·专题综述·

孤立性快速眼动睡眠期行为障碍转化为α-突触核蛋白病的预警因素及标志物研究进展

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【摘要】 α-突触核蛋白病是临床常见的神经系统变性疾病，早期诊断困难。为使患者尽早获得疾病修饰治疗的最佳时机，探索α-突触核蛋白病的预警因素或标志物即显得尤为重要。孤立性快速眼动睡眠期行为障碍（iRBD）是α-突触核蛋白病的前驱症状，在此阶段发挥预警作用可阻止或延缓其转化为α-突触核蛋白病。本文从非运动症状、神经影像学标志物、生物学标志物和基因学等方面阐述iRBD转化为α-突触核蛋白病的预警因素及标志物研究进展。

【关键词】 REM睡眠行为障碍； α突触核蛋白； 综述

Alarming signs and biomarkers of isolated rapid eye movement behavior disorder transforming into α-syncleinopathies

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【Abstract】 α - synucleinopathies are a group of common neurodegenerative diseases. Once diagnosed, the disease′s pathology is already in the middle or late stages, and the best timing for disease modification therapy is missed. Thus, it is very important to explore the early warning signs or early markers of α - synucleinopathies. Isolated rapid eye movement behavior disorder (iRBD) is the prodromal phase of α - synucleinopathies and may serve as an early warning for future transforming into α - synucleinopathies at this stage. The early warning mechanisms for the iRBD transforming into α - synucleinopathies in terms of non - motor symptoms, neuroimaging markers, neuro biological markers, and genetics are illustrated through perspective studies.

【Key words】 REM sleep behavior disorder; α-synuclein; Review

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α-突触核蛋白病是临床较常见的神经系统变性疾病，主要包括帕金森病、路易体痴呆（DLB）和多系统萎缩（MSA），由于早期诊断困难，大多数患者确诊即已处于病程中晚期，错失了疾病修饰治疗的最佳时机。故探寻α-突触核蛋白病的预警机制或标志物对于此类患者的早诊断、早治疗显得尤为重要。孤立性快速眼动睡眠期行为障碍（iRBD）是α-突触核蛋白病最早发生和特异性最高的非运动症状之一，逾80%的患者可能转化为α-突触核蛋白病[1]，提示iRBD阶段可对未来转化为α-突触核蛋白病发挥预警作用。本文拟对α-突触核蛋白病的前瞻性研究结果进行总结，从非运动症状、神经影像学标志物、生物学标志物、基因学等方面阐述iRBD转化为α-突触核蛋白病的预警因素。

一、非运动症状的预警作用

α-突触核蛋白病可累及多系统而出现非运动症状且异质性较高，大多数患者在出现运动症状之前数年即已表现有非运动症状，相关预警因素主要包括快速眼动睡眠期肌肉失弛缓（RSWA）、嗅觉减退、

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自主神经功能障碍及颜色辨别能力下降等。

1.快速眼动睡眠期肌肉失弛缓 RSWA是快速眼动睡眠期行为障碍(RBD)的神经生理学标记,可作为其转化为α-突触核蛋白病的预警因素[2-3]。一项针对55例RBD患者的2年随访研究显示,16.36%(9/55)患者转化为α-突触核蛋白病;进一步绘制RSWA评分预测转化风险的受试者工作特征(ROC)曲线,发现混合型RSWA预测RBD转化为α-突触核蛋白病的效果最佳,其曲线下面积(AUC)为0.778(95%CI:0.648~0.908,$P=0.009$)[4]。RSWA可随病程的迁延而频率逐渐增加,其严重程度与表型的转化速度存在相关性,一项针对60例iRBD患者进行的为期3年的前瞻性研究显示,其转化为帕金森病的3年转化率为20%(12/60),其中伴RSWA患者的3年转化率为28.33%(17/60),提示RSWA可以预测转化为α-突触核蛋白病的时间[5]。

2.嗅觉减退 是α-突触核蛋白病最早的前驱症状之一[6-7]。一项纳入1280例RBD患者的多中心试验显示,有49.06%(628/1280)的iRBD患者出现嗅觉减退,而且存在嗅觉减退的患者转化为α-突触核蛋白病的风险比(*HR*)为2.620(95%CI:1.670~4.120,$P<0.05$)[1],并于发生转化前20年即已存在嗅觉减退[8]。Jennings等[9]采用多巴胺转运蛋白(DAT)显像对185例嗅觉减退患者和95例健康对照者进行为期4年的随访,发现嗅觉减退合并多巴胺转运蛋白功能障碍可预测4年内iRBD转化为α-突触核蛋白病的转化率,约为66.67%(14/21)。上述研究提示,嗅觉减退可以作为iRBD转化为α-突触核蛋白病的预警因素。

