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# 学者介绍



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## 综述

## 多系统萎缩生物标志物的研究进展

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**[摘要]** 多系统萎缩是以自主神经、锥体外系、锥体束等多系统受累为特点的一种帕金森综合征, 对左旋多巴反应不佳。该病临床诊断难度大, 多数生物标志物特异度和敏感度均不高。因此, 有研究建议将多项指标结合应用以提高诊断的准确度。除体液中的生物化学标志物外, 影像学、病理学等生物标志物的相关研究也取得了一定进展。该文综述近年来多系统萎缩生物标志物的研究进展, 包括血液和脑脊液中的蛋白和 miRNA, 以及影像学特征和外周组织中的  $\alpha$ -突触核蛋白沉积。

**[关键词]** 多系统萎缩; 生物标志物; 神经影像

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## Progress in biomarkers of multiple system atrophy

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**[Abstract]** Multiple system atrophy is a neurodegenerative disease, which is characterized by a combination of autonomic failure, Parkinsonian features, pyramidal and cerebellar dysfunction, and is poorly reactive to levodopa. Few biomarkers with high sensitivity or specificity have been applicable in the diagnosis of multiple system atrophy, making it a challenge to correctly diagnose this disease. Therefore, some researches combined several biomarkers to improve the diagnosis accuracy. Apart from those in body fluid, progress has been made in new biomarkers of neuroimaging and pathology. In this review, the advances in the identification of biomarkers of multiple system atrophy are summarized, and some candidate biomarkers that worth more investigation, including proteins and miRNAs in blood or cerebrospinal fluid, parameters in molecular and functional imaging, and pathologic features of peripheral tissue are described.

**[Key words]** multiple system atrophy (MSA); biomarker; neuroimaging

多系统萎缩 (multiple system atrophy, MSA) 是以自主神经、锥体外系、锥体束等多系统受累为主要病理特征, 且对左旋多巴治疗反应不佳的一种帕金森综合征。目前, MSA 的诊断共识将其分为“确诊”“很可能”和“可能”3个等级。确诊 MSA 需依据病理诊断<sup>[1]</sup>。MSA 可根据临床症状分为以帕金森综合征为主要表现的 MSA-P 型和以小脑性共济失调为主要表现的 MSA-C 型<sup>[1]</sup>。少突胶质细胞中的一个类型——嗜银性胶质细胞, 其细胞质包涵体 (glial cytoplasmic inclusion, GCI) 是 MSA 的病理特征<sup>[2]</sup>。因此 MSA 的神经病理确诊标准为与大量广泛分布的 GCI 密切相关的黑质-纹状体或橄榄-脑桥-小脑退行性病变<sup>[3]</sup>。目前 MSA 无有效治疗方法, 临床上主要对症治疗, 改善患者生活质量。

MSA 临床症状异质性强, 与其他  $\alpha$ -突触核蛋白相关

疾病及 tau 蛋白相关疾病常有类似临床特征, 且缺乏特异度高的生物标志物。患者生前确诊难度大, 多依据临床表现进行诊断。一项研究<sup>[4]</sup>显示, 临床诊断为 MSA 的 134 例患者中, 尸检结果确诊者仅占 62%。因此, 高敏感度和特异度的生物标志物对 MSA 的诊断、预后以及临床试验中的疗效评估都极为重要。本文总结近年来 MSA 生物标志物的研究进展。

## 1 体液生物标志物

MSA 体液标志物包括血清和脑脊液中的  $\alpha$ -突触核蛋白、DJ-1、tau 蛋白、儿茶酚胺及其代谢产物、细胞因子、miRNA 等; 但研究结果并不完全一致, 对 MSA 的临床诊断意义也并不明确<sup>[5]</sup>。

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## 1.1 蛋白质

对于 MSA 患者脑脊液中总  $\alpha$ -突触核蛋白含量是否降低, 各研究结论不一致。仅有 1 项研究<sup>[6]</sup>显示, MSA 患者与帕金森病 (Parkinson's disease, PD) 患者脑脊液中总  $\alpha$ -突触核蛋白含量存在差异; 因此, 将脑脊液中总  $\alpha$ -突触核蛋白含量作为 2 种疾病鉴别诊断依据尚不充分。MSA 患者脑脊液及血清中神经丝蛋白轻链 (neurofilament light chain, NF-L) 较健康者及 PD 患者均有明显升高<sup>[7]</sup>, 脑脊液中神经丝蛋白重链 (neurofilament heavy chain, NF-H) 较健康者及 PD 患者也有显著升高<sup>[6]</sup>, 有一定的临床应用价值。

另外, 需要指出的是体液单个生物标志物的特异度及敏感度均较低, 2 种及以上的标志物相结合可提高疾病诊断和鉴别诊断的特异度或敏感度。如将脑脊液中 DJ-1 和总 tau 蛋白相结合, 鉴别 MSA 和 PD 的敏感度 (82%) 和特异度 (81%) 均较高<sup>[8]</sup>, 但还需要大样本量的临床验证。

