·专题综述·

快速眼动睡眠期行为障碍与神经变性病发病机制研究进展

姜海洋 黄金莎 王涛

【摘要】 快速眼动睡眠期行为障碍系指快速眼动睡眠期肌肉失弛缓，并出现梦境（通常是暴力梦境）相关肢体运动（梦境演绎行为）。其人群发病率为0.38%～2.01%，在神经变性病尤其是α-突触核蛋白病患者中的发病率明显增加。快速眼动睡眠期行为障碍可早于α-突触核蛋白病数十年出现，因此可以作为预测神经变性病的早期标记。本文拟就近年来关于快速眼动睡眠期行为障碍发病机制及其与神经变性病之间的关系进行简要综述。

【关键词】 REM睡眠行为障碍； 神经变性疾病； 综述

Research progress on the pathogenesis of rapid eye movement sleep behavior disorder and neurodegenerative diseases

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【Abstract】 Rapid eye movement sleep behavior disorder (RBD) is a sleep disorder characterized by the disappearance of muscle relaxation and enacting one's dreams during rapid eye movement (REM), with most of the dreams being violent or aggressive. Prevalence of RBD, based on population, is 0.38%–2.01%, but it becomes much higher in patients with neurodegenerative diseases, especially α-synucleinopathies. RBD may herald the emergence of α-synucleinopathies by decades, thus it may be used as an effective early marker of neurodegenerative diseases. In this review, we summarized the progress on the pathogenesis of RBD and its relationship with neurodegenerative diseases.

【Key words】 REM sleep behavior disorder; Neurodegenerative diseases; Review

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快速眼动睡眠期行为障碍（RBD）系指快速眼动睡眠期（REM）肌肉失弛缓，伴恶梦和梦境相关激烈言语或肢体复杂不自主运动。根据病因可以分为两种类型，一种是特发性快速眼动睡眠期行为障碍，不存在其他明确的神经系统疾病；一种是继发性快速眼动睡眠期行为障碍，也称症状性快速眼动睡眠期行为障碍，系快速眼动睡眠期行为障碍合并其他神经系统疾病如发作性睡病、神经变性病等。近年来，随着前瞻性临床研究结果的公布，特发性快速眼动睡眠期行为障碍被认为是神经变性病尤其是α-突触核蛋白病的早期临床标记[1-5]。2010年，Claassen等[6]发现，快速眼动睡眠期行为障碍较帕金森病（PD）、路易体痴呆（DLB）或多系统萎缩（MSA）的首发症状早数十年。近年来，越来越多的研究关注快速眼动睡眠期行为障碍发病机制及其与神经变性病之间的关系，本文拟就此方面研究进

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展进行简要综述。

一、快速眼动睡眠期行为障碍的临床特点

快速眼动睡眠期行为障碍根据发病年龄可以分为早发型(50岁前发病)和晚发型(50岁及以后发病),二者在社会人口学资料、疾病表现形式等方面存在明显差异。早发型快速眼动睡眠期行为障碍患者中女性、特发性快速眼动睡眠期行为障碍、使用抗抑郁药、合并发作性睡病和自身免疫性疾病比例均较高[7-12]。此外,早发型患者较晚发型的睡眠障碍方式缓和,可能与早发型患者中女性、合并发作性睡病比例较高有关[7]。晚发型快速眼动睡眠期行为障碍患者合并神经变性病比例较高,且睡眠障碍通常早于α-突触核蛋白病如帕金森病、路易体痴呆和多系统萎缩15年出现[1-5]。研究显示,嗅觉和色觉基线水平下降的快速眼动睡眠期行为障碍患者更易进展为α-突触核蛋白病[13-17]。