3.自主神经功能障碍 iRBD患者早期即存在自主神经功能障碍表现[8],以心血管系统、胃肠道系统和泌尿系统最为常见,主要表现为肾上腺素能神经元和心脏迷走神经功能障碍、性功能障碍、排尿障碍及便秘等[1,10-11]。大多数iRBD患者的自主神经功能障碍介于正常人与帕金森病患者之间,呈轻至中度[10]。一项针对1280例iRBD患者的前瞻性研究结果显示,合并便秘(*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;$P<0.05$)的患者转化为帕金森病的风险较高[1],可能原因为迷走神经背核调控肠道蠕动,帕金森病运动症状出现之前迷走神经背核已经发生路易体相关病变;然而关于勃起功能障碍风险比较高的原因及其机制尚未见诸报道,有待进一步探究。上述研究表明,自主神经功能障碍是iRBD转化为α-突触核蛋白病的预警因素[12]。

4.颜色辨别能力下降 目前针对iRBD患者的颜色辨别能力异常的研究较少。其作为α-突触核蛋白病的非运动症状[1,8,13-14],可通过Farnsworth Munsell 100色相测试进行评估。研究显示,iRBD转化为帕金森病或路易体痴呆前20余年即有可能出现嗅觉减退,转化前10~16年可出现颜色辨别能力下降[8];存在颜色辨别能力下降的iRBD患者发生帕金森病的转化率为74%,而颜色辨别能力正常患者的转化率为30%[13]。Postuma等[1]对iRBD患者进行颜色辨别能力测试,发现此类患者在发病前12.8年即已存在颜色辨别能力下降,这些患者转化为帕金森病或路易体痴呆的风险比为1.690(95%CI:1.010~2.780,$P<0.05$),提示颜色辨别能力下降也可作为预测iRBD的预后标记。

二、神经影像学标志物的预警作用

1.结构性MRI 结构性MRI研究显示,与正常对照者(31例)相比,iRBD患者(27例)不仅顶叶和枕叶皮质厚度较薄,运动皮质、额叶和颞叶皮质亦较薄,并与其运动和非运动症状相对应;在随后3年的随访中,6例(22.22%)转化为α-突触核蛋白病,其额叶、顶叶和枕叶皮质厚度较未转化者(21例)更薄,提示皮质厚度可以作为iRBD转化为α-突触核蛋白病的预警标志物(*HR*=0.784,95%CI:0.640~0.960;$P=0.020$)[15]。黑质后部自由水含量的影像学研究显示,iRBD患者黑质后部自由水含量高于正常对照者,而低于帕金森病患者;后续的纵向队列研究显示,黑质后部自由水含量不仅与疾病种类有关,同时还与病程有关,提示iRBD患者黑质后部自由水含量随病程迁延而增加[16]。

2.多巴胺转运蛋白显像 多巴胺转运蛋白功能可以反映黑质纹状体多巴胺转运功能,iRBD患者的PET和SPECT显像均可见多巴胺摄取率降低、多巴胺转运蛋白功能缺陷,其中^{123}I-FP-CIT SPECT是研究最深入的DAT-SPECT模式。多中心研究显示,与多巴胺转运蛋白功能正常的iRBD患者相比,多巴胺转运蛋白功能障碍患者转化为α-突触核蛋白病的风险更高(*HR*=1.980,95%CI:1.050~3.730;$P<0.05$)[1]。DAT-SPECT显像可预测iRBD患者3年内转化为α-突触核蛋白病的风险,基线期壳核多巴胺摄取率下降的iRBD患者转化为α-突触核蛋白病的3年转化率为20%、基线期壳核多巴胺摄取率正常

