•综述•

帕金森病亚型及其治疗药物研究进展

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摘要: 帕金森病 (Parkinson's disease, PD) 是一种进行性神经系统退行性疾病, 具有高度的临床异质性, 根据其运动症状将PD患者分为震颤为主型、姿势异常及步态障碍为主型/强直运动不能型和混合型。不同的亚型表现出不同的预后特征, 对药物的敏感性也不同, 因此PD的早期分型对于疾病的治疗和预后具有重要意义。本文回顾了PD不同亚型的临床分型方法, 总结了最新的生化标志物及影像学特征, 就其在发病率、预后症状及病理机制等方面的差异进行综述分析。目前的临床治疗药物和方法已根据分型对PD进行初步针对治疗, 且已有关于不同亚型的动物PD模型研究, 为PD亚型的机制研究和临床前药效学评价提供了新的方法和策略。

关键词: 帕金森病; 亚型; 标志物; 预后; 病理; 治疗

中图分类号: R964 **文献标识码**: A **文章编号**: 0513-4870(2022)08-2245-08

The research advance on subtypes and relevant therapy of Parkinson's disease

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disease with a high clinical heterogeneity. According to its motor symptoms, PD patients are divided into predominant tremor-dominant, postural instability and gait difficulty-dominant/akinetic-rigid and mixed subtypes. Different subtypes show different prognostic characteristics and different sensitivities to drugs. Therefore, the early classification of PD is of great significance for the treatment and prognosis of the disease. This paper reviews the clinical classification methods of different subtypes of PD, summarizes the latest biochemical markers and imaging features, and analyzed the differences in incidence, prognosis and pathological mechanism. The current clinical treatment drugs and methods have been preliminarily targeted for treatment based on PD classification, and there are many animal models of PD subtypes have been studied, providing new methods and strategies for mechanism research and preclinical pharmacodynamics evaluation of PD subtypes.

Key words: Parkinson's disease; subtype; biomarker; prognosis; pathology; therapy

帕金森病 (Parkinson's disease, PD) 是最常见的与年龄相关的神经退行性疾病之一, 在60岁以上人群中患病率高达1%, 据估计, 2016年全球约有610万人被诊断患有帕金森病, 比1990年高出2.4倍[1]。PD在临床上主要表现出静息性震颤、肌强直、运动迟缓和姿势反射丧失等运动症状, 以及睡眠障碍、认知障碍、自主神经功能障碍等非运动症状。

PD作为中老年人常见的运动障碍性疾病具有高

收稿日期: 2022-03-28; 修回日期: 2022-04-26.
基金项目: 国家自然科学基金资助项目 (82141204); 中国医学科学院医学与健康科技创新工程项目 (2021-I2M-1-005).
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DOI: 10.16438/j.0513-4870.2022-0355

度临床异质性, 其表型的表达也随病程变化。Alonso等[2]于1986年将这种异质性进行归类, 并概括为PD亚型, 为PD亚型的研究奠定了基础。根据临床症状的不同, 将PD分为震颤为主型 (tremor-dominant, TD)、姿势异常及步态障碍为主型 (postural instability and gait difficulty-dominant, PIGD)/强直运动不能型 (akinetic-rigid, AR) 和混合型 (mixed, MIX) 3种亚型, 目前这种症状分型的标准已得到国际同行的共识。

不同亚型PD患者运动症状差异的原因、预后的区别及接受药物治疗后的反应尚未有较为全面的报道, 就此, 本文总结了PD运动分型的化学生物标志物和结构影像学特征等辅助诊断方法, 就PD亚型发病现状、预后规律、病理机制、动物模型及治疗药物和方法进行综述, 旨在进一步提高对PD亚型发病机制的理解, 为完善PD运动分型诊断标准及药物的研发提供研究理论基础, 对减缓疾病进展, 提高PD患者生活质量具有重要意义。

