·专题综述·

特发性快速眼动睡眠期行为障碍向神经系统变性疾病转化的生物学标志物研究进展

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【摘要】 特发性快速眼动睡眠期行为障碍(iRBD)是神经系统变性疾病的前驱症状,多数患者可转化为神经系统变性疾病,可靠的生物学标志物对早期识别高风险转化者和预测疾病转化表型具有重要意义。本文从临床症状学、神经电生理学、神经影像学、体液、病理学、基因标志物等方面综述iRBD转化为神经系统变性疾病的生物学标志物研究进展,以优选适宜疾病修饰治疗的患者,并延缓神经系统变性疾病进展。

【关键词】 REM睡眠行为障碍; 神经变性疾病; 生物标记; 综述

Progress on biomarkers of idiopathic rapid eye movement sleep behavior disorder conversion to neurodegenerative diseases

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【Abstract】 Idiopathic rapid eye movement sleep behavior disorde (iRBD) is a precursor symptom of neurodegenerative diseases, and most patients will convert to neurodegenerative diseases later in the disease. Reliable biological markers are of great significance for early identification of high-risk converters and predicting phenoconversion pattern. This paper reviews the research progress of biological markers in predicting conversion to neurodegenerative diseases in iRBD from clinical symptomology, neuroelectrophysiology, neuroimaging, body fluid, pathology and gene markers, in order to select patients suitable for disease modification therapy and delay the development of neurodegenerative diseases.

【Key words】 REM sleep behavior disorder; Neurodegenerative disease; Biomarkers; Review

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特发性快速眼动睡眠期行为障碍(iRBD)被认为是神经系统变性疾病的前驱症状,尤其是α-突触核蛋白病,主要包括帕金森病(PD)、多系统萎缩(MSA)和路易体痴呆(DLB)。有文献报道,逾80%的iRBD患者可转化为α-突触核蛋白病[1]。神经系统变性疾病早期症状不典型,临床诊断困难,常使患者错失最佳治疗期,如果能够在iRBD阶段采取针对性治疗措施对预防神经系统变性疾病的发生发展具有重要意义。本文拟对iRBD转化为神经系统变性疾病的生物学标志物研究进展进行综述,以期筛选适宜疾病修饰治疗的患者,并延缓神经系统变性疾病的进展。

一、临床症状学标志物

1.运动障碍 研究显示,约43%的iRBD患者可转化为帕金森病[2]。iRBD患者首次就诊时通常无运动症状主诉,但客观检查如交替拍打试验、3米步行测验(3MWT)等提示运动功能减退[3]。多中心纵向研究显示,运动功能量化测验异常提示iRBD

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转化为痴呆或帕金森综合征的风险增加（*HR* = 3.160，95%CI：1.860～5.370；*P* < 0.05）[1]。基于运动功能量化测验的随访研究显示，iRBD患者转化为帕金森病或路易体痴呆前5～8年即已存在运动功能减退[4]。上述研究表明运动功能量化测验是监测iRBD进展和预测转化的有效工具。

2.认知功能障碍　逾1/3的iRBD患者存在轻度认知损害（MCI），包括注意力减退、记忆力减退、执行功能障碍、视空间能力障碍[3]。研究显示，伴轻度认知损害的iRBD患者较认知功能正常者转化为神经系统变性疾病的风险更高[1,5]，入组时存在记忆力减退、执行功能障碍、视空间能力障碍的iRBD患者在随访过程中向神经系统变性疾病的转化率增加；此外，与转化为帕金森综合征的iRBD患者相比，转化为痴呆的iRBD患者入组时简易智能状态检查量表（MMSE）评分更低、记忆力更差[6]。一项长达6年的随访研究纳入109例iRBD患者，根据临床结局分为帕金森病组（20例）、路易体痴呆组（18例）和无转化组（71例），其结果显示，iRBD患者转化为路易体痴呆前6年即可出现连线测验B（TMT-B）完成时间延长，转化前2～4年即可出现词语流畅性测验（VFT）、听觉词语学习测验（AVLT）符合要求或者学习和回忆正确词语个数减少；该项研究还发现，持续性认知功能减退主要见于转化为路易体痴呆的iRBD患者，而未出现疾病转化或转化为帕金森病的iRBD患者认知功能相对稳定[7]，提示密切随访观察iRBD患者认知功能变化对监测疾病进展和预测转化表型至关重要。

