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不安腿综合征与代谢紊乱、心血管疾病关系的研究进展

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摘　要：不安腿综合征(RLS)的发病机制和病理生理未完全明确，近来有研究发现不安腿综合征和心血管疾病、糖尿病及相关代谢紊乱有一定的相关性，两者均影响交感神经系统和下丘脑－垂体－肾上腺轴(HPA)，易相伴发生。交感－副交感神经功能的紊乱和 HPA 轴调节的失衡、睡眠障碍、不良的生活方式等也许在它们间的联系中起着重要的作用，但是，它们间的潜在机制未完全阐明。对于两者的潜在机制有待我们进一步研究。

关键词：不安腿综合征；心血管疾病；2 型糖尿病；代谢紊乱；交感肾上腺功能紊乱；下丘脑－垂体－肾上腺轴；睡眠障碍

不安腿综合征(restless legs syndrome, RLS)是一种常见的神经系统疾病。1685 年英国医生 Thomas Willis 首次将其描述为：因为上肢和下肢的不适而使病人无法入睡。直到 1945 年瑞典神经科医生 Karl Axel Ekbom 将其正式命名为不安腿综合征[1]。RLS 主要表现为休息或安静时下肢(偶可累及上肢)感觉不适，尤其在夜间，需要或强迫性活动下肢以缓解症状。RLS 发病机制尚不完全明确，该病患病率在北美和欧洲报道较多，普通人群中患病率为 0.6% ~24%，在 65 岁以上人群中患病率

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在0.96% ~ 35%[2]。女性患病率是男性的2倍[3],且发病高峰有两个年龄段:20 ~ 29岁和50 ~ 59岁[4]。亚洲国家对于该病的报道较少,日本一项研究发现老年人中RLS的患病率为1.06%[5]。RLS分为两类:一类是原发性RLS,与遗传因素有关,有家族史[6,7],呈常染色体显性遗传,基因定位可能为2p14和16q12.1[8];另一类为继发性RLS,伴发于尿毒症、糖尿病、妊娠等,可能为脑内某区域铁缺乏、多巴胺衰竭或周围神经中小纤维病变引起的[9,10]。目前RLS治疗为对症治疗,有多巴胺受体激动剂或多巴胺替代剂、鸦片类药物、镇静催眠药、抗惊厥药、苯二氮䓬类等。

近年国外多项研究发现RLS与心血管疾病和代谢紊乱(如糖尿病、高血压、血脂异常、肥胖等)有着密切相关,现介绍如下。

1 RLS患者常伴发糖尿病、心血管疾病及其他代谢紊乱

成年RLS患者有明显的夜间血压升高和心率加快[11-13],并且与睡眠期周期性肢体运动(periodic limb movements in sleep, PLMS)无明显相关,若与PLMS伴发,则血压升高更明显,可达22/11 mmHg($P<0.05$)[13]。还有研究发现RLS患者的心率变异率小[14]。实验发现一些可降低交感神经兴奋性的药物,如β-受体阻滞剂(普萘洛尔)和α-受体阻滞剂(压宁定),均可减轻RLS症状[15,16]。这均提示过度兴奋的交感神经系统与RLS发病机制有关。RLS还可能与下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal, HPA)的活动有关。2010年德国Schilling等[17]发现RLS患者夜间氢化可的松明显高于健康者对照组。现已知氢化可的松水平与PLMS的频率无关,所以RLS与HPA过度兴奋有关。不过也有一小样本研究发现RLS患者夜间氢化可的松无明显升高,由于该研究中RLS患者症状轻,对照组中PLMS指数相对较高,所以结果可靠性有待商榷。不过,RLS患者夜间强迫性的肢体活动是否可引起交感神经系统和HPA轴的兴奋性增高未见报道。