1 PD亚型分型标准及标志物

1.1 临床PD运动分型方法

1990年, Jankovic等[3]将800名未经治疗的早期PD患者进行异质性归类后, 首次提出了亚型的分型方法。临床上有两种常用的PD评定量表, 其中帕金森病评定量表 (unified Parkinson disease rating scale, UPDRS) 从心理情绪、日常生活活动、运动症状及并发症4个方面对PD患者进行全面的评定, 而MDS-统一帕金森病评分量表 (movement disorder UPDRS, MDS-UPDRS) 是2008年发布的修订版本, 旨在解决UPDRS的局限性。临床研究根据这两种量表第II和第III部分中的TD类项目和PIGD类项目对PD患者进行打分, 根据分数将其分为TD型、PIGD型和MIX型: 若使用UDPRS评分时, 当TD类项目评分/PIGD类项目总分 ⩾ 1.15时, 判定为TD型, 当比值 ⩽ 1时, 判定为PIGD型, 评分在这之间的判定为MIX型; 若使用MDS-UPDRS评分时, 则是将比值 ⩽ 0.90的受试者判定为PIGD型。此方法又被称为经典运动分型法。

此外, 还有一种在经典分型法基础上发展而来的运动分型法, 主要根据专家经验或UPDRS中震颤及异常不自主运动症状评分, 将PD分为TD型、AR型和MIX型。两种方法相比, 经典分型法更为严格, 对亚型的定义也更准确, 因具有良好的灵敏度和特异性, 一直得到广泛的认可和应用。

1.2 PD亚型诊断标志物

相较于TD型, PIGD/AR型的患者往往病程进展更快、预后较前者差, 而TD型的治疗效果更差, 因此PD分型的早期诊断对于疾病的治疗尤为重要。然而PD亚型的诊断严重依赖于运动症状的临床检查, PD患者复杂的临床表型和疾病进程突显了对诊断标志物的需求。

1.2.1 神经递质 神经递质通过传递各种信息从而调节机体生理功能, 乙酰胆碱 (acetylcholine, ACh) 和多巴胺 (dopamine, DA) 两种神经递质的失衡也是PD发病机制之一。研究发现, PIGD型PD患者血浆内ACh水平显著高于其他亚型, 其水平可作为PIGD型PD发生的独立危险因素, 5-羟色胺 (5-hydroxytryptamine, 5-HT) 水平则低于TD组, 而DA、高香草酸等其他单胺类递质浓度在PD亚型之间没有显著差异[4]。

1.2.2 神经退行性蛋白 神经轴突丢失是神经系统疾病永久性残疾的病理基础。神经纤维丝轻链 (neurofilament light chain, NfL) 是PD严重程度的潜在生物标志物, 研究发现, PIGD型PD患者中的NfL显著高于TD型, 较高的NfL与整体认知与UPDRS运动评分显著相关, 可作为PIGD的诊断和预后生物标志物[5]。Ding等[6]发现, PD患者血浆中Aβ-42水平和α-syn含量与PIGD评分显著线性相关 (P = 0.000 2, P = 0.005), 较低的Aβ-42和较高的α-syn含量可作为PD亚型诊断的标志物, 而另外两种神经退行性蛋白Tau和p-Tau181在PD亚型之间没有显著差异。

1.2.3 尿酸、胆红素和血脂水平 研究发现, 人体内的一些天然抗氧化物对中枢神经系统具有良好的保护作用, 其在PD患者血清内的变化可作为PD亚型的诊断标准。如PD患者血清内尿酸 (uric acid, UA) 水平降低, 其中MIX型UA浓度最低, 而TD和PIGD亚型之间则没有显著差异[7], 但也有研究提出[8,9], PIGD型PD患者血清内UA水平明显低于TD型。另外, PIGD亚型的间接胆红素和高密度胆固醇水平较TD型也有更显著的下降[10], 因此也可作为亚型诊断的潜在生物标志物。

1.3 结构和影像学

影像学检测可快速无创地检测PD患者脑内各项指标, 成为寻找疾病特征性影像标志物的新型技术手段。磁共振成像 (magnetic resonance imaging, MRI) 具有高时空分辨率、无创、无辐射的特点, 并可根据目的需求选择不同的MRI序列。表1[11-29]从功能、结构和代谢3个方面总结了文献报道用于检测PD亚型的MRI技术、影像学标志物及其在不同亚型间的区别。