的患者仅为6%，且转化者基线期壳核多巴胺摄取率较未转化者降低25%；而帕金森病患者出现运动症状时壳核多巴胺摄取率已降低40%～50%。由此可见，iRBD患者DAT-SPECT壳核多巴胺摄取率降低即提示已存在多巴胺能神经元缺失，但尚未达到运动症状的阈值，故可作为帕金森病的影像学预警标记[17]。iRBD患者的多巴胺转运蛋白显像模式（即多巴胺摄取率）介于帕金森病患者和正常人之间，当iRBD患者多巴胺转运蛋白显像呈类帕金森病模式时，其预测转化为α-突触核蛋白病的风险为58%（*HR*=4.950，95%CI：1.160～21.080；*P*=0.013）；而当多巴胺转运蛋白显像呈类帕金森病模式合并嗅觉减退时，其预测转化为α-突触核蛋白病的风险为67%（*HR*=7.890，95%CI：1.850～33.690；*P*=0.002）[18]。一项纳入263例iRBD患者和243例正常对照者的多中心临床研究显示，有19.77%（52/263）的患者随访2年后转化为α-突触核蛋白病，其危险因素包括壳核多巴胺摄取率降低（*P*<0.000 001）、便秘（*P*<0.000 001）和年龄>70岁（*P*=0.0002），上述危险因素的综合风险比为5.710（95%CI：2.850～11.430，*P*<0.05）[19]。此外，目前尚无足够证据证实静息态fMRI、磁敏感加权成像（SWI）、扩散张量成像（DTI）、动脉自旋标记（ASL）、经颅多普勒超声（TCD）等影像学标志物与iRBD转化为帕金森病有关[20]，有待进一步探究。

三、生物学标志物的预警作用

1.体液和皮肤黏膜组织α-突触核蛋白　帕金森病Braak分期是一项反映α-Syn自脑干逐渐累及皮质过程的指标[12]，异常折叠α-Syn沉积可导致细胞死亡和突触功能障碍，是帕金森病、路易体痴呆、多系统萎缩等α-突触核蛋白病的病理生理学机制，故异常折叠α-Syn沉积在α-突触核蛋白病的发病机制中发挥重要作用[21]。目前研究主要针对脑脊液、血液和周围组织活检中异常折叠α-Syn水平对iRBD转化为α-突触核蛋白病的预测能力，脑脊液异常折叠α-Syn的敏感性和特异性均较高，实时震动诱导转化（RT-QuIC）测定脑脊液异常折叠α-Syn的灵敏度达90%～100%，特异度可达90%～98%[22]，异常折叠α-Syn沉积阳性的患者转化率更高[23]，提示RT-QuIC测定脑脊液异常折叠α-Syn可以作为潜在的iRBD诊断与预后预测的标志物。此外，鼻黏膜异常折叠α-Syn测定亦可作为一种侵入性更低的检测方法，RT-QuIC测定的鼻黏膜异常折叠α-Syn的特异度可达89.8%，但灵敏度仅为45.2%[24]。尽管血浆神经来源外泌体异常折叠α-Syn在帕金森病的早期诊断中具有一定作用，但iRBD患者血浆神经来源外泌体异常折叠α-Syn水平并未升高[25]。横断面研究显示，iRBD患者血浆神经来源外泌体异常折叠α-Syn水平高于正常对照者和多系统萎缩患者，但与帕金森病患者无显著差异，提示血浆神经来源外泌体异常折叠α-Syn可作为α-突触核蛋白病分型诊断的潜在生物学标志物[26]。周围组织活检α-Syn也是近年研究热点，尤其是磷酸化α-Syn。针对帕金森病和路易体痴呆患者的尸检结果显示，磷酸化α-Syn主要沉积于自主神经、肠黏膜和唾液腺[27-28]；但是肠黏膜及其下组织磷酸化α-Syn预测iRBD转化为α-突触核蛋白病的灵敏度仅为24%[29]，下唇内侧唾液腺磷酸化α-Syn预测转化风险的灵敏度为50%[30]。近年来，皮肤组织活检作为侵入性较低且较成熟的活检方法，临床推广度较高[28]，且较肠黏膜和唾液腺活检的接受度高，门诊即可操作。Doppler等[31]采用多点皮肤组织活检术发现，磷酸化α-Syn在iRBD患者中的阳性检出率为56%，在帕金森病早期患者中为80%，而正常对照者未检出磷酸化α-Syn。Antelmi等[32]的研究显示，iRBD患者磷酸化α-Syn的阳性检出率为75%，正常对照者亦未检出磷酸化α-Syn；在该作者的另一项研究中iRBD患者磷酸化α-Syn的阳性检出率更高，约为86.7%，而1型发作性睡病继发RBD的患者则未检出磷酸化α-Syn[33]。Al-Qassabi等[34]对iRBD患者行单点皮肤组织活检发现，磷酸化α-Syn的阳性检出率为82.1%。上述4项研究的综合灵敏度为58%～87%，特异度达100%[35]，提示周围组织活检，特别是皮肤组织活检对iRBD的诊断效能较强。但周围组织磷酸化α-Syn表达变化与iRBD转化率之间的关系至今尚无文献报道。

