外瘤(Adrenal Incidentaloma, AI)患者或增生和偶发的垂体肿瘤。肾上腺意外瘤即因非肾上腺疾病的其他原因行影像学检查时意外发现的直径 ≥1 cm 的肾上腺占位性病变，最早在 1982 年由外科医生 Geelhoed 和 Druy [8]提出。AI 在成人中检出率约 10%，SCS 占 AI 病因的 5%~20%，这些患者存在亚临床皮质醇自主分泌轻度增高的现象[9] [10] [11]。

肾上腺疾病所致的 CS 称为肾上腺源性 CS，其病因包括肾上腺皮质腺瘤、腺癌、原发性双侧肾上腺大结节性增生(PBMAH)及原发性色素沉着结节性肾上腺皮质病(PPNAD)等，其中肾上腺腺瘤型 CS 占 10%~22%。皮质腺瘤是最常见的 AI 类型，约占外科病例的 50% [4]，此类 CS 患者首选外科手术治疗。

此外，发生 CS 的原因还包括外源性和内源性因素[12]。外源性 CS 多由于患者使用过量的糖皮质激素所致。内源性 CS 又分为促肾上腺皮质激素(ACTH)依赖性和非依赖性两种。其中垂体疾病导致 ACTH

过量分泌所致的 CS 称为库欣病，年约占 CS 的 70% [13]。异位内分泌肿瘤分泌过量 ACTH 导致的 CS，称为异位 ACTH 综合征，是依赖性 CS 的一种少见类型[12]；异位 ACTH 综合征往往因肿瘤自主功能强，引起较严重的临床症状，易威胁患者生命[12]。

目前有关于亚临床库欣综合征的研究较少，作为库欣综合征的前期疾病状态，亚临床库欣综合征可能由以上病因引起，需要更多的临床研究来证实。

4. 诊断标准

SCS 为自主分泌的皮质醇激素轻度增高，目前对于皮质醇激素分泌量的界定，仍是一个具有争议的问题[2]。

1996 年日本学者 Nawata H [14]等在 SCS 诊断标准中采用了 8 mg DST 的确认试验，并指出血清皮质醇 ≥ 1 μg/dL 被认为是 SCS。为了进一步明确 SCS 皮质醇激素分泌量的界定，2003 年至 2018 年期间，美国国立卫生研究院、日本内分泌学会等多个组织对 SCS 的激素诊断切点进行了不同的临床试验。在所有指南中，推荐 1 mg DST 作为诊断 SCS 的第一个筛查试验。

2011 年意大利临床内分泌医师协会[15]通过回顾性研究指出，在 1 mg DST 后，皮质醇水平 ≤ 1.8 μg/dL (≤50 nmol/L)是正常生理状态。皮质醇水平在 1.9 至 5.0 μg/dL (50~140 nmol/L)之间表明“可能存在自主性皮质醇分泌”，皮质醇水平 > 5.0 μg/dL (140 nmol/L)可以确诊 SCS。

2018 年日本内分泌协会[16]评估了 530 例(SCS，疑似 SCS 和无功能 AI)患者，研究表明 1 mg DST 后血清皮质醇 ≥ 1.8 μg/dL 的患者会存在健康隐患；血清皮质醇为 2~3 μg/dL 时并发症增加。

目前日本对唾液皮质醇在 SCS 诊断中的作用进行了研究，将其用于区分 SCS 与无功能肾上腺肿瘤，其诊断 SCS 的特异性较低[17]。因唾液皮质醇留样标准尚无统一定论，目前除美国 Endo-crime Society 的指南外，所有非日本指南均未采用唾液皮质醇作为筛查试验[16] [18] [19]。

5. 临床特点

基于库欣综合征的既定临床特征，目前有大量文献报道关于 SCS 中皮质醇自主分泌轻度增高的潜在临床影响。SCS 并不罕见，目前已成为 AI 患者中最常见的功能异常，患病率高达 20% [20] [21]。肾上腺肿瘤不受反馈调节，自主分泌皮质醇，抑制血管舒张系统、激活肾素一血管紧张素系统[22]，同时亦可影响脂肪细胞、胰岛 p 细胞的代谢[20]，导致脂肪生成作用、胰岛素抵抗和糖异生作用增强，胰岛素敏感性降低，因此 AI 患者中的 SCS 人群与高血压，胰岛素抵抗，2 型糖尿病，肥胖，代谢综合征和死亡率增加有关[23]-[28]。SCS 为一种内分泌功能紊乱综合征，除存在上述并发症外，对全身多个系统均有影响，如对生长激素(GH)及凝血功能的影响。