二、快速眼动睡眠期行为障碍的诊断

快速眼动睡眠期行为障碍患者均存在反复发作的夜间梦境演绎行为(DEBs),但具有上述行为的并非均是快速眼动睡眠期行为障碍[18]。严重睡眠呼吸暂停(OSA)、创伤后应激障碍(PTSD)、夜间额叶癫痫、非快速眼动睡眠期(NREM)异态睡眠(如梦游、夜惊)等也可能出现生动梦境和梦境演绎行为。使用或戒断酒精或某些药物也可能发生梦境演绎行为。因此,为区分上述情况,需要详细的病史资料和多导睡眠图(PSG)监测。肌肉失迟缓系指快速眼动睡眠期持续性或间断性颏下肌群或肢体肌电张力增高[19]。根据2014年美国睡眠医学会(AASM)标准[7],诊断确定的(definite)快速眼动睡眠期行为障碍应同时满足以下条件:(1)睡眠中反复出现的发声和(或)复杂行为表现,单夜视频多导睡眠图监测到反复出现的发声和(或)动作。(2)多导睡眠图监测到的上述行为发生于快速眼动睡眠期。(3)多导睡眠图监测到的肌肉失迟缓符合美国睡眠医学会制定的睡眠相关事件评分手册标准。(4)上述异常不能用其他睡眠障碍、精神病、药物因素或物质滥用等解释。快速眼动睡眠期行为障碍患者觉醒后警醒程度、动作协调性和定向力均正常。发生以下情况时,临床医师可以基于临床判断暂时诊断为快速眼动睡眠期行为障碍:多导睡眠图监测到快速眼动睡眠期异常行为,但肌肉失迟缓未达到美国睡眠医学会制定的睡眠相关事件评分手册标准,或者临床存在典型快速眼动睡眠期行为障碍病史,但多导睡眠图监测未达到快速眼动睡眠期行为障碍的诊断标准。对于没有条件进行视频多导睡眠图监测的患者亦是如此。此外,某些药物如三环类抗抑郁药和选择性5-羟色胺再摄取抑制剂(SSRI)可以诱发快速眼动睡眠期行为障碍,此时可以诊断为快速眼动睡眠期行为障碍,但应密切随访。国内某些睡眠中心进行连续两夜视频多导睡眠图监测以排除环境因素的干扰,然而,2015年Högl和Stefani[20]更新的诊断标准提出,单夜视频多导睡眠图监测到快速眼动睡眠期睡眠即可明确诊断。此项更新的诊断标准的提出是根据Innsbruck Barcelona睡眠工作组(SINBAR)的研究,增加指浅屈肌肌电图以更好地补充颏肌和双侧胫骨前肌肌电图,并认为常规胫骨前肌肌电图并不具有特异性,这是由于老年患者易合并周围神经病和神经根损害,导致快速眼动睡眠期肌肉异常活动,从而造成混淆。更新的诊断标准还借用Sixel-Döring等[21]的快速眼动睡眠期行为障碍严重程度分级:0分,仅有肌肉失迟缓而无快速眼动睡眠期异常行为;1分,有肢体远端小幅度动作;2分,有肢体近端肌肉活动;3分,有躯干运动;其中,监测到快速眼动睡眠期发声评1分,未监测到评0分。因此,对于未予治疗的帕金森病患者,如果视频多导睡眠图监测无法达到快速眼动睡眠期行为障碍的诊断标准,但有快速眼动睡眠期异常行为,则可以作为神经变性病的早期标记[22]。此外,更新的诊断标准系指将不符合原有的时相性和紧张性肌张力增高定义为"任意形式的肌张力增高",并进行定量分析,从而提出的诊断标准[20]。

三、快速眼动睡眠期行为障碍的发病机制

维持快速眼动睡眠期肌肉弛缓的两种功能相反神经元分别称为"REM-on"神经元和"REM-off"神经元,共同组成"开-关"模型,负责调控非快速眼动睡眠期与快速眼动睡眠期的转换[23-24]。快速眼动睡眠期行为障碍动物(猫)模型显示,"REM-on"神经元位于蓝斑(LC)腹侧,向上投射引起脑电活动和意识改变,向下投射抑制肌张力和快速眼动睡眠期自主神经功能[25]。Jeannerod等[26]于1965年通过特异性毁损猫蓝斑核α周围区域(相当于人蓝斑下核)成功制备快速眼动睡眠期肌肉失弛缓动物模型,表现为猫在睡眠情况下出现类似捕食、盯梢、打斗和舔舐行为。研究显示,蓝斑核α周围区域经乙酰胆碱激活后投射谷氨酸能神经元至髓内大细胞核,后者经