3.嗅觉减退　iRBD患者嗅觉减退比例高达67%，是预测iRBD转化为痴呆或帕金森综合征最强的非运动症状标志物（*HR* = 2.620，95%CI：1.670～4.120；*P* < 0.05）[1]，疾病转化前20余年即已存在[4]。伴嗅觉减退的iRBD患者多巴胺转运蛋白（DAT）功能减退，且随访期间视空间能力和语言记忆功能减退更明显[8]，为嗅觉减退预测iRBD转化为帕金森病或路易体痴呆提供了更多证据。虽然嗅觉减退是iRBD转化为神经系统变性疾病的重要危险因素，但无法预测究竟转化为帕金森病还是路易体痴呆[9]。

4.视觉障碍　iRBD患者视觉障碍主要表现为颜色辨别能力下降，可通过Farnsworth-Munsell 100色相测试进行评估。iRBD患者转化为帕金森病或路易体痴呆前12.8年即出现颜色辨别能力下降[4]。伴颜色辨别能力下降的iRBD患者转化为帕金森病或路易体痴呆的风险显著增加（*RR* = 1.690，95%CI：1.010～2.780；*P* < 0.05）[1]，上述研究提示颜色辨别能力下降对预测iRBD转化为痴呆或帕金森综合征具有重要意义。基于光学相干断层扫描术（OCT）的研究显示，iRBD患者视网膜中央凹周围神经节细胞复合体厚度减少与嗅觉减退和多巴胺转运减少相关[10]，提示其可能是预测iRBD预后的潜在标志物，但尚待进一步随访研究证实。

5.自主神经功能障碍　iRBD患者自主神经功能评价主要包括帕金森病预后量表-自主神经功能部分（SCOPA-AUT）等量表，以及心率变异性（HRV）监测、心脏间碘苯甲胍闪烁显像、自主神经反射测验等客观检查。iRBD患者早期常出现自主神经功能障碍[4]。伴便秘（*HR* = 1.670，95%CI：1.240～2.240；*P* < 0.05）和勃起功能障碍（*HR* = 2.130，95%CI：1.100～4.130；*P* < 0.05）的iRBD患者转化为痴呆或帕金森综合征风险显著增加[1]。伴严重心脏迷走神经功能障碍的iRBD患者更倾向转化为路易体痴呆而非帕金森病，可能与路易体痴呆较帕金森病具有更严重的自主神经功能障碍有关[11]。基于多导睡眠图（PSG）监测的研究显示，iRBD患者RR间期标准差、相邻窦性心搏RR间期差值平方和的均方根（RMSSD）和高频值降低，提示其心率变异性降低；紧张性快速眼动睡眠期肌肉失弛缓（RSWA）比例与标准化低频值和低频值/高频值比值呈负相关，与标准化高频值呈正相关[12]；快速眼动睡眠期肌肉失弛缓是预测iRBD转化为神经系统变性疾病的重要标志物[13-14]，因此认为，心率变异性相关参数对iRBD转化为α-突触核蛋白病具有一定预测价值。iRBD患者心脏间碘苯甲胍闪烁显像摄取率下降与快速眼动睡眠期肌肉失弛缓比例增加相关[15]。与入组时相比，随访3年时iRBD患者心脏间碘苯甲胍闪烁显像摄取率降低[16]。心脏间碘苯甲胍闪烁显像联合嗅觉测试有助于早期识别处于帕金森病或路易体痴呆前驱期的iRBD患者[17]，心脏间碘苯甲胍闪烁显像摄取率下降可能是预测iRBD转化为α-突触核蛋白病的潜在标志物。

二、神经电生理学标志物

PSG监测到快速眼动睡眠期肌肉失弛缓是神经系统变性疾病患者出现梦境演绎行为前的最早期症状之一[18]。颏下肌和胫骨前肌快速眼动睡眠期肌肉失弛缓比例＞46.4%的iRBD患者转化为帕金森综合征或轻度认知损害的危险比（*HR*）为2.750

（$P=0.040$），3年疾病转化率为25%，5年疾病转化率为45%；iRBD患者诊断年龄>65岁且颏下肌和胫骨前肌快速眼动睡眠期肌肉失弛缓>46.4%时，5年疾病转化率增至55%[13]。不同类型（紧张性、时相性、混合性）快速眼动睡眠期肌肉失弛缓对预测iRBD转化为神经系统变性疾病的价值存在差异，混合性快速眼动睡眠期肌肉失弛缓比例对疾病转化的预测价值最高，曲线下面积（AUC）为0.778（95%CI：0.648～0.908，$P=0.006$），灵敏度为88.9%、特异度为60.9%，截断值为4.4%[14]；时相性快速眼动睡眠期广泛性脑电活动减慢是预测iRBD转化为神经系统变性疾病的标志物，曲线下面积为0.749（95%CI：0.625～0.874，$P=0.001$），灵敏度为86.4%、特异度为74.4%，截断值为2.204[19]。循环交替模式（CAP）是反应睡眠微结构的重要指标，PSG监测显示，循环交替模式和安静清醒期脑电图时间-频率结构对预测iRBD转化为神经系统变性疾病具有一定价值[20-21]。

