·专题综述·

发作性睡病与焦虑研究进展

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【摘要】 发作性睡病是以日间过度思睡、猝倒发作、入睡前幻觉、睡眠瘫痪为主要临床表现的罕见睡眠障碍，绝大多数患者伴焦虑。发作性睡病与焦虑的神经回路之间存在神经元的相互连接与投射，二者可能存在共同的病理生理学机制，且部分用于治疗发作性睡病猝倒发作的药物可改善焦虑。本研究对发作性睡病伴焦虑的流行病学、发病机制和治疗进行综述，以提高临床对发作性睡病伴焦虑的诊断与治疗水平，改善患者预后。

【关键词】 发作性睡病；　焦虑；　综述

Progress on narcolepsy and anxiety

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【Abstract】 Narcolepsy is a rare sleep disorder characterized by excessive daytime sleepiness (EDS), cataplexy, sleep hallucination and sleep paralysis, and the vast majority of patients are accompanied by anxiety. There are neuronal interconnections and projections between the neural circuits of narcolepsy and anxiety, which may share common pathophysiology mechanisms, and some medications used clinically to treat cataplexy in narcolepsy may also improve anxiety. In this study, we propose to review the epidemiologic research, pathogenesis and therapeutic advances in narcolepsy with anxiety, with the aim of increasing the diagnosis and treatment of narcolepsy with anxiety and improving the prognosis of narcolepsy with anxiety patients.

【Key words】 Narcolepsy;　Anxiety;　Review

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发作性睡病（narcolepsy）是一种以日间过度思睡（EDS）、猝倒发作、入睡前幻觉、睡眠瘫痪为主要临床表现的罕见睡眠障碍，通常伴肥胖、性早熟、自主神经功能障碍、精神障碍和偏头痛[1-4]。发作性睡病全球患病率为0.025%～0.05%，不同种族、国家或地区存在一定差异[4-5]，男性多于女性，任何年龄阶段均可发病，高峰发病年龄为15～35岁[6]。睡眠障碍国际分类第3版（ICSD-3）根据是否伴猝倒发作和下丘脑分泌素（Hcrt，亦称促食欲素）水平降低，将发作性睡病分为1型（NT1）和2型（NT2），前者伴猝倒发作且Hcrt水平显著降低，后者则不伴猝倒且Hcrt水平无显著下降。研究显示，高达76%的发作性睡病患者伴焦虑或恐惧[7]。本研究拟对发作性睡病伴焦虑的流行病学、发病机制和治疗进行综述，以期提高临床对发作性睡病伴焦虑的诊断与治疗水平。

一、流行病学

焦虑是一种情绪状态；焦虑障碍则具有病理性、持续性和致残性且伴有一定躯体化症状，亦称焦虑症。临床常见的焦虑障碍包括惊恐障碍、广场恐惧障碍、社交焦虑障碍、特定恐惧障碍、分离性焦虑障碍、广泛性焦虑障碍、强迫障碍和创伤后应激障碍（PTSD）[8-11]。一项研究对60例NT1患者进行神经心理学测验发现，约53.33%（32/60）患者存在焦虑或惊恐发作，约35%（21/60）存在焦虑障碍，且

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发作性睡病患者精神障碍表型主要为焦虑障碍而非抑郁障碍[8]。惊恐发作是惊恐障碍的典型表现，通常与入睡前幻觉期间恐怖的幻视和幻听有关。社交焦虑障碍与被他人目睹到不可抗拒地突然进入快速眼动睡眠期(REM)而发生猝倒发作的羞耻感有关[8]。我们课题组前期对发作性睡病患者的神经功能进行分析，发现发作性睡病患者焦虑倾向指数增加，且并发阻塞性睡眠呼吸暂停低通气综合征(OSAHS)的患者更易发生焦虑[6]。一项病例对照研究显示，约25%发作性睡病患者伴焦虑障碍，进一步根据年龄分层，年龄较小(18～24岁)的发作性睡病患者焦虑障碍患病率显著高于非发作性睡病者(32%对13%)[12]。而NT1与NT2患者焦虑障碍患病率并无显著差异[13-14]。广泛性焦虑障碍是临床最常见的焦虑障碍[15]，发作性睡病患者广泛性焦虑障碍发生率显著高于健康人群(7%对1%，P=0.006)[13]。有文献报道，约10%甲型H1N1流感病毒致发作性睡病的患儿存在广泛性焦虑障碍[16]。约20%的发作性睡病患者伴社交焦虑障碍[17]。有学者提出，发作性睡病患者精神障碍的诊断往往早于发作性睡病，因此推测两种疾病之间可能存在生物学联系[14]。一项为期14年的队列研究显示，发作性睡病伴焦虑障碍患者在确诊为发作性睡病前即已诊断出焦虑障碍[18]；而且，不同类型焦虑障碍的发生时间存在差异，强迫障碍和社交焦虑障碍通常发生于发作性睡病确诊前，惊恐障碍发生于发作性睡病确诊后[13]。女性和青少年(12～17岁)焦虑障碍诊断早于发作性睡病的比例较高[19]，且女性焦虑障碍患者发生发作性睡病的风险较高[15]；此外，焦虑障碍与猝倒发作密切相关，约33.3%的焦虑障碍患者伴典型猝倒发作[20]。睡眠瘫痪是发作性睡病的主要临床表现之一，亦与焦虑和焦虑障碍密切相关[21-23]，睡眠瘫痪易与焦虑障碍共病，约35%经历过睡眠瘫痪的受试者合并焦虑障碍(P=0.043)[23-24]。