RLS引发的交感神经系统过度兴奋、副交感神经系统被抑制和持续HPA轴的激活,均能促进和加速糖耐量异常和胰岛素抵抗、高血压、血脂异常、向心性肥胖和其他代谢的紊乱,加速动脉粥样硬化的发生,对于2型糖尿病和心血管疾病的发生、发展有着重要的影响[18-20]。Innes等[21]荟萃分析了11项不安腿综合征研究,证实RLS和心血管疾病有明显的相关性。美国研究者Winkelman[22]发现,在伴有中重度RLS症状的患者中,心血管疾病(包括缺血性心脏病和脑血管事件)患病率为7.7%。而芬兰学者Juuti等[23]在其研究中发现每周至少发生1次RLS的患者,其心血管事件的患病率高达36%。Berger等[24]在对德国人群的大样本研究中发现RLS和2型糖尿病也有明显相关性。

RLS的睡眠障碍表现为入睡困难、夜间易醒、睡眠时间短、睡眠质量差、白天困倦等[25],并且通过激活HPA轴和交感肾上腺系统,抑制副交感神经系统等导致情绪异常[26-28],诱发自主神经系统功能紊乱。所以,RLS病人的不良睡眠和情绪也有可能促发了糖尿病、心血管等相关疾病。

2 心血管疾病、糖尿病和其他代谢紊乱易伴发不安腿综合征

心血管疾病、糖尿病和代谢紊乱均可伴随炎症反应、神经内分泌和代谢改变,也可导致交感神经系统和HPA轴的激活[29],诱发或加重RLS和RLS相关的睡眠期周期性肢体运动(PLMS)。而且,心血管疾病、糖尿病和肥胖也可引起睡眠和情绪的异常[30-32],后者同样通过影响自主神经系统、HPA轴的功能、神经内分泌改变等促使RLS的发生和进展,并导致疼痛的出现[33]。Rothdach等[34]在对德国老年人研究发现2型糖尿病病人的RLS患病率为2.6%。Cuellar等[35]则发现2型糖尿病患者的RLS的患病率高达44.8%。在意大利的一项研究中发现,RLS病例组(132例)和没有患不安腿综合征的对照组(128例)相比较,两组间糖耐量异常的发生率RLS组中为40.9%,对照组为18%($P<0.001$),有显著性差异[36]。

3 RLS和心血管疾病、糖尿病及其他代谢紊乱的共同危险因素

RLS和心血管疾病、糖尿病及其他代谢紊乱的密切关系反应了它们有共同的危险因素。这些危险因素包括睡眠障碍、情绪异常、持续的应激、交感肾上腺的激活、HPA轴的过度兴奋,还有糖耐量异常、肥胖和其他导致心血管疾病的危险因素。

RLS和成年人肥胖、糖耐量异常相关,而后者又都是2型糖尿病、心血管疾病的危险因素。RLS还和一些不良的生活方式有关。近来有大型的流行病学调查证明吸烟的人群中RSL发生率升高,且RLS的发生率和吸烟的数量呈线性相关[37,38]。

还有研究发现过少的体力活动与 RLS 发生相关[39,40]。Sakkas 等[41]对血透病人及 Aukerman 等[42]对社区的老年人群的研究发现,适当的体力锻炼能显著缓解 RLS 患者症状。吸烟和缺乏运动的生活方式与交感肾上腺系统及代谢紊乱均有一定联系,同时也是心血管疾病、糖尿病、高血压和代谢紊乱的危险因素[43-45],生活方式的改善和良好的个人行为能减少心血管疾病和糖尿病的发生,促进自主神经系统的平衡,改善睡眠,同样也能改善 RLS 患者的症状。

4　结语

不安腿综合征和心血管疾病、糖尿病及相关的代谢紊乱间的相互关系是复杂的,双向的,潜在的机制是多样的;而且互相促进使疾病恶化。自主神经功能的紊乱和 HPA 轴调节的失衡、睡眠障碍、不良的生活方式等也许在它们间的联系中起着重要的作用,但是,它们间的潜在机制未完全阐明;大多数研究对于它们之间的病因学联系也没有肯定的结论。目前对于不安腿综合征的前瞻性研究报道很少,这使得我们无法明确不安腿综合征的病因和预后。我们可以做些前瞻性研究,如随访观察糖尿病病人与匹配对照后普通人群中 RLS 的发病率;比较不安腿综合征患者中糖尿病、心血管疾病的患病率和普通人群中的差异。

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