如表1所示, 与TD型相比, 在结构方面, PIGD型PD患者脑区结构损伤更严重、体积减小更显著; 在功能方面, TD型PD患者在小脑−丘脑−皮质 (cerebellum-thalamus-cortex, CTC) 环路中表现出更多改变, 而PIGD型患者的功能改变主要涉及纹状体−丘脑−皮质 (striatum-thalamus-cortex, STC) 环路; 在代谢方面, 两

Table 1 Potential markers of magnetic resonance imaging (MRI) by Parkinson's disease (PD) subtypes. ↑: Increase significantly; ↓: Decrease significantly; PIGD: Postural instability and gait difficulty-dominant; TD: Tremor-dominant; VBM: Voxel-based morphometry; GM: Grey matter; DTI: Diffusion tensor imaging; FA: Fractional anisotropy; T1: T1-weighted magnetic resonance imaging; BOLD-fMRI: Blood oxygenation level dependent-functional MRI; ALFF: Amplitude of low frequency fluctuation; ReHo: Regional homogeneity; FC: Functional connectivity; VMHC: Voxel-mirrored homotopic correlation; FCD: Functional connectivity density; ICA: Independent component analysis; T2*: T2* relaxation time; ESWAN: Enhanced gradient echo T2*-weighted angiography; SWI: Susceptibility-weighted phase imaging; NM-MRI: Neuromelanin-sensitive MRI; NM: Neuromelanin; MRS: MR spectroscopy; NAA: *N*-Acetyl aspartic acid; Cr: Creatine; GABA: *γ*-Aminobutyric acid; MEGA-PRESS: MEscher-GArwood Point Resolved Spectroscopy; -: Nothing

Term	Technology	Index	PIGD-PD (compared with TD-PD)	TD-PD (compared with PIGD-PD)	Ref.
Structure	VBM	GM	Areas involving motor, cognitive, limbic, and associative functions: GM ↓	-	[11]
	DTI	FA	Frontal part of the medial and lateral NBM-WM tract of both hemispheres: FA ↓	-	[12,13]
	T1	-	Hippocampal subfield: volume ↓; right ventromedial nucleus: volume ↑; right parafascicular nucleus: volume ↓	-	[14,15]
Function	BOLD-fMRI	ALFF	-	Bilateral putamen and cerebellar posterior lobe: ALFF ↑; bilateral temporal gyrus and left superior parietal lobule: ALFF ↓	[16]
		ReHo	-	Left temporal lobe, left cerebellum, bilateral middle cingulate gyrus: ReHo ↑; left paracentral lobule, bilateral wedges, right superior frontal gyrus, right anterior cingulate gyrus: ReHo ↓	[17,18]
		FC	Right insular cortex and bilateral anterior cingulate cortex: FC ↓	The basal ganglia and the cortex around the talar fissure: FC ↑	[19,20]
		VMHC	-	Cerebellum posterior lobe: VMHC ↓	[21]
		FCD	-	Cerebellum globa: FCD ↑; bilateral frontal lobe: FCD ↓	[22]
		ICA	Occipital lobule and cerebellum posterior lobule and basal ganglia: ICA ↓	-	[23]
Metabolism	ESWAN	T2*	Putamen and thalamus: iron deposition ↑	-	[24]
	SWI	-	Globus pallidus: iron content ↑	-	[25]
	NM-MRI	NM	Lateral SN, medial SNc: NM ↓	-	[26,27]
	MRS	-	-	Bilateral putamen: NAA/Cr ↑	[28]
	MEGA-PRESS	GABA	-	Left basal ganglia region: GABA ↓	[29]

种亚型PD患者脑内的铁沉积、神经黑色素及各种代谢物存在显著差异, 对于疾病的诊断和机制研究具有重要意义。

1.4 PD亚型发病现状

一项纵向研究表明[30], 无论患者治疗状况如何, 初始评估时的运动基线数据可准确预测85%病例亚型, 因此早期的亚型诊断可靠性较强。为了进一步总结PD亚型的发病现状及规律, 该研究共纳入了26项临床PD亚型相关研究, 纳入标准包括: 在首次诊断时确定为原发性PD; PD患者为某医院或机构在一段时间内接收的PD患者, 排除针对性招募试验; 研究均根据UPDRS或MDS-UPDRS相关评分进行分类, 分组为PIGD/AR组、TD组 (及MIX组)。