突触后膜释放谷氨酸以阻断脊髓下运动神经元[27]，导致肌张力缺失。大鼠背侧下核（SLD）相当于猫蓝斑核α周围区域[28]。2017年，Valencia Garcia等[29]采用小发夹RNA（shRNA）技术使大鼠背侧下核表达囊泡谷氨酸转运体2（vGluT2）的谷氨酸能神经元失活，并于1个月后行睡眠监测，结果显示，大鼠快速眼动睡眠期比例仅较基线下降30%，但呈现出快速眼动睡眠期肌肉失弛缓，证实背侧下核谷氨酸能神经元下行投射至髓内腹侧核甘氨酸能和（或）γ-氨基丁酸（GABA）能运动前神经元致快速眼动睡眠期肌肉失弛缓，但并无神经元上行投射至丘脑板内核，提示背侧下核并不参与快速眼动睡眠期的发生，但对快速眼动睡眠期肌肉失弛缓的维持具有至关重要的作用。该动物模型首次定量研究快速眼动睡眠期肌张力变化和异常行为，但仍有缺陷：背侧下核胆碱能和γ-氨基丁酸能神经元进行性损害也可以引起快速眼动睡眠期肌电图改变和异常行为，该动物模型完全抑制背侧下核谷氨酸能神经元，而不包含“REM-on”和“REM-off”神经元。此外，快速眼动睡眠期行为障碍患者间断性出现肌肉失迟缓，如何与该动物模型相联系尚待进一步研究。关于“REM-off”神经元的研究相对明确，该神经元位于中脑导水管周围灰质腹外侧核（vlPAG）和脑桥外侧被盖（LPT），这两个区域神经元失活可以导致异相睡眠增加[23,30]。

然而，目前对调节快速眼动睡眠期特异性神经核团和确切神经网络的认识尚不明确。脑干损伤如脑血管病、炎症和肿瘤可以导致快速眼动睡眠期行为障碍，提示脑干尤其是中脑和脑桥被盖与快速眼动睡眠期行为障碍密切相关[31-32]。Garcia-Lorenzo等[33]对帕金森病合并快速眼动睡眠期行为障碍患者进行神经色素敏感成像（neuromelanin-sensitive imaging）研究，结果显示，其蓝斑/蓝斑下区域信号强度较帕金森病不合并快速眼动睡眠期行为障碍患者降低，提示蓝斑/蓝斑下复合体变性可能导致快速眼动睡眠期行为障碍。晚近一项神经影像学研究显示，快速眼动睡眠期行为障碍患者双侧壳核体积较性别和年龄相匹配的正常对照者缩小，可以作为快速眼动睡眠期行为障碍的一项神经结构标记[34]。

激活5-羟色胺能系统的药物如氟西汀、文拉法辛和帕罗西汀，以及阻断乙酰胆碱能传递的药物如三环类抗抑郁药氯丙咪嗪均可诱发快速眼动睡眠期行为障碍和肌肉失迟缓[35]，可能是由于此类药物阻止正常睡眠相关肌张力降低（5-羟色胺再摄取抑制剂）或肌张力缺失（抗胆碱能药物）。为明确抗抑郁药相关快速眼动睡眠期行为障碍究竟是药物不良反应，还是神经变性病早期独立危险因素，Postuma等[36]的研究显示，尽管抗抑郁药相关快速眼动睡眠期行为障碍较“纯粹的”特发性快速眼动睡眠期行为障碍进展为神经变性病的风险低，但抗抑郁药相关快速眼动睡眠期行为障碍是潜在的神经变性病早期标记。