## 1.2 RNA

miRNA 是由 20 ~ 25 个核苷酸组成的单链非编码 RNA, 参与调节许多生理过程<sup>[9]</sup>。多种生物样本中 miRNA 都较稳定, 如血清、血浆、唾液和脑脊液等。因此, 近年有许多关于诊断 MSA 及鉴别 PD 和 MSA 的生物标志物的研究聚焦于体液标本中的 miRNA, 证明了组间表达的差异, 且显示了一些 miRNA 在中枢神经系统中高表达, 参与了细胞凋亡的调节、基因转录后的修饰、神经炎症过程等<sup>[10]</sup>。

一项研究<sup>[11]</sup>显示, 与健康对照相比, MSA 患者血浆中 miR-30c-5p 表达明显上调, 且其表达水平与病程长短相关, 用于 MSA 患者和健康对照的鉴别准确度较高 (敏感度为 80%, 特异度为 90%), 用于鉴别 MSA 与 PD 的敏感度为 82%, 特异度则较低 (54%)。该研究团队还发现: 与健康对照相比, MSA 患者血浆中 miR-24、miR-148b、miR-223<sup>\*</sup>、miR-324-3p 表达上调, miR-339-5p 表达下降; 与 PD 患者相比, MSA 患者血浆中 miR-148b 表达上调<sup>[12]</sup>。除血浆中 miRNA 表达变化外, 2017 年一项研究<sup>[13]</sup>报道, 脑脊液中 miR-34a、miR-34b 和 miR-34c 在 MSA 患者与健康对照间有差异, 在 MSA 患者中表达偏低。有些 miRNA 还可能与 MSA 不同类型相关。miR-24 和 miR-148b 与 MSA 中小脑共济失调症状具有相关性, 提示这些 miRNA 参与 MSA 的小脑退行性变<sup>[13]</sup>。

单个 miRNA 用于鉴别 PD 与 MSA 或诊断 MSA 时, 敏感度及特异度均不高, 联合多种 miRNA 可能提高诊断的准确性。脑脊液中 miR-133b 和 miR-148b 联合应用, 可

较好地地区分 PD 和 MSA<sup>[13]</sup>。研究<sup>[14]</sup>表明: 脑脊液中 3 种 miRNA 联合检测可有效区分  $\alpha$ -突触核蛋白相关疾病与健康对照; 其中 miR-7-5p、miR-34c-3p 和 miR-let-7b-5p 可区分 MSA 与健康对照, miR-9-3p 和 miR-106b-5p 联合检测可鉴别 MSA 与 PD。

体液中 miRNA 应用于 MSA 的诊断有一定前景, 但目前仍有许多局限性: 尚无统一的内源性对照 miRNA 用于标准量化 miRNA; 脑脊液 miRNA 含量较低, 不同样本处理方法可造成 miRNA 定量差异较大; 既往研究样本数量有限, 从而影响结论的可靠性。因此, 还需大样本队列研究探索 miRNA 在 MSA 诊断和鉴别诊断中的应用。

## 2 神经影像学标志物

### 2.1 磁共振成像

MSA 结构磁共振成像 (magnetic resonance imaging, MRI) 中灰质的萎缩不仅常用于鉴别 MSA 和其他神经退行性病变, 如原发性 PD、路易体痴呆 (dementia with Lewy bodies, DLB)、进行性核上性麻痹 (progressive supranuclear palsy, PSP)、皮质基底节变性等, 还可用于鉴别 MSA 中 P 型及 C 型。十字面包征和壳核裂隙征都是经典 MSA 征象。十字面包征即 T2 加权相中脑桥可见高信号十字交叉, 该征提示脑桥及脑桥小脑束退行性病变, 但皮质脊髓束正常; 壳核裂隙征指 T2 加权相中壳核外缘可见高信号。两者诊断 MSA 的特异度较高, 但敏感度偏低<sup>[15]</sup>。此外, MSA-P 中还可可见壳核的萎缩和低信号, MSA-C 中可见脑干、小脑萎缩及小脑中脚 (middle cerebellar peduncle, MCP) 的高信号<sup>[16]</sup>。多数 MSA 患者在疾病不同阶段都可见上述多个征象<sup>[17]</sup>, 将多个征象相结合用于鉴别 MSA 和 PD 的敏感度及特异度明显升高<sup>[18]</sup>。