本文将分组为PIGD/AR型、TD型与PIGD/AR型、TD型、MIX型的两种研究的人数进行统计。结果发现, 在纳入的研究中, 在基线时被诊断为PIGD型或TD型的患者人数较高且相似, 而MIX型PD患者人数则相对较少。但是一项20年的随访中发现, 随着疾病的进展, TD的比例逐渐下降, 而PIGD的比例增加[31], 因此也为PD亚型发病率的统计和预测提供了难度。统计结果分别如表2[5,6,8,14,16,32-39]、表3[7,30,40-48]所示。

2 不同亚型PD患者预后

正如研究者所观察到的, PIGD/AR亚型的运动症状和认知功能下降更为迅速[49], TD型PD患者预后相对较好, 生活质量高于MIX型和PIGD/AR型患者。运动和非运动预后症状对日常生活活动和生活质量都有

Table 2 The incidence of PD subtypes including PIGD/akinetic-rigid (AR) and TD

Statistics	Number of patients		Ref.
	PIGD/AR	TD	
	42	123	[32]
	37	36	[6]
	20	30	[8]
	27	31	[14]
	46	30	[5]
	10	14	[33]
	35	30	[34]
	47	36	[35]
	72	30	[36]
	59	63	[37]
	64	26	[38]
	39	45	[39]
	19	12	[16]
Total number	517	506	
Percentage	50.5%	49.6%	

Table 3 The incidence of PD subtypes including PIGD/AR, TD and mixed (MIX)

Statistics	Number of patients			Ref.
	PIGD/AR	TD	MIX	
	43	13	110	[40]
	11	51	63	[7]
	39	11	106	[30]
	55	14	21	[41]
	234	157	45	[42]
	47	66	19	[43]
	39	22	7	[44]
	32	76	8	[45]
	47	38	43	[46]
	21	26	29	[47]
	188	108	88	[48]
Total number	756	582	539	
Percentage	40.3%	31.0%	28.7%	

重大影响, 更好地了解PD亚型不同特征的影响有助于为PD患者设计更合适的治疗方法。

2.1 PD患者运动症状预后

与TD型PD患者相比, 以姿势不稳和步态困难为主的PD患者可能会遇到独特的认知困难, PIGD患者在无障碍行走和避障的客观测量中表现更差[38], 跌倒的风险也更高[50], 对强运动冲动作用表现出更高的敏感性[51]。在早中期原发性PD患者中, PIGD亚型较TD亚型静态平衡功能下降也更为明显[52]。

2.2 PD患者非运动症状预后

相比于TD型, PIGD/AR型患者的运动量减轻, 社会活动减少, 更易出现心理、精神及情绪方面的变化, 导致更多的非运动症状出现及加重, 对患者的日常生活影响也更大。

PD中的轻度认知障碍是一种常见的认知状态, 患病率高达40%[53], 现有研究认为, PIGD/AR型PD患者更有可能患认知障碍[54]。有研究进一步通过线性混合模型进行评估, 发现PIGD型患者在帕金森认知评估量表上表现出更快的进展[55], 蒙特利尔认知评估量表总分、延迟记忆及定向的评分也均低于TD组, 因此PIGD/AR型PD患者痴呆症的发病率显著高于TD型[33]。

研究发现[37], 睡眠障碍与临床亚型之间也存在显著关系, PIGD型PD患者整体睡眠质量较差, 易出现睡眠障碍和疲劳, 主要表现为夜间睡眠差、入睡困难、难以维持睡眠、夜尿多且夜间肢体痉挛疼痛, 且非震颤型患者抑郁发生率更高, 症状更严重。但也有研究发现, 在未接受过药物治疗的患者中, PD亚型与精神症状没有相关性, 因此在疾病进展后期出现的认知障碍可能是药物导致的神经元损伤增加的结果[39]。

前瞻记忆 (prospective memory, PM) 被定义为对未来意图的记忆, 据报道[56], 相对于PIGD型, TD型PD患者在基于时间的PM能力上具有选择性缺陷, 并因此可能会影响该亚型的功能自主性。另外, PIGD型患者嗅觉功能衰退更为明显[34], 且具有更明显的血压生物节律调节异常[57], 自主神经调节功能障碍程度也较TD及混合型更为严重[58], 但在发声、韵律和流利度等方面的语音特征[59], 焦虑[60]及便秘的严重程度在PD亚型之间没有明显差异。这些非运动症状与生活质量有显著相关性, 及时识别和治疗这些非运动症状可能会改善PD患者的生活质量。