三、神经影像学标志物

1. SPECT和PET　突触前膜多巴胺转运蛋白配体^{123}I-FP-CIT是目前研究应用最多的DAT-SPECT示踪剂，^{123}I-FP-CIT SPECT有助于筛查出短期内高风险转化的iRBD患者，壳核多巴胺摄取率下降>25%可筛查出3年内转化为α-突触核蛋白病的iRBD患者，曲线下面积为0.84[22]，纹状体多巴胺摄取率降低的iRBD患者5年内转化为帕金森病或路易体痴呆的风险显著增加（HR = 6.900，95%CI：2.800～16.900；$P<0.0001$）[23]。司来吉兰是常用的抗帕金森病药物，^{123}I-FP-CIT SPECT显像显示，经司来吉兰治疗的iRBD患者壳核多巴胺摄取率下降，尾状核多巴胺摄取率则无明显变化[24]。上述研究提示DAT-SPECT有助于筛选适宜疾病修饰治疗的iRBD患者并对治疗效果进行评价。DAT-SPECT结合临床症状可增强疾病转化及转化方向预测价值，广义线性模型分析显示，多巴胺转运功能下降、直立性低血压（OH）、非运动症状、词语记忆和视空间能力障碍是预测iRBD患者转化为神经系统变性疾病的最佳标志物组合（HR = 26.050，95%CI：6.300～107.650；$P<0.0001$）[25]。一项国际多中心临床研究显示，年龄>70岁且黑质-壳核多巴胺转运功能下降的伴便秘的iRBD患者2年内疾病转化风险高达5.71（95%CI：2.850～11.430，$P<0.000\,001$），MMSE评分较低且双侧尾状核多巴胺转运功能显著不对称的iRBD患者易转化为路易体痴呆，反之则更易转化为帕金森病[26]。神经系统变性疾病^{18}F-FDG PET显像可呈现不同的脑代谢模式，有前驱快速眼动睡眠期行为障碍症状的首次就诊帕金森病患者的^{18}F-FDG PET帕金森病相关模式表达，以辅助运动区、运动前区、丘脑、壳核/苍白球、小脑、脑桥灰质和白质葡萄糖代谢相对升高、以及枕区、后顶区代谢相对降低为特征，因此认为，iRBD患者^{18}F-FDG PET帕金森病相关模式表达是预测其转化为α-突触核蛋白病的有效影像学标志物[27]，对评价疾病进展和预测转化亚型具有潜在价值[28]。然而，SPECT和PET检查费用昂贵，且存在一定的辐射性，使其临床应用受到限制。

2. MRI　MRI呈现多系统萎缩典型征象，如壳核萎缩、壳核T_2WI低信号、壳核“裂隙征”、小脑萎缩、小脑T_2WI高信号、小脑中脚萎缩、小脑中脚T_2WI高信号、脑干萎缩、脑桥“十字征”等预测iRBD转化为多系统萎缩的灵敏度为80%、特异度为94.6%[29]。将基于形变的形态学测量（DBM）与临床运动和认知指标相结合并计算的基于脑-临床特征的形变分数，可作为预测iRBD转化为路易体痴呆的重要标志物[30]。iRBD和α-突触核蛋白病患者病变脑区主要位于蓝斑、中缝核尾部、黑质、前脑基底核等，这些脑区除参与调节情绪、睡眠、记忆等外，还支配皮质小动脉和毛细血管以调节氧供，且iRBD患者语言理解、视觉处理、再认相关皮质微血管脑血流量（CBF）显著减少[31]，提示脑血流量监测对iRBD转化为神经系统变性疾病具有重要意义。基于动脉自旋标记（ASL）的脑血流量分析显示，iRBD患者右侧额下回、额中回、岛叶低灌注[32]，这些脑区与认知功能密切相关，提示基于ASL的脑灌注模式对预测iRBD转化为神经系统变性疾病具有一定价值。健康人群SWI序列可见黑质致密部卵圆形高信号，称为黑质背外侧高信号（DNH）或“燕尾征”，约45%的iRBD患者黑质背外侧高信号缺失[33]且纹状体多巴胺转运功能下降[34-35]，约79%的原发性帕金森病患者黑质背外侧高信号缺失[36]，提示黑质背外侧高信号缺失可能是预测iRBD转化为帕金森病的重要影像学标志物。

四、体液标志物

1. 脑脊液标志物　脑脊液指标变化可反映脑组织微环境改变，实时震动诱导转化（RT-QuIC）可用于检测路易体病（路易体痴呆、帕金森病、iRBD、单纯性自主神经功能衰竭）患者脑脊液病理性α-突触