二、发病机制

1.终纹床核和中央杏仁核分泌素受体表达变化　Hcrt主要参与情绪和应激反应的调节，发作性睡病和焦虑均与Hcrt表达变化密切相关，二者可能存在共同的病理生理学机制[8,25]。Hcrt由Hcrt-1和Hcrt-2两种肽组成，Hcrt-2受体对Hcrt-1和Hcrt-2的亲和力相似，而Hcrt-1受体则对Hcrt-1的亲和力更高[26]。发作性睡病与Hcrt水平降低有关，分布于下丘脑后部和下丘脑外侧区的Hcrt能神经元特异性丢失是NT1的特征性病理改变；NT2可能由Hcrt能神经元部分缺失所致，但是对其潜在的病理生理学机制知之甚少。Hcrt-1和Hcrt-2受体共同表达于多个脑区，例如大脑皮质、海马、丘脑、下丘脑和中缝核等[27]，其中焦虑相关边缘系统终纹床核(BNST)和杏仁核中Hcrt-1受体水平高于Hcrt-2受体[27-28]。杏仁核通过基底外侧杏仁核(BLA)或者杏仁核插入区(ITCs)中共表达钙结合蛋白的γ-氨基丁酸(GABA)能神经元抑制焦虑样行为[29]。动物实验显示，Hcrt-1可抑制大鼠焦虑样行为，Hcrt-1缺乏小鼠焦虑样行为增加[30]。亦有研究显示，Hcrt-1具有促焦虑作用，而Hcrt-2有抗焦虑作用[28-31]。长期Hcrt-1或其受体缺乏具有与脑室内注射Hcrt-1相似的促焦虑样作用，可能与长期Hcrt-1或其受体缺乏的过度代偿有关[32]。基底外侧杏仁核中Hcrt-2受体参与焦虑的调节，敲除或敲低基底外侧杏仁核中Hcrt-2受体可增加小鼠焦虑样行为[29,31]；Hcrt-2受体激动剂结合并激活位于基底外侧杏仁核或杏仁核插入区的GABA能神经元，可减少小鼠焦虑样行为[29]。基底外侧杏仁核刺激中央杏仁核(CeA)外侧和内侧分支，对焦虑相关区域进行调节[31]，Hcrt能神经元通过直接或间接作用(通过丘脑室旁核)于终纹床核和中央杏仁核神经元，促进小鼠焦虑样行为[33]。

2.5-羟色胺和去甲肾上腺素表达变化　位于下丘脑后部和外侧区的Hcrt能神经元在全脑范围内广泛投射，包括中缝背核5-羟色胺(5-HT)能神经元和蓝斑核去甲肾上腺素能神经元[34]。Hcrt能神经元与参与情绪调控的5-HT能和去甲肾上腺素能神经元之间存在功能连接，Hcrt可以激活5-HT能和去甲肾上腺素能神经元，二者又负反馈调节Hcrt，其中，5-HT通过5-HT1A受体介导直接抑制Hcrt神经元的兴奋[33]；去甲肾上腺素可通过作用于与Hcrt能神经元连接的突触前膜α2肾上腺素能受体，抑制谷氨酸释放，间接抑制Hcrt能神经元的兴奋，此外，去甲肾上腺素还通过α1肾上腺素能神经元介导，直接抑制Hcrt能神经元兴奋，但较间接抑制作用弱[33]。5-HT、去甲肾上腺素和多巴胺与调节情绪的杏仁核存在结构连接[35]。NT1患者Hcrt水平降低可以导致5-HT、去甲肾上腺素和多巴胺水平降低[14,36]，考虑为NT1伴焦虑的病理生理学机制；然而，NT2患者不存在Hcrt水平的显著降低，故Hcrt缺失或表达下调无法解释NT2伴焦虑的机制[14]。

3.应激反应　Hcrt诱导的应激反应由促肾上腺

皮质激素释放因子(CRF)介导,直接作用于Hcrt能神经元的CRF受体[37],通过与Hcrt相互作用从而产生负面情绪[38]。发生应激刺激之后,CRF可激活Hcrt能神经元,使Hcrt能神经元逆向直接投射至下丘脑-垂体-肾上腺(HPA)轴,对应激反应做出适应性行为[31,39],该通路有助于激活并维持应激反应相关觉醒。动物实验显示,CRF1受体敲除小鼠的Hcrt能神经元对急性应激反应速度减慢[33];Wistar大鼠Hcrt-1水平升高与急性应激反应有关[40]。过度激活的Hcrt能系统更易导致创伤后应激障碍,但一项战争相关创伤后应激障碍研究显示,男性慢性创伤后应激障碍患者脑脊液和血浆Hcrt-1水平均显著低于健康对照者,且脑脊液Hcrt-1水平与疾病严重程度呈负相关[41],故认为,急性应激反应可能与Hcrt水平升高有关,而慢性应激则导致Hcrt水平降低[33]。