3 不同亚型PD病理机制研究

PD亚型在运动和认知功能等病程进展中存在明显差异, 推测PD亚型之间可能存在不同的神经病理机制。近年来, PD亚型之间的脑结构与功能的改变及机制研究已逐渐成为研究的焦点。

研究发现, PIGD/AR型PD患者皮质内路易小体平均病理分级显著高于其他亚型, 皮质淀粉样蛋白-β斑块负荷和脑路易体病变更为严重[61,62], 双侧海马体积显著减小[14], 这也可能是该亚型更容易出现认知障碍或痴呆症的原因。也有研究者认为, PD各亚型皮质下/皮质通路的退化是不同的, 无论行走状况如何, PIGD型PD患者的前额叶皮层活性均高于TD型[63]。

不同的临床亚型可能存在不同的铁沉积模式。研究发现[25,64], 与MIX型相比, PIGD型患者在红核、黑质网状部、壳核、苍白球异常铁沉积较多, 在丘脑铁沉积较少; 与TD型相比, PIGD型PD患者仅在丘脑铁沉积较多; 而TD型PD患者较MIX型PD患者相比在黑质网状部、壳核有较多的铁沉积。这些数据表明, 铁沉积的分布对于PD患者的表型表达具有重要意义。

另有学者认为脑内*N*-乙酰基天门冬氨酸 (*N*-acetyl aspartic acid, NAA)、肌酸 (creatine, Cr)、胆碱复合物 (choline containing compounds, Cho)、γ-氨基

丁酸 (γ-aminobutyric acid, GABA) 等代谢物水平的变化也是PD异质性的病理机制之一。NAA是正常神经元的标志物, 神经元线粒体功能障碍导致NAA浓度减低, 在炎症介导的神经变性中, 活化的T淋巴细胞不断浸润, 激活小胶质细胞, 细胞膜结构被破坏更新, 从而导致Cho水平增加, 因此PD患者脑内NAA/Cho比值显著降低, 表明PD患者运动回路神经元存在功能障碍, 且在PIGD组中运动功能损伤更为严重。另外, PD患者左侧基底神经节区GABA浓度下降, TD组较PIGD组减低程度更为显著[29], 这些差异的出现也提示TD和PIGD亚型之间神经病理学改变严重程度和进展具有异质性。

最近研究发现[65], 肠道微生物也可能与PD发病机制有关, 通过检测PD患者粪便样本中的肠道微生物群, 发现与TD型相关的细菌物种具有更高的多样性和丰富度。这些研究也为PD异质性病理机制提供了新的思路。

4 PD分型研究的动物模型

多项研究已证明, PD在临床表现出高度的异质性, 不同药物对PD患者的药效也存在不一致性, 因此PD亚型分子生物学机制及药物前期的药效学评价极为重要, 而在动物水平进行PD分型是临床前研究的一种重要方式。现研究中常用的PD动物模型主要包括: 6-羟基多巴胺 (6-hydroxydopamine hydrobromide, 6-OHDA)、1-甲基-4-苯基-1,2,3,6-四氢吡啶 (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP) 及鱼藤酮等神经毒素诱导的PD模型, 脂多糖诱导PD模型, 转基因和基因敲除PD模型等。随着研究的深入, 在动物水平上的分型研究也越来越多, Salamone等[66]和Ishiwari等[67]曾先后提出, DA耗竭或拟胆碱药诱导的大鼠非定向咀嚼样运动可模拟帕金森样震颤, 是一种TD型PD模型。本实验室研究发现[68], 6-OHDA制备的大鼠PD模型不仅出现运动障碍, 还会产生明显的肌肉震颤症状, 与人类PD的静止性震颤症状表现相似, 通过肌电 (electromyogram, EMG) 检测大鼠的震颤水平, 结合大鼠旋转行为所模拟的强直-运动不能症状, 首次在动物水平上进行PD分型, 将6-OHDA损伤大鼠分为有旋转无震颤组、有震颤无旋转组和既有震颤又有旋转组3大类型, 从而模拟临床不同的PD亚型。本实验室在后续的多项研究中对百可利减轻PD震颤症状的评价均是对PD进行分型后的结果[69,70], 这也是PD运动分型迈向临床前研究的重要一步。