具体量化上述结构变化也可以有效提高诊断的准确度, 如测量 MCP 宽度以量化 MCP 萎缩程度, 当矢状位 MCP 宽度 < 8 mm 可鉴别 MSA 和原发性 PD, 敏感度及特异度均可达到 100%<sup>[19]</sup>。有研究采用了更加准确测量横断面灰质萎缩的方法, 包括人工或半自动感兴趣区域 (region of interest, ROI) 体积分析及基于体素的形态学全脑分析 (voxel-based morphometry, VBM)<sup>[20]</sup>。以上定量方法可准确反映 MSA 患者幕上、幕下部分脑区的萎缩程度<sup>[21-22]</sup>; 但鉴别早期 MSA-P 和原发性 PD (病程 < 3 年) 时, VBM 准确程度不佳<sup>[23]</sup>。另外, 萎缩率是评价疾病进程的重要指标<sup>[24]</sup>。目前, 2 项纵向研究分析 MSA 患者全脑萎缩率 (whole-brain atrophy rate, WBAR)<sup>[25-26]</sup>, 发现早期 MSA 患者比原发性 PD 患者 WBAR 更高, 该指标可



应用于监测疾病进展程度,较临床评分更为客观,但需要更大样本和更长随访时间验证。

除了常规的MRI序列,某些MRI特殊序列对MSA诊断和鉴别也有重要意义,如弥散加权成像(diffusion weighted imaging, DWI)中,MSA患者壳核信号较PD患者增加<sup>[27-28]</sup>。一项纵向研究<sup>[29]</sup>显示,壳核、脑桥、小脑白质DWI信号变化与MSA病程、疾病严重程度相关。由于MSA壳核、纹状体、黑质中铁沉积增加,磁敏感加权成像(susceptibility weighted imaging, SWI)可显示其与原发性PD、PSP相比,MSA-P在壳核和苍白球有更多的铁沉积<sup>[30-31]</sup>。以磁化传递成像(magnetization transfer imaging, MTI)计算特定ROI的磁化传递率(magnetization transfer ratio, MTR),结果表明MSA患者苍白球、壳核、黑质的MTR较原发性PD患者降低<sup>[32]</sup>。另外,磁敏感定量成像技术(quantitative susceptibility mapping, QSM)等也可应用于MSA的诊断<sup>[33-37]</sup>;但由于样本量小,结论并不一致。

## 2.2 MRI 功能成像

近年来将功能MRI应用于鉴别 $\alpha$ -突触核蛋白相关疾病成为新的发展方向。多项研究<sup>[38-39]</sup>利用弥散张量成像(diffusion tensor imaging, DTI)评估MSA患者白质传导束变化,结果发现与原发性PD患者相比,MSA患者小脑、苍白球部分各向异性(fractional anisotropy, FA)减小,平均扩散率(mean diffusion, MD)增大。有研究<sup>[40]</sup>显示MSA中主要受影响的神经网络为默认模式网络及感觉运动网络。功能影像也可应用于MSA经颅磁刺激治疗后的疗效评价,功能网络中的变化可能与患者的运动症状改善有一定相关性<sup>[41]</sup>。

## 2.3 分子核素显像

正电子发射型计算机断层显像(positron emission tomography, PET)可反映脑区某些物质代谢过程,也可用于MSA诊断和鉴别<sup>[42]</sup>。如<sup>18</sup>F-FDG-PET显示MSA患者壳核、脑干、小脑的葡萄糖代谢降低;<sup>18</sup>F-多巴及<sup>11</sup>C-DTBZ(dihydrotetrabenazine)作配体的PET则显示MSA患者尾状核、壳核等区域的多巴胺摄取减少;<sup>11</sup>C-PMP-PET可见MSA-P皮层和皮层下乙酰胆碱酯酶活性降低;<sup>11</sup>C-PK11195-PET可见MSA中背外侧前额叶皮质、尾状核、壳核、苍白球等处小胶质细胞活化。但上述只是现象的观察,还需要更多的纵向研究结果验证。Tau-PET虽可用于鉴别tau蛋白相关的PD综合征和MSA,但有严重细胞质内包涵体病变的MSA患者可呈现假阳性。

有关于<sup>18</sup>F-AV-1451 PET<sup>[43]</sup>和<sup>11</sup>C-PBB3 PET的研究<sup>[44]</sup>显示,MSA患者后壳核、皮层及皮层下有tau蛋白明显沉积,致使鉴别诊断效能下降。

目前,国际运动障碍协会PD诊断指南中已将间碘苄胍(metaiodobenzylguanidine, MIBG)心肌显像用于鉴别PD和其他综合征<sup>[45-47]</sup>。PD与MSA心肌MIBG摄取有显著差异<sup>[46, 48-49]</sup>。与PD相比,部分MSA患者心肌MIBG摄取轻度降低,与健康对照差异并不显著;但该变化与MSA病程和严重程度并无明确相关性<sup>[50-52]</sup>,其对MSA确诊作用有限,只可用于与PD的鉴别。