4.快速眼动睡眠期异常 发作性睡病是发生于REM的睡眠障碍,REM睡眠由脑干背外侧被盖核(LDT)和脚桥被盖核(PPT)中胆碱能神经元启动,而单胺能神经递质活性增强则REM睡眠终止[42]。中缝背核中5-HT能神经元可以抑制乙酰胆碱(ACh)能神经元和去甲肾上腺素能神经元,发作性睡病患者5-HT水平降低,对乙酰胆碱和去甲肾上腺素的抑制作用减弱,导致REM睡眠中断、REM睡眠次数增多[43]。研究显示,创伤后应激障碍患者去甲肾上腺素水平升高、REM睡眠连续性中断、REM密度增加,表现为REM-觉醒和REM-非快速眼动睡眠期(NREM)1期转换增多[44-45],故发作性睡病患者在应激刺激下,乙酰胆碱和去甲肾上腺素水平升高,导致REM睡眠中断、REM缩短,以及REM-觉醒和REM-NREM 1期转换增多[46]。REM睡眠可抑制条件性恐惧记忆,具有抗焦虑作用[47]。研究显示,焦虑障碍患者REM潜伏期缩短、REM密度减少[48]。根据焦虑患者对睡眠的主观判断,约22.6%患者高估其总睡眠时间(TST),REM-觉醒次数和REM占比增加;约51.1%患者低估其总睡眠时间,认为难以进入REM,并迅速觉醒,REM占比减少[49]。广泛性焦虑障碍患儿REM潜伏期缩短,尤以女性更显著[50]。部分惊恐障碍患者REM潜伏期延长、REM密度增加[48]。强迫障碍患者REM潜伏期延长、REM密度和占比增加,并出现入睡期始发的REM睡眠[51]。

三、治疗

社交焦虑障碍患者外周血苯二氮䓬类受体密度减少;广泛性焦虑障碍患者外周血γ-氨基丁酸受体(GABAR)密度和结合率降低[36]。苯二氮䓬类药物通过促进与其受体结合、激活GABAR,发挥抗焦虑作用,但是由于激活γ-氨基丁酸A型受体($GABA_AR$)有助于睡眠,并不推荐用于发作性睡病伴焦虑的治疗[52]。目前,尚无发作性睡病伴焦虑的药物治疗指南,临床常用于治疗猝倒发作的药物为选择性5-羟色胺再摄取抑制剂(SSRI)如氟西汀、舍曲林和选择性5-羟色胺和去甲肾上腺素再摄取抑制剂(SSNRI)如文拉法辛,二者均可通过升高突触间隙5-HT和去甲肾上腺素水平以改善焦虑[53]。年龄较小(18~24岁)的发作性睡病患者抗焦虑药物应用率较高,约36%应用选择性5-羟色胺再摄取抑制剂、21%应用选择性5-羟色胺和去甲肾上腺素再摄取抑制剂、13%应用三环类抗抑郁药物[12]。哌甲酯是一种抑制去甲肾上腺素和多巴胺再摄取的中枢兴奋剂,用于治疗发作性睡病的日间过度思睡,但有文献报道其可加重主观焦虑[54]。莫达非尼是一种强效促觉醒药物,可减弱多巴胺转运蛋白活性,升高多巴胺水平,从而加重健康人群焦虑、增加小鼠焦虑样行为[55-57],但亦有莫达非尼降低斑马鱼焦虑样行为的报道[58]。2019年3月,美国食品与药品管理局(FDA)批准选择性多巴胺和去甲肾上腺素再摄取抑制剂Solriamfetol用于治疗OSAHS和成年发作性睡病患者的日间过度思睡[59],但动物实验并未发现Solriamfetol有促进小鼠焦虑样行为的不良反应[55]。Pitolisant是一种口服有效的组胺H3受体阻断剂/反向激动剂,分别于2016和2019年获欧盟和美国批准用于治疗成人发作性睡病的日间过度思睡和猝倒发作[60]。2023年6月30日,中国国家药品监督管理局(NMPA)正式批准盐酸替洛利生用于治疗成人发作性睡病的日间过度思睡或猝倒发作,但亦有服药后出现焦虑的报道[59,61-62]。然而,上述各项研究样本量均较小,尚待开展发作性睡病伴焦虑药物治疗的大样本随机对照临床试验。

综上所述,发作性睡病相对罕见,绝大多数患者伴焦虑或焦虑障碍,且焦虑障碍的诊断常早于发作性睡病;患者关注点主要集中于日间过度思睡,通常无焦虑主诉,易延误治疗,临床医师应详细询问病史,同时进行焦虑和发作性睡病的评估,减少临床误诊、误治。未来尚待开展大样本随机对照临床试验,以进一步探究发作性睡病伴焦虑的发病机制,为其精准诊断与治疗提供依据。

利益冲突 无

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