5 不同亚型PD治疗药物及方法

目前临床上有多种可有效改善PD的药物, 每类药物都有自己的优劣势和治疗特点。根据第四版中国帕金森病治疗指南, 震颤为主的早发型PD患者建议服用抗胆碱能类药物和多巴胺受体激动类药物, 强直为主型PD患者则建议先服用金刚烷胺或B型单胺氧化酶抑制剂, 如需进一步获益则加用复方左旋多巴。

药物治疗是PD治疗方法和手段的首选, 但是长期服用这些药物可能会出现药效下降, 并导致认知功能下降、瓣膜病变、异动症等不良反应。康复与运动疗法对PD步态障碍、姿势平衡障碍有一定的改善作用, 可辅助药物治疗, 延缓病程进展。

低频重复经颅磁刺激 (repetitively transcranial magnetic stimulation, rTMS) 能持续增加或降低皮质脊髓的兴奋性, 对运动功能障碍的改善均有益。研究表明[45], 低频rTMS在PIGD型和MIX型PD中疗效更显著, 有利于改善患者的运动症状, 但对TD型PD的效果不明显。与rTMS从大脑外部予以刺激不同, 深部脑刺激 (deep brain stimulation, DBS) 是将两根电极精确植入PD相关脑区, 因此, 刺激靶点的选择对DBS的治疗效果相当重要。有研究发现[71,72], 苍白球内侧部 (internal globus pallidus, GPi) 和丘脑底核 (subthalamic nucleus, STN) DBS治疗后, PD患者UPDRS III评分均得到显著提高, 且TD型PD患者的震颤症状改善更大, 但GPi深部刺激产生的步态反应可能更大, 因此对PIGD患者的治疗效果较差。

近年来, 采用中药及天然产物治疗PD的尝试越来越多。镇颤舒胶囊是由黄芪、川芎、葛根等10种中药组成的药方, 对早期TD型PD较PIGD型有更好的疗效[42]。本实验室筛选得到的天然黄酮类化合物黄芩素 (百可利), 具有抗炎、抗氧化等多种药理学作用, 在MPTP和鱼藤酮诱导的多种经典PD动物模型中表现出较好的神经保护和抗抑郁样作用, 其中在6-OHDA制备的不同类型的帕金森样大鼠中, 百可利可通过抑制多巴胺神经元凋亡, 减少神经炎症, 清除自由基及调节神经递质等方面显著抑制大鼠自主运动障碍和震颤幅度。通过多方面的临床前实验, 百可利表现出较好的应用前景, 可能是预防和治疗帕金森病的有效药物[69,70,73,74]。

6 总结与展望

既往研究表明TD型PD患者预后相对较好, 常为良性病程, 且震颤型患者生活质量高于非震颤型患者, 而PIGD型患者在行走避障、情绪/认知、睡眠/疲劳、记忆、嗅觉、心血管症状等的障碍方面较TD型患者更严重。了解这种预后与亚型的关联性, 对患者管理和病情预测具有重要临床意义。因此, 为了更准确的进行PD亚型分类, 在临床症状观察基础上, 本文总结了血清的生物标志物和结构的影像标志物, 也为PD亚型的

病理机制探讨和早期诊断提供思路和策略。

目前针对帕金森发病机制及治疗的研究较多, 但大多是将PD患者作为一个整体来对待。然而, 由于PD发病机制的异质性, PD患者表现出不同的临床症状和预后特征, 因此为了提高药物的有效性, 在后续研发中, 应不断深入探究导致PD亚型的关键性分子机制变化及功能改变, 增加不同PD亚型的临床药效学评价以及药物开发, 从而减缓疾病进展, 提高患者生活质量。

作者贡献: 孔德文撰写了大部分文章; 杜立达、蒋楠撰写了文章部分内容; 杨海光完成了部分表格制作和文章修改; 方莲花和杜冠华指导了综述的框架设计并修改了文章。

利益冲突: 所有作者声明不存在利益冲突关系。

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