综上所述,除一些直观的MRI特殊征象外,MSA患者脑部结构改变的具体量化及反映脑部生物化学指标代谢改变的分子显像将是未来的发展趋势。

## 3 组织活检的病理标志物

$\alpha$ -突触核蛋白相关疾病的病理特征为 $\alpha$ -突触核蛋白在神经元、神经胶质细胞的异常聚集;原发性PD、DLB以神经元累及为主,而MSA以神经胶质细胞受累为主<sup>[53]</sup>。越来越多的证据表明 $\alpha$ -突触核蛋白相关疾病中,多种外周组织中也存在 $\alpha$ -突触核蛋白的异常聚集,包括皮肤、唾液腺、交感神经节、迷走神经、胃肠道和心脏等<sup>[54-55]</sup>。因此,外周组织活检有助于该类疾病的诊断和鉴别。

### 3.1 外周神经及神经节活检

早期即有研究<sup>[56-59]</sup>显示,MSA患者的腓肠神经、心脏交感神经均有退行性病变,提示MSA作为 $\alpha$ -突触核蛋白相关疾病,同时累及中枢及外周神经系统。一项研究检测皮肤活检组织中的磷酸化 $\alpha$ -突触核蛋白(phosphorylated  $\alpha$ -synuclein, p- $\alpha$ SN),结果发现12例MSA患者中,8例(67%)患者皮肤神经中p- $\alpha$ SN阳性,与tau蛋白相关疾病和正常组的鉴别特异度为100%。与PD患者p- $\alpha$ SN主要沉积于自主神经纤维不同,MSA患者p- $\alpha$ SN主要沉积于无髓鞘躯体感觉纤维<sup>[60]</sup>。但另2项分别纳入10例和13例MSA患者的研究<sup>[61-62]</sup>结果则显示:皮神经中p- $\alpha$ SN沉积均为阴性。上述研究结果不完全一致的原因可能与皮肤活检部位、活检组织处理方式和检测方法差异等有关。

MSA患者外周交感神经节的病理改变可能与其自主神经功能障碍有关<sup>[58-59]</sup>;但多数研究样本量小,研究结论不完全一致,阴性结果居多。如对8例MSA患者脑及外周神经节进行p- $\alpha$ SN的免疫组织化学染色,其中仅2例患者的交感神经节中发现神经元胞质包涵体(neuronal



cytoplasmic inclusion, NCI)<sup>[63]</sup>。另一项研究则显示 42.3% 的 MSA 患者交感神经节中, 神经元细胞质和突触的  $\alpha$ - 突触核蛋白免疫组织化学检测阳性, 施万细胞中未见  $\alpha$ - 突触核蛋白沉积, 且  $\alpha$ - 突触核蛋白阳性与 MSA 病程有一定关联<sup>[64]</sup>。一项日本研究<sup>[65]</sup> 则报道, MSA 患者存在外周神经系统的施万细胞胞质 p- $\alpha$ SN 聚集, 但仅在 33.3% 的交感神经节中找到施万细胞胞质阳性的包涵体 (Schwann cell cytoplasmic inclusion, SCCI)。

近年来, 随着 PD 患者异常  $\alpha$ - 突触核蛋白沉积起源于肠道假说的提出, 有研究<sup>[56-66]</sup> 证明大部分 PD 患者肠道神经系统中都存在  $\alpha$ - 突触核蛋白沉积的病理改变, 且可在脑黑质区出现病理改变前。但 2016 年一项研究<sup>[67]</sup> 发现, PD、MSA 患者及健康对照者均出现胃肠黏膜  $\alpha$ - 突触核蛋白免疫染色阳性, 且组间无明显差异。

### 3.2 下颌下腺活检

多项研究<sup>[68-70]</sup> 显示, 对下颌下腺细针活检组织进行  $\alpha$ - 突触核蛋白免疫组织化学染色, PD 患者阳性率较高,

与健康对照存在显著差异。另有 2 项研究分别纳入 2 例 MSA 患者, 则检测结果均为阴性<sup>[71-72]</sup>。由于 MSA 患者行下颌下腺组织  $\alpha$ - 突触核蛋白免疫组织化学染色的研究较少, 样本量极有限, 结果还需进一步验证。

## 4 总结

关于 MSA 生物标志物的研究众多, 但可应用于临床诊断的阳性结果有限, 体液中的蛋白质、miRNA 及分子影像等方向值得进一步探索。许多研究中 MSA 患者均为临床诊断, 诊断准确度差异较大, 患者有很大的异质性, 从而影响了研究结果的质量。许多生物标志物的采样、样本处理方法、数据处理等无统一标准, 且多数研究的样本量较小, 可能为各研究间结论不完全一致的原因。未来需要更多大样本的临床研究验证现有生物标志物的特异度、敏感度, 发现更多疾病早期生物标志物, 并联合检测多项生物标志物以提高疾病诊断和鉴别诊断的准确度。

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