核蛋白(α-Syn)表达变化,其灵敏度为95.3%、特异度为98%[37]。一项为期7.1年的纵向研究纳入52例iRBD患者,通过RT-QuIC技术检出47例(90.38%)脑脊液病理性α-Syn阳性,其中31例(65.96%)随访期间转化为路易体痴呆(16例)或帕金森病(15例);5例(9.62%)脑脊液病理性α-Syn阴性患者中仅1例转化为帕金森病,余4例未转化为其他疾病;由此可见,病理性α-Syn阳性患者随访期间疾病转化风险高于阴性患者(*HR* = 0.143, 95%CI: 0.019 ~ 1.063; *P* = 0.028),故认为,iRBD患者脑脊液病理性α-Syn阳性可能提示其处于帕金森病或路易体痴呆前驱期[38],但RT-QuIC技术在国内推广度较低,临床应用具有一定局限性。

2. 血液标志物 iRBD患者转化为帕金森病或路易体痴呆前4.67年即可出现血浆微小RNA-19b(miRNA-19b)含量降低,提示血浆miRNA-19b含量有助于预测iRBD转化为α-突触核蛋白病风险[39]。含≤2个唾液酸链的转铁蛋白统称为碳水化合物缺乏性转铁蛋白(CDT),转铁蛋白及其受体基因多态性可改变帕金森病发病风险[40-42]。最新一项研究采用高效液相色谱(HPLC)检测iRBD患者血清CDT异构体比例,并根据酒精摄入量对CDT含量进行校正,同时采用DAT-SPECT显像评价黑质变性程度,结果显示,iRBD患者血清CDT含量校正值与黑质变性程度呈负相关,低血清CDT含量的iRBD患者转化为神经系统变性疾病的风险显著增加(*HR* = 3.200, 95%CI: 1.000 ~ 9.900; *P* = 0.045)[43],提示血清CDT含量是预测疾病转化的有效血液标志物。

五、病理学标志物

病理学研究显示,约87%的iRBD患者C_8椎旁区或下肢远端皮肤组织存在磷酸化α-Syn沉积,而继发于发作性睡病的快速眼动睡眠期行为障碍患者则未发现这一现象[44],提示皮肤组织病理学检查对诊断iRBD具有一定价值。一项对28例iRBD患者皮肤组织行自动免疫组化分析的研究显示,约82.14%(23/28)患者C_8椎旁区皮肤组织存在磷酸化α-Syn沉积;有28.57%(8/28)患者随访3年后转化为神经系统变性疾病,包括帕金森病(4例)、路易体痴呆(2例)、很可能的多系统萎缩(1例)、很可能的痴呆(1例),其中帕金森病(4例)和路易体痴呆(2例)患者3年前即存在皮肤组织磷酸化α-Syn沉积[45]。皮肤组织磷酸化α-Syn沉积量及其分布有助于鉴别帕金森病与多系统萎缩[46-47],提示皮肤组织病理学检查可能有助于预测iRBD向神经系统变性疾病的转化表型。

六、基因标志物

晚近研究证实,帕金森病、路易体痴呆、多系统萎缩相关*GBA*基因变异与iRBD具有相关性[48]。约52.5%携带*GBA*基因变异的iRBD患者转化为神经系统变性疾病,而仅35.6%未携带*GBA*基因变异的iRBD患者发生疾病转化,存在严重*GBA*基因变异(导致戈谢病Ⅱ型或Ⅲ型)的iRBD患者疾病转化率显著增加,且转化进程增快[49]。iRBD患者*SNCA*基因变异亦对疾病转化具有潜在预测价值,帕金森病和路易体痴呆患者*SNCA*基因变异发生部位不同,帕金森病主要与*SNCA*基因3'端变异相关,路易体痴呆则与*SNCA*基因5'端变异相关,特定的*SNCA*基因5'端变异可能影响疾病转化表型[50]。

综上所述,运动障碍、认知功能障碍、嗅觉减退、颜色辨别能力下降、自主神经功能障碍、快速眼动睡眠期肌肉失弛缓、DAT-SPECT显示多巴胺转运功能下降、脑脊液病理性α-Syn阳性、基因变异均有助于预测iRBD转化为神经系统变性疾病,其中运动功能和认知功能的临床动态评估有助于监测疾病进展;DAT-SPECT有助于预测短期内疾病转化,适用于筛查适宜疾病修饰治疗的iRBD患者。目前,有效预测疾病转化表型的生物学标志物尚待进一步研究。通过可靠的易于获取的生物学标志物早期识别iRBD高风险转化者并预测疾病转化表型,优选适宜疾病修饰治疗的人群,对延缓神经系统变性疾病进展具有重要意义。

利益冲突 无

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