5.1. 代谢异常

对以往的文章进行广泛回顾，SCS 患者代谢紊乱(糖代谢、脂代谢)的风险增加。意大利转诊中心对 210 名 AI 患者进行回顾性研究，Terzolo M [26]等发现 53.8%的患者出现高血压，21.4%的患者出现肥胖，22.4%的患者出现高血糖。在 Giordano R [28]等人的研究中：共有 118 名 AI 患者参与评估，在 3 年的随访结束后，相较于无功能 AI 患者，SCS 患者血脂异常的百分比显著升高。Libuse Tauchmanovà [29]等通过临床队列研究，表明在 SCS 患者中，60.7%有动脉高血压，28.6%有糖耐量异常，35.7%有 2 型糖尿病，71.4%有血脂异常。一项对 SCS 患者进行了长达 15 年的随访研究显示，与 AI 相比，SCS 患者的心血管发病率和死亡率增加，肺部感染和心血管并发症是死亡的主要原因[30]。典型库欣综合征患者常伴有葡萄糖耐受不良和糖尿病[31] [32]，据报道 10%~69%的 SCS 患者会出现糖耐量受损或糖尿病[33]。

同样，SCS 患者会出现骨代谢异常，特别是脊柱骨折的发生风险增加[34]。Morelli V [35]等人在 AI 患者的横断面研究中表明，SCS 患者椎体骨折的发生率明显高于普通人群。一项荟萃分析报告，SCS 患者的椎体骨折患病率为 63.6% [36]。该风险与年龄、性别、性腺状态或骨矿物质密度无关[37]。

5.2. 凝血异常

SCS 可导致凝血功能的紊乱，使血液呈现高凝状态，增加血栓形成的风险。Libuse Tauchmanovà [29]等通过临床队列研究指出有 53.6%的患者出现止血参数异常。2011 年，Swiatkowska-Stodulska R 及其同事指出[38]，与正常人群相比，SCS 患者的蛋白 C 活性及游离蛋白 S 活性均明显升高，而血栓调节蛋白浓度则明显降低；其另一项对比研究表明[39]，SCS 患者的凝血因子 VIII、IX、X、XI 及血管性血友病因子均较正常人群升高，其中以 vWF 升高最为显著；此外，同型半胱氨酸也可反应血栓形成风险，同时炎症因子(如 α1 抗胰蛋白酶)亦会导致凝血失衡，SCS 患者血浆中的 HCY 及 α-1ATp 的浓度亦较正常人群升高[40]。

5.3. 内分泌功能异常

慢性皮质醇激素过多会直接或间接造成垂体及其他内分泌轴的改变，干扰多种其他激素的分泌[41]，如抑制垂体－性腺轴和垂体－生长激素轴，表现为女性月经异常[42]、男性性欲减退和儿童发育生长迟缓[43] [44] [45]。

SCS 可导致 GH 分泌异常。Palmieri S 及其同事[46]采用病例对照研究，分别将 24 名亚临床库欣综合征患者分为，皮质醇分泌不明显和皮质醇分泌显著增高两组。通过对比这 24 名患者治疗前后 GH 的分泌情况，证明了 SCS 可抑制 GH 的分泌，且经肾上腺切除术后 GH 分泌水平将有所回升。

已有研究显示高皮质醇水平对下丘脑－垂体－甲状腺轴亦存在抑制作用[47]。然而目前国内外关于 SCS 对甲状腺激素影响的研究数据有限，且研究结果也不一致，需要更多的临床研究来支持。

6. 转归及预后

SCS 患者的病程时间长，病情变化缓慢，不易被察觉。对 SCS 患者进行 1 至 7.5 年不等的随访；在随访期间患者没有出现肿块增大及肾上腺外恶性肿瘤的迹象、激素分泌没有增加、病情没有明显加重[48] [49] [50]。连续对 284 例肾上腺偶发瘤的患者进行纵向随访，Barzon [51]等报道，病情进展 5 年和 3 年后 SCS 的累积发病率分别为 8.6%和 6.68%。

近年来通过 AI 被诊断为 SCS 患者的概率在逐渐增加，这类患者仅有皮质醇激素自主分泌轻度增高的现象，而血清皮质醇水平与并发症的发生率呈正相关，可以造成葡萄糖代谢障碍、血脂异常、高血压、骨脆性增高、内脏脂肪堆积、感染风险高、肌肉损伤、情绪障碍和高凝状态等健康问题，当疾病持续进展，出现明显的临床特征再做干预，此时已丧失临床干预的最佳时机，这些不良特征会对患者远期产生不良影响，甚至是诱发患者死亡。

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