2.其他生物学标志物　血浆神经丝蛋白轻链（NfL）是神经细胞损伤时释放的神经元细胞骨架蛋白，Wilke等[36]发现，iRBD转化为帕金森病的患者血浆神经丝蛋白轻链年增加率为7.7%，显著高于正常对照者的4.4%（*P*=0.009），提示血浆神经丝蛋白轻链可以作为预测iRBD转化为帕金森病的生物学标志物。亦有研究显示，iRBD转化为α-突触核蛋白病的患者血浆微小RNA-19b（miRNA-19b）水平明显下降，提示血浆miRNA表达变化也可以作为预测iRBD转化为α-突触核蛋白病的生物学标志物[37]。

蛋白质组学分析可以发现多条与iRBD发病相关的蛋白和分子通路，但其对疾病转化的预测价值有待进一步验证[38-39]。

四、基因学的预警作用

IRBD致病基因与帕金森病、路易体痴呆、多系统萎缩均不尽相同，可以说一定程度上拥有自身独特的基因背景[1]。业已证实，帕金森病致病基因如*LRRK2*[40]和*MAPT*[41]以及路易体痴呆致病基因*ApoEε4*单倍型[42]均与iRBD无关联性。有研究显示，*GBA*基因变异既与帕金森病、路易体痴呆、多系统萎缩相关，又与iRBD相关[43]。约10%的iRBD患者存在*GBA*基因变异，携带*GBA*基因变异的帕金森病患者并发可能的RBD的发生率高于不携带*GBA*基因变异患者（*OR* = 3.130，95%CI：1.060 ~ 9.230；*P* = 0.039）[43]。研究显示，在相似病程的RBD患者中，有52%携带*GBA*基因变异的患者转化为α-突触核蛋白病且疾病转化时间更短，而未携带*GBA*基因变异的患者仅有35%发生疾病转化[44]。iRBD、帕金森病与路易体痴呆患者的*SNCA*基因变异位点均不相同，且携带不同*SNCA*基因变异位点的iRBD患者发生疾病转化的时间也不尽一致[45]。研究显示，跨膜蛋白175（TMEM175）编码的p.M393T（*OR* = 1.370，95%CI：1.150 ~ 1.610；*P* = 0.0003）和p.Q65P（*OR* = 0.720，95%CI：0.570 ~ 0.910；*P* = 0.005）均是帕金森病发病的影响因素，同时p.M393T还是iRBD发病的影响因素（*OR* = 1.420，95%CI：1.230 ~ 1.640；*P* < 0.0001）[46]。基因学研究目前尚处于起步阶段，未来尚待更大样本量的队列研究验证；同时可通过全基因组关联分析（GWAS）、多基因风险评分（PRS）和罕见基因变异负荷检验（burden analysis）分析，进一步探讨基因变异与RBD转化的关系。

综上所述，非运动症状、神经影像学标志物、生物学标志物、基因学等研究进展对预测iRBD转化为α-突触核蛋白病起推动作用，但其多模态标志物整合应用的敏感性和特异性尚待进一步提高。未来可以针对上述预警因素对iRBD患者进行早期评估和及时随访，从而探究高风险人群的干预措施，以期实现iRBD转化为α-突触核蛋白病患者的早期诊断与治疗。

利益冲突 无

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·小词典·

中英文对照名词词汇（二）

二甲基亚砜 dimethyl sulfoxide（DMSO）
二喹啉甲酸法 bicinchoninic acid method（BCA）
反义寡核苷酸 antisense oligonucleotide（ASO）
泛酸激酶2 pantothenate kinase 2（PANK2）
泛酸激酶相关神经变性 pantothenate-kinase-associated neurodegeneration（PKAN）
非快速眼动睡眠期 non-rapid eye movement（NREM）
非运动症状 non-motor symptom（NMS）
非运动症状量表 Non-Motor Symptoms Scale（NMSS）
分数低频振幅 fractional amplitude of low-frequency fluctuation（fALFF）
富亮氨酸重复序列激酶2 leucine-rich repeat kinase 2（LRRK2）
富亮氨酸胶质瘤失活基因1 leucine-rich glioma-inactivated 1（LGI1）
改良Rankin量表 modified Rankin Scale（mRS）
甘油醛-3-磷酸脱氢酶 glyceraldehyde-3-phosphate dehydrogenase（GAPDH）
高密度脂蛋白胆固醇 high-density lipoprotein cholesterol（HDL-C）
功能连接 functional connectivity（FC）
孤立性快速眼动睡眠期行为障碍 isolated rapid eye movement sleep behavior disorder（iRBD）
谷氨酸脱羧酶 glutamic acid decarboxylase（GAD）