四、快速眼动睡眠期行为障碍与神经变性病的潜在分子学机制

Hypocretin（Hcrt）/Orexin仅由下丘脑背侧和外侧神经元分泌[37]，对维持机体生理功能如摄食、血压、体温、神经内分泌和睡眠-觉醒周期发挥重要作用[38-41]。*Orexin*基因敲除小鼠[42]、Hcrt/Orexin能神经元缺失的转基因小鼠[43]以及Orexin受体2（*OX2R*）基因无义突变的小鼠和狗[44-45]均呈现睡眠周期片段化，其中前两者还出现快速眼动睡眠期猝倒发作[42-43]，而后者仅受轻微影响[44]。Mieda等[46]研究显示，Hcrt/Orexin能神经元缺失的转基因小鼠脑组织异位表达编码Hcrt/Orexin前体蛋白的基因，可以避免快速眼动睡眠期猝倒发作和其他异常；予中枢性Hcrt-1/Orexin-1可以迅速抑制猝倒发作并增加3小时觉醒时间。分泌Hcrt/Orexin的神经元可以投射至多个神经系统，其中下丘脑以外投射密度最集中的区域是蓝斑核[38,47]。Bourgin等[48]报道，于蓝斑核局部注射Hcrt-1/Orexin-1可以剂量依赖性抑制快速眼动睡眠期，减少非快速眼动睡眠期3期（也称慢波睡眠）时间，增加觉醒时间，并且可以通过抗体中和以阻断上述效应。Gerashchenko等[49]认为，大鼠脑脊液Hcrt/Orexin水平下降与快速眼动睡眠期时间增加有关。上述研究均提示Hcrt/Orexin是调节快速眼动睡眠期的重要因子，其表达异常可以导致异常快速眼动睡眠期。2010年，Knudsen等[50]研究显示，脑脊液Hcrt-1/Orexin-1表达下调是发作性睡病患者发生快速眼动睡眠期行为障碍的独立危险因素，提示合并快速眼动睡眠期行为障碍的神经变性病患者可能存在Hcrt/Orexin能神经元数目减少或分泌下降。研究显示，帕金森病患者脑脊液Hcrt-1/Orexin-1水平在正常范围内[51-56]；亦有研究显示，帕金森病患者脑脊液Hcrt-1/Orexin-1水平低于正常对照者[57-58]；晚近有2项研究显示，帕金森病患者下丘脑Hcrt/Orexin能神经元缺失（50%）[59-60]。

Thannickal等[61]认为，造成上述结果差异的原因可能是脑脊液Hcrt/Orexin水平并不与Hcrt/Orexin能神经元数目成正比，残留的Hcrt/Orexin能神经元可能通过Hcrt/Orexin代偿性分泌增加在一定时间内维持脑脊液Hcrt/Orexin处于正常水平，因此，早期帕金森病患者脑脊液Hcrt/Orexin水平可能无明显变化。关于多系统萎缩患者Hcrt/Orexin能神经元是否受累的研究结论不尽一致，Benarroch等[62]的免疫组织化学染色显示，多系统萎缩患者Hcrt/Orexin能神经元数目较正常对照者减少；Abdo等[63]则认为，多系统萎缩患者脑脊液Hcrt-1/Orexin-1处于正常水平，且与年龄匹配的正常对照者差异无统计学意义。关于路易体痴呆的研究显示，新皮质区Hcrt/Orexin水平下降与α-突触核蛋白（α-Syn）水平和嗜睡有关，提示Hcrt/Orexin表达变化与路易体痴呆患者睡眠障碍有关[64]。此外，有研究显示，路易体痴呆患者下丘脑外侧Hcrt/Orexin能神经元和蓝斑核Hcrt/Orexin轴突末端数目减少，且下丘脑外侧Hcrt/Orexin能神经元数目与神经原纤维缠结（NFTs）程度呈明显负相关[65]。关于阿尔茨海默病（AD）患者、路易体痴呆患者与非痴呆对照者的研究显示，路易体痴呆患者脑脊液Hcrt/Orexin水平低于阿尔茨海默病患者和非痴呆对照者[66]。Friedman等[67]研究显示，尽管阿尔茨海默病患者脑脊液Hcrt-1/Orexin-1水平在正常范围内，但水平较低者出现日间觉醒片段化增加，提示Hcrt-1/Orexin-1可能参与睡眠-觉醒周期的调节。关于亨廷顿病（HD）患者Hcrt/Orexin能神经元的研究，既往已有文献报道，亨廷顿病转基因小鼠R6/2和亨廷顿病患者下丘脑外侧Hcrt/Orexin能神经元明显萎缩和缺失[68]。Gabery等[69]也于2010年得出相似结论。然而迄今为止，Hcrt/Orexin如何参与快速眼动睡眠期的调节，从而影响神经变性病的发生与发展尚无明确定论，尚待更多研究。

综上所述，大鼠背侧下核神经核团对维持快速眼动睡眠期肌肉弛缓至关重要，背侧下核谷氨酸能神经元下行投射至髓内腹侧核甘氨酸能和（或）γ-氨基丁酸能运动前神经元导致快速眼动睡眠期肌肉失弛缓，但并不参与快速眼动睡眠期的发生。脑脊液Hcrt/Orexin水平下降与1型发作性睡病的发病密切相关，提示Hcrt/Orexin参与快速眼动睡眠期的调节。然而，背侧下核胆碱能和γ-氨基丁酸能神经元如何参与快速眼动睡眠期肌肉失迟缓的调节以及Hcrt/Orexin如何参与快速眼动睡眠期的调节尚待进